

A Readily-Reconfigurable Continuous-Stirred Tank Photochemical Reactor Platform

*Daniel Francis,^{a,b} A. John Blacker,^{*a,b,c} Nikil Kapur,^{*a,d} Stephen P. Marsden^{*a,b}*

a) Institute of Process Research and Development, University of Leeds, Leeds LS2 9JT, UK; b) School of Chemistry, University of Leeds, Leeds LS2 9JT, UK; c) School of Chemical and Process Engineering, University of Leeds, Leeds LS2 9JT, UK; d) School of Mechanical Engineering, University of Leeds, Leeds LS2 9JT, UK

Keywords. Continuous flow reactors, photochemistry, photoredox, multiphasic.

ABSTRACT. A new modular photochemical continuous-stirred tank reactor design is described, based upon the development of light-source units that can be fitted to the previously described fReactor CSTR platform. In contrast to many tubular or plate-based designs, these units are especially well-suited to handling multiphasic mixtures, exemplified here in solid-liquid and gas-liquid photochemical reactions. The use of slurries as input feeds allows for intensification of a photochemical bromination, while the modular nature of the system facilitates simple integration of downstream reaction steps, exemplified here in a continuous synthesis of an intermediate for the drug valsartan.

INTRODUCTION

Recent years have seen a huge growth in the application of photochemically-mediated synthetic transformations, driven in part by extensive developments in photoredox catalysis.¹ Well-documented issues with scaling photochemical reactions, especially around light penetration into larger reaction vessels, secondary photoreactions at extended reaction times, and control of thermal effects, have resulted in the widescale adoption of continuous flow photochemical reactors on laboratory scale² and, increasingly, on development and production scale.^{3,4} The majority of reactor designs are based upon simple tubular reactors or patterned microreactors, which are suitable for homogeneous reactions, but less so for biphasic systems (liquid/liquid, gas/liquid). With the latter, these often result in segmented flow with relatively low mass transfer that relies on mixing induced by wall effects, which in turn is strongly influenced by the flow rate. Additionally, many real-life processes involve the input or formation of particulate materials (e.g. inorganic bases, poorly soluble reactants or reagents, insoluble salt by-products) and so a pressing need for photochemical reactors capable of handling solid/liquid biphasic systems has been identified.⁵ Reports to date have included using immersion well reactors in semi-continuous recirculatory mode,⁶ plate flow reactors combining oscillatory flow with static mixers,⁷ and the use of continuous stirred tank reactors (CSTRs).⁸ We recently described a modular, readily-reconfigurable CSTR platform, the ‘fReactor’, which is capable of handling gas, liquid and solid multi-phasic mixtures,⁹ and subsequently demonstrated preliminary applications as a continuous flow photochemical reactor.¹⁰ Encouraged by this success, we now report the design, construction and application of an optimised photochemical reactor platform which combines the flexibility of multiple, small scale CSTRs (the fReactor platform) with dedicated LED-based photochemical modules to allow easy and safe operation within the laboratory environment.

RESULTS AND DISCUSSION

Reactor Design

Figure 1 shows the equipment layout, with the photo-modules sitting atop the conventional fReactor platform, which in turn sits on a standard laboratory stirrer hotplate. Syringe pumps are used to feed reactants into the fReactor platform, giving a broad selection of flowrates. Each photo-module contains a single wavelength LED: for this work, the LEDs used were either 365nm or 460nm with a nominal radiant light output of 4.3 W and 3.9W, respectively. The LED is positioned to direct the light through the glass window into the reactor (window diameter 15 mm, with a safety cutout installed so light output is cut if the unit is lifted from the fReactor). Cooling is effected through natural convection around each photo-module unit and can be enhanced with a small external fan. Extensive details of the single and multiphasic capabilities of the CSTRs are reported elsewhere;⁹ briefly, each reaction vessel (PEEK material, volume 1.7ml) contains a single cross stirrer bar and is equipped with 4 standard ports accepting standard low pressure HPLC fittings, allowing for flexibility in connecting reactors to each other (1/8" OD FEP tubing) and to feed sources, sampling ports and instrumentation (e.g. thermocouples). Here, we daisy chain the fReactors together (with a single or dual feed into the first reactor and output from the last) giving an improved residence time distribution when compared to a single larger reactor of equivalent total volume.⁹ The fReactor platform sits on a standard stirrer-hotplate, which drives the cross-stirrer within each reactor and allows for heating if required.

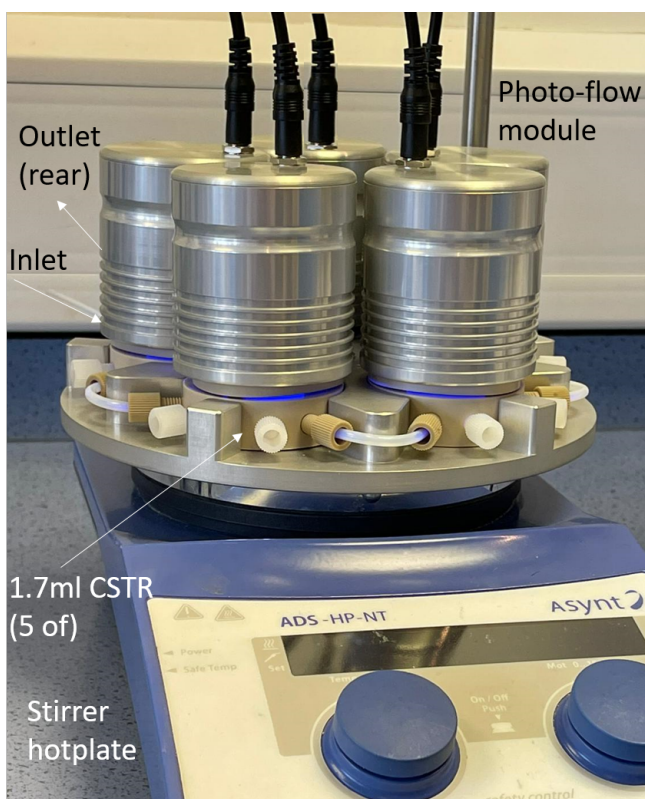


Figure 1: Arrangement of the photo-flow modules on the individual CSTRs. Here, a complete set of five modules in series are shown.

Photochemical Reactions

(1) Wohl-Ziegler Bromination

We began our studies by investigating photochemically-initiated benzylic bromination using *N*-bromosuccinimide (NBS; the Wohl-Ziegler reaction), since this synthetically useful transformation has been the focus of many studies in continuous flow¹¹ (including for applications to the synthesis of pharmaceutical intermediates^{11a,b}) and would provide a useful benchmark of performance for the reactors. We began by adopting conditions previously employed by Kappe for bromination in a Booker-Milburn-style¹² tubular reactor (coiled FEP tubing surrounding a 25W cool-white or 25W black-light lamp), namely a homogeneous solution of 1.05 equivalents of NBS to 0.5M methylene (4-methylacetophenone in our initial work) in

acetonitrile.^{11c} Using reactors equipped with 365nm LEDs, we were pleased to find that the reaction gave good conversion to the brominated product, and that the conversion scaled effectively linearly with the number of reactors at constant residence time per reactor, i.e. a five-fold faster flow-rate could be employed using five reactors versus one without negative impact on conversion (Figure 2).

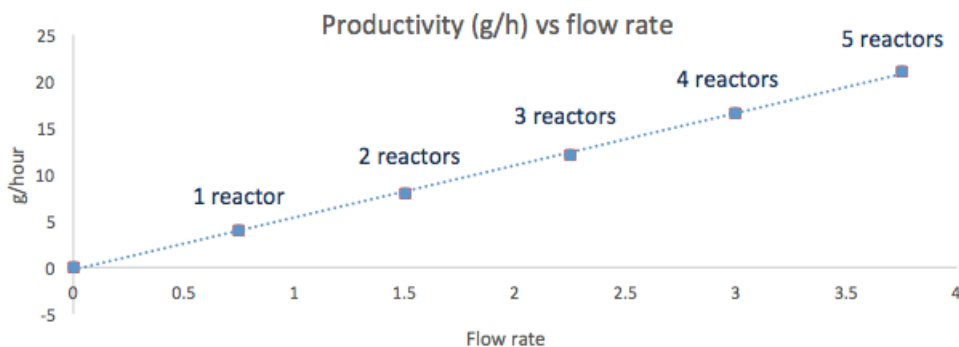
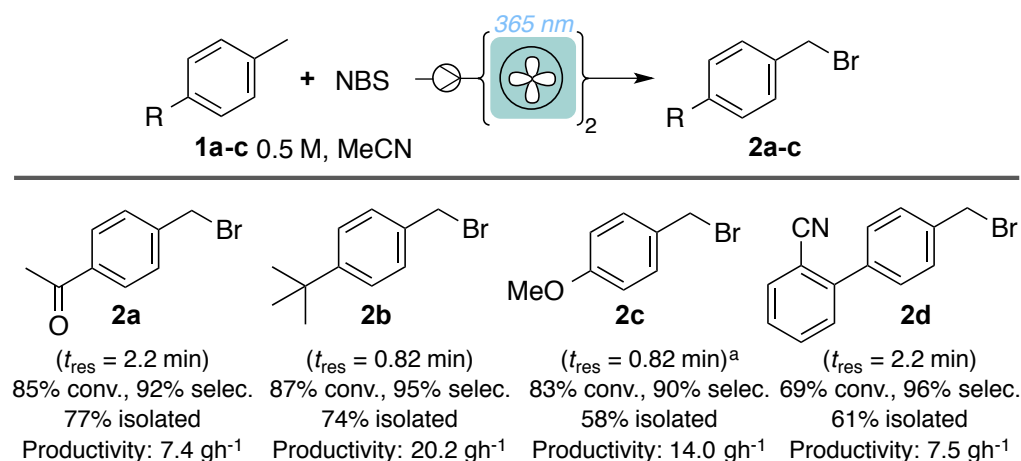


Figure 2. Linear response of productivity in benzylic bromination of **1a** to increased flow rate with scale-out of linked reactors.

We chose to use two reactors in sequence to demonstrate the performance of the CSTRs in preparative reactions (Scheme 1). At a flow rate of 1.25 mLmin⁻¹ **1a** gave an 85% conversion at steady-state, with good selectivity for monobrominated product **2a** (a small amount of 1,1-dibrominated product was also observed) leading to a 77% isolated yield (7.4 gh⁻¹ productivity). The more electron-rich substrates **1b** and **1c** underwent faster reaction and similar conversions and selectivities to **1a** could be achieved at a higher flow rate of 4 mLmin⁻¹, leading to comparable isolated yields but much improved productivities (up to >20 gh⁻¹). In the case of 4-methoxytoluene **1c**, it was found that a solvent switch to dioxane was required to prevent significant competition from electrophilic aromatic bromination.



Scheme 1 Wohl-Ziegler bromination using two sequential photochemical CSTRs. ^a reaction solvent = dioxane

An advantage of the modular nature of the CSTR platform is the ease with which additional operations can be coupled with the photochemical transformation. We demonstrated this by coupling a benzylic bromination with a subsequent nucleophilic substitution step, following a sequence used in the synthesis of the anti-hypertensive drug valsartan (Scheme 2).¹³ Thus, carrying out the benzylic bromination of toluene **1d** in our two-reactor configuration at a flow rate of 0.75 mLmin⁻¹ gave a ca. 77% conversion to bromide **2d** at steady state, with excellent (98%) selectivity. The output from the photochemical modules was mixed with a feed of valine methyl ester and triethylamine at ambient temperature in aqueous acetonitrile in the third fReactor and pumped through a further two modules (giving a total of 3 non-irradiated modules) on the fReactor platform. This led to the formation of the substitution product **3** in an unoptimised 44% isolated yield, representing a productivity of 3.2 gh^{-1} .

			(%)	(%)	(%) ^c	(gh ⁻¹)
1	2a	2.6	81	87	65	20.8
2	2b	0.82	72	96	58	63.2
3 ^b	2c	1.63	89	85	71	34.3
4 ^c	2d	2.17	53	98	41	15.1

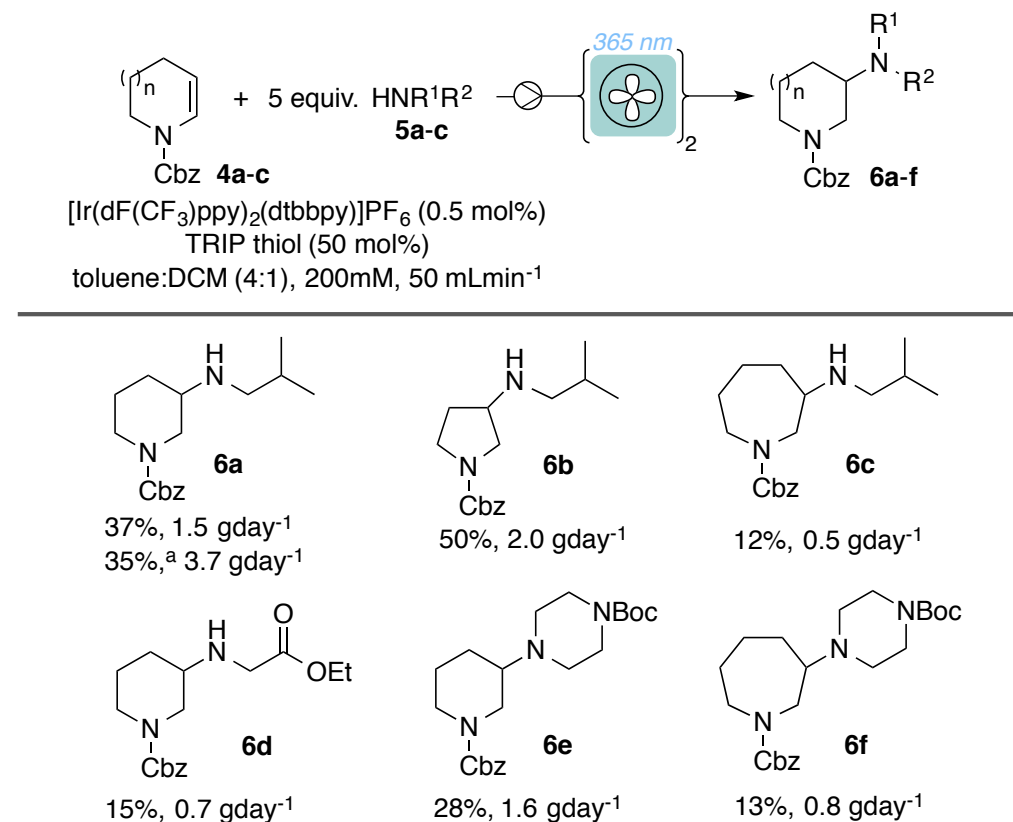
^a isolated yield; ^b reaction solvent = dioxane; ^c substrate concentration 1.5M

(2) Photoredox-catalysed Hydroamination of Enecarbamates

We next wished to demonstrate applicability to a photoredox-catalysed process, and selected our recently-reported hydroamination of enecarbamates.¹⁴ The discovery-scale batch reaction conditions represent a challenge for continuous processing, being dilute (50 mM in substrate), heterogeneous (partially insoluble photocatalyst at 2 mol%) and requiring long reaction times for completion (16 hours). We therefore undertook some optimisation studies in flow using photoflow modules operating at 365 nm (Supporting Information) using enecarbamate **4a** and isobutylamine **5a** as reactants, which allowed us to identify more intensive conditions for the continuous process. We reduced the catalyst loading to 0.5 mol%, to reduce both the cost and amount of insoluble material as we attempted to increase the reactant concentration. In neat toluene, the system still contained insoluble catalyst even at 50 mM substrate, and although the reactor is capable of handling the heterogeneous mixture we found that the process was more reproducible if a homogeneous solution was achieved. Using 20% v/v THF/toluene led to a 50% conversion at 100 mM, but further intensification was not possible as the catalyst solubility was reached. Using 20% dichloromethane/toluene allowed further intensification to 200 mM, and using two reactors in sequence at a flow-rate of 50 μLmin^{-1} (overall residence time ca. 1h), we were able to achieve a steady-state conversion to product **6a** of 42%, translating to a 37%

isolated yield (85% based on recovered **4a**) and productivity equating to 1.5 gday⁻¹ (Table 2). Five additional substrate combinations were examined, with >1.5 gday⁻¹ productivities observed for **6b** and **6e**. As in the batch series, the reactions to form aminated azepanes such as **6c** and **6f** were rather sluggish, leading to low conversions – nevertheless, despite the low overall isolated yield these still returned 0.5 gday⁻¹ quantities of material, which may be sufficient to progress e.g. discovery projects. To further boost the productivity, the formation of **6a** was carried out using five reactors in series, enabling an increase in flow rate to 125 μLmin⁻¹; we were pleased to find that the conversion and isolated yield remained essentially unchanged but the productivity was raised to ca. 3.7 gday⁻¹, a >50-fold increase in productivity over the standard batch reaction.

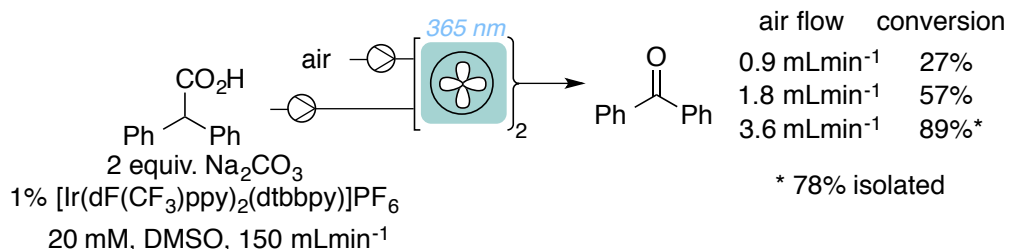
Table 2. Photoredox-catalysed hydroamination of enecarbamates in flow. ^a



^aIsolated yields.

(3) Photoredox-catalysed Decarboxylative Oxidation (Biphasic Gas-Liquid Reaction)

The potential of the fReactor platform to handle gaseous reaction components has already been demonstrated in the context of a catalytic hydrogenation reaction,^{9,15} and we also demonstrated the benzophenone-mediated aerobic benzylic oxidation of tetralin using our prototype photochemical reactor.¹⁰ We wished to demonstrate the capabilities of the optimised reactor design in a biphasic gas-liquid process, and chose MacMillan's photoredox-catalysed decarboxylative oxidation of carboxylic acids.¹⁶ For ease of operation, rather than the final optimised conditions described in that paper we adopted simplified conditions (alternative photocatalyst, no viologen salt additive and use of air rather than oxygen as the source of terminal oxidant). The substrate (1,1-diphenylacetic acid), catalyst and base were co-injected as a homogeneous solution, while air was added via a syringe pump. The conversion was found to be dependent upon the air flow-rate, indicating that the availability of dissolved oxygen was a limiting factor. At a liquid residence time of ca. 20 minutes using 2 reactors, an 89% conversion was achieved at a gas flow rate of 3.6 mLmin⁻¹, corresponding to a 78% isolated yield of benzophenone. This is comparable to the 86% isolated yield obtained in MacMillan's optimised protocol, and represents a 5-fold more productive reaction (flow: 0.14 mmolh⁻¹ product; batch: 0.43 mmol product in 16 hours equates to 0.026 mmolh⁻¹) using simpler/safer reaction conditions.



Scheme 3 Biphasic gas-liquid reaction: photoredox-catalysed decarboxylative oxidation of a carboxylic acid.

CONCLUSIONS

A new design for a modular photochemical continuous stirred tank reactor platform is described, based on our original 'fReactor' platform. The dedicated photo-units give a high radiant light output and offer easy and safe operation within the laboratory environment. The CSTRs equipped with the photoflow modules are capable of handling common process-relevant heterogeneous mixtures (solid/liquid, liquid/liquid and gas/liquid), thus widening the window of opportunity for novel photochemical reactions. In particular the ability to work above the solubility limit of individual reagents allows for highly productive reactions (up to 0.24 kgL⁻¹h⁻¹ in benzylic brominations), and integration with downstream chemical transformations is straightforward. The photochemical modules are now available commercially, along with the fReactor platform (www.asynt.com/product/freactor-photo-flow/). The ease-of-use and flexibility of CSTRs with demonstrably good productivity support the drive to create efficient and sustainable chemical processes.

ASSOCIATED CONTENT

Supporting Information.

The following file is available free of charge: full experimental procedures, compound characterisation data and ¹H/¹³C NMR spectra of products.

AUTHOR INFORMATION

Corresponding Author

*j.blacker@leeds.ac.uk; n.kapur@leeds.ac.uk; s.p.marsden@leeds.ac.uk

Author Contributions

The manuscript was written through contributions of all authors.

Note

The University of Leeds licenses the design of fReactors and photo-flow modules to Asynt Limited.

Funding Sources

EPSRC Impact Acceleration Account at the University of Leeds (EP/R511717/1) and the Royal Academy of Engineering for support of NKs Chair.

ACKNOWLEDGMENT

We thank Asynt Limited, Redbrick Molecular Limited and Sterling Pharma Solutions Limited for useful discussions and support of this work.

REFERENCES

- (1) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363. (b) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox catalysis in organic chemistry. *J. Org. Chem.* **2016**, *81*, 6898–6926.
- (2) (a) Donnelly, K.; Baumann, M. Scalability of Photochemical Reactions in Continuous Flow Mode. *J. Flow. Chem.* **2021**, doi: 10.1007/s41981-021-00168-z. (b) Rehm, T. H. Flow Photochemistry as a Tool in Organic Synthesis. *Chem. Eur. J.* **2020**, *26*, 16952–16974. (c) Politano, F.; Oksdath-Mansilla, G. Light on the Horizon: Current Research and Future Perspectives in Flow Photochemistry. *Org. Process Res. Dev.* **2018**, *22*, 1045–1062. (d) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016**, *116*, 10276–10341.
- (3) For examples of scale-up applications of continuous photochemistry, see: (a) Graham, M. A.; Noonan, G.; Cherryman, J. H.; Douglas, J. J.; Gonzalez, M.; Jackson, L. V.; Leslie, K.; Liu, Z.-Q.; McKinney, D.; Munday, R. H.; Parsons, C. D.; Whittaker, D. T. E.; Zhang, E.-X.; Zhang, J.-W. Development and Proof of Concept for a Large-Scale Photoredox Additive-Free Minisci

Reaction. *Org. Process Res. Dev.* **2021**, *25*, 57–67. (b) Beaver, M. G.; Zhang, E.-X.; Liu, Z.-Q.; Zheng, S.-Y.; Wang, B.; Lu, J.-P.; Tao, J.; Gonzalez, M.; Jones, S.; Tedrow, J. S. Development and Execution of a Production-Scale Continuous [2 + 2] Photocycloaddition. *Org. Process Res. Dev.* **2020**, *24*, 2139–2146. (c) Corcoran, E. B.; McMullen, J. P.; Lovesque, F.; Wismer, M. K.; Naber, J. R. Photon Equivalents as a Parameter for Scaling Photoredox Reactions in Flow: Translation of Photocatalytic CN Cross-Coupling from Lab Scale to Multikilogram Scale. *Angew. Chem. Int. Ed.* **2020**, *59*, 11964–11968. (d) Lévesque, F.; Di Maso, M. J.; Narsimhan, K.; Wismer, M. K.; Naber, J. R. Design of a Kilogram Scale, Plug Flow Photoreactor Enabled by High Power LEDs. *Org. Process Res. Dev.* **2020**, *24*, 2935–2940. (e) Lee, D. S.; Sharabi, M.; Jefferson-Loveday, R.; Pickering, S. J.; Poliakoff, M.; George, M. W. Scalable Continuous Vortex Reactor for Gram to Kilo Scale for UV and Visible Photochemistry. *Org. Process Res. Dev.* **2020**, *24*, 201–206. (f) Yayla, H.G.; Peng, F.; Mangion, I.K.; McLaughlin, M.M.; Campeau, L.-C.; Davies, I.W.; DiRocco, D.A.; Knowles, R.R. Discovery and Mechanistic Study of a Photocatalytic Indoline Dehydrogenation for the Synthesis of Elbasvir. *Chem. Sci.* **2016**, *7*, 2066–2073. (g) Elliott, L. D.; Berry, M.; Harji, B.; Klauber, D.; Leonard, J.; Booker-Milburn, K.-I.; A Small-Footprint, High-Capacity Flow Reactor for UV Photochemical Synthesis on the Kilogram Scale. *Org. Process Res. Dev.* **2016**, *20*, 1806–1811. (h) Beatty, J. W.; Douglas, J. J.; Miller, R.; McAtee, R. C.; Cole, K. P.; Stephenson, C. R. J. Kilo scale: Photochemical Perfluoroalkylation with Pyridine N-Oxides: Mechanistic Insights and Performance on a Kilogram Scale. *Chem* **2016**, 456–472. (i) Turconi, J.; Griollet, F.; Guevel, R.; Oddon, G.; Villa, R.; Geatti, A.; Hvala, M.; Rossen, K.; Göller, R.; Burgard, A. Semisynthetic Artemisinin, the Chemical Path to Industrial Production. *Org. Process Res. Dev.* **2014**, *18*, 417–422.

(4) For an impressive recent example of batch photochemistry on scale, see: Robinson, A.; Dieckmann, M.; Krieger, J.-P.; Vent-Schmidt, T.; Marantelli, D.; Kohlbrenner, R.; Gribkov, D.; Simon, L. L.; Austrup, D.; Rod, A.; Bochet, C. G. Development and Scale-Up of a Novel Photochemical C–N Oxidative Coupling. *Org. Process Res. Dev.* **2021**, *25*, 2205–2220.

- (5) Bonfield, H. E.; Knauber, T.; Lévesque, F.; Moschetta, E. G.; Susanne, F.; Edwards, L. J. Photons as a 21st Century Reagent. *Nature Commun.* **2020**, *11*, 804.
- (6) Grimm, I.; Hauer, S. T.; Schulte, T.; Wycich, G.; Collins, K. D.; Lovis, K.; Candish, L. Upscaling Photoredox Cross-Coupling Reactions in Batch Using Immersion-Well Reactors. *Org. Process Res. Dev.* **2020**, *24*, 1185–1193.
- (7) (a) Debrouwer, W.; Kimpe, W.; Dangreau, R.; Huvaere, K.; Gemoets, H. P. L.; Mottaghi, M.; Kuhn, S.; Van Aken, K. Ir/Ni Photoredox Dual Catalysis with Heterogeneous Base Enabled by an Oscillatory Plug Flow Photoreactor. *Org. Process Res. Dev.* **2020**, *24*, 2319–2325. (b) Rosso, C.; Gisbertz, S.; Williams, J.; Gemoets, H.; Debrouwer, W.; Pieber, B.; Kappe, C. O. An Oscillatory Plug Flow Photoreactor Facilitates Semi-Heterogeneous Dual Nickel/Carbon Nitride Photo-Catalytic C-N Couplings. *React. Chem. Eng.* **2020**, *5*, 597. (c) Wen, Z.; Maheshwari, A.; Sambiagio, C.; Deng, Y.; Laudadio, G.; Van Aken, K.; Yuhan Sun, Y.; Gemoets, H. P. L.; Noël, T. Optimization of a Decatungstate-Catalyzed C(sp³)-H Alkylation Using a Continuous Oscillatory Millistructured Photoreactor. *Org. Process Res. Dev.* **2020**, *24*, 2356–2361. (d) Bianchi, P.; Williams, J. D.; Kappe, C. O. Continuous Flow Processing of Bismuth-Photocatalyzed Atom Transfer Radical Addition Reactions Using an Oscillatory Flow Reactor. *Green Chem.* **2021**, *23*, 2685–2693.
- (8) (a) Duvadie, R.; Pomberger, A.; Mo, Y.; Altinoglu, E. I.; Hsieh, H.-W.; Nandiwale, K. Y.; Schultz, V. L.; Jensen, K. F.; Robinson, R. I. Photoredox Iridium–Nickel Dual Catalyzed Cross-Electrophile Coupling: From a Batch to a Continuous Stirred-Tank Reactor via an Automated Segmented Flow Reactor. *Org. Process Res. Dev.* **2021**, *25*, 2323–2330. (b) Pomberger, A.; Mo, Y.; Nandiwale, K. Y.; Schultz, V. L.; Duvadie, R.; Robinson, R. I.; Altinoglu, E. I.; Jensen, K. F. A Continuous Stirred-Tank Reactor (CSTR) Cascade for Handling Solid-Containing Photochemical Reactions. *Org. Process Res. Dev.* **2019**, *23*, 2699–2706. (c) Harper, K. C.; Moschetta, E. G.; Bordawekar, S. V.; Wittenberger, S. J. A Laser Driven Flow Chemistry

Platform for Scaling Photochemical Reactions with Visible Light. *ACS Cent. Sci.* **2019**, *5*, 109–115.

(9) Chapman, M. R.; Kwan, M. H. T.; King, G.; Jolley, K. E.; Hussain, M.; Hussain, S.; Salama, I. E.; Gonzalez Nino, C.; Thompson, L. A.; Bayana, M. E.; Clayton, A. D.; Nguyen, B.; Turner, N. J.; Blacker, A. J. Simple and Versatile Laboratory Scale CSTR for Multiphasic Continuous-Flow Chemistry and Long Residence Times. *Org. Process Res. Dev.* **2017**, *21*, 1294–1301.

(10) Manson, J. A.; Clayton, A. D.; Gonzalez Nino, C.; Labes, R.; Chamberlain, T. W.; Blacker, A. J.; Kapur, N.; Bourne, R. A. *Chimia* **2019**, *73*, 817–822.

(11) (a) Steiner, A.; Roth, P. M. C.; Strauss, F. J.; Gauron, G.; Tekautz, G.; Winter, M.; Williams, J. D.; Kappe, C. O. Multikilogram per Hour Continuous Photochemical Benzylic Brominations Applying a Smart Dimensioning Scale-up Strategy. *Org. Process Res. Dev.* **2020**, *24*, 2208–2216. (b) Steiner, A.; Williams, J. D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, C. O. Continuous Photochemical Benzylic Bromination Using *in situ* Generated Br₂: Process Intensification Towards Optimal PMI and Throughput. *Green Chem.* **2020**, *22*, 448–454. (c) Bonfield, H. E.; Williams, J. D.; Ooi, W. X.; Leach, S. G.; Kerr, W. J.; Edwards, L. J. A Detailed Study of Irradiation Requirements Towards an Efficient Photochemical Wohl-Ziegler Procedure in Flow. *ChemPhotoChem* **2018**, *2*, 938–944. (d) Chen, Y.; de Frutos, O.; Mateos, C.; Rincon, J. A.; Cantillo, D.; Kappe, C. O. Continuous Flow Photochemical Benzylic Bromination of a Key Intermediate in the Synthesis of a 2-Oxazolidinone. *ChemPhotoChem* **2018**, *2*, 906–912. (e) Kim, Y. J.; Jeong, M. J.; Kim, J. E.; In, I.; Park, C. P. Microreactor-Mediated Benzylic Bromination in Concentrated Solar Radiation. *Aust. J. Chem.* **2015**, *68*, 1653–1656. (f) Cantillo, D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, C. O. A Scalable Procedure for Light-Induced Benzylic Brominations in Continuous Flow. *J. Org. Chem.* **2014**, *79*, 223–229. (g) Manabe, Y.; Kitawaki, Y.; Nagasaki, M.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. Revisiting the Bromination of C–H Bonds with Molecular Bromine by Using a Photo-

Microflow System. *Chem. Eur. J.* **2014**, *20*, 12750–12753. (h) Šterk, D.; Jukič, M.; Časar, Z.

Application of Flow Photochemical Bromination in the Synthesis of a 5-

Bromomethylpyrimidine Precursor of Rosuvastatin: Improvement of Productivity and Product Purity. *Org. Process Res. Dev.* **2013**, *17*, 145–151.

(12) Hook, D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. A Practical Flow Reactor for Continuous Organic Photochemistry. *J. Org. Chem.* **2005**, *70*, 7558–7564.

(13) Beutler, U.; Boehm, M.; Fuenfschilling, P. C.; Heinz, T.; Mutz, J.-P.; Onken, U.; Mueller, M.; Zaugg, W. A High-Throughput Process for Valsartan. *Org. Process Res. Dev.* **2007**, *11*, 892–898.

(14) Francis, D.; Nelson, A.; Marsden, S. P. Synthesis of β -Diamine Building Blocks by Photocatalytic Hydroamination of Enecarbamates with Amines, Ammonia and N–H Heterocycles. *Chem. Eur. J.* **2020**, *26*, 14861–14865.

(15) Guan, F.; Kapur, N.; Sim, L.; Taylor, C. J.; Wen, J.; Zhang, X.; Blacker, A. J. A Universal Reactor Platform for Batch and Flow: Application to Homogeneous and Heterogeneous Hydrogenation. *React. Chem. Eng.* **2020**, *5*, 1903–1908.

(16) Faraggi, T. M.; Li, W.; MacMillan, D. W. C. Decarboxylative Oxygenation via Photoredox Catalysis. *Isr. J. Chem.* **2020**, *60*, 410–415.