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Application of Microflow Conditions to Visible Light Photoredox Catalysis

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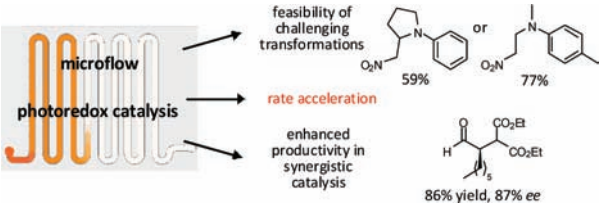
ABSTRACT



Applications of microflow conditions for visible light photoredox catalysis have successfully been developed. Operationally simple microreactor and FEP (fluorinated ethylene propylene copolymer) tube reactor systems enable significant improvement of several photoredox reactions using different photocatalysts such as $[Ru(bpy)_3]^{2+}$ and Eosin Y. Apart from rate acceleration, this approach facilitates previously challenging transformations of nonstabilized intermediates. Additionally, the productivity of the synergistic, catalytic enantioselective photoredox α-alkylation of aldehydes was demonstrated to be increased by 2 orders of magnitude.

Visible light promoted photochemistry has already been recognized as a highly valuable tool for synthesis a century ago.[1] Only recently have photocatalytic (redox) transformations[2] been regaining increasing attention as an interesting synthetic methodology in the context of green chemistry and due to their potential for developing new chemical reactions. While efficiency is typically not an issue for the classic laboratory scale, larger practical synthetic applications of photoredox catalysis and photosensitization are scarce as they often require specialized equipment. Furthermore, the productivity in batch reactors is impeded by the limited light penetration through the reaction media as rationalized by Lambert–Beer's law. In this context, continuous microflow methods present a valuable alternative approach to circumvent known drawbacks. Their high surface-to-volume ratio (small channel depth) not only ensures improved sample irradiation[3] but also contributes to spatial homogeneity, resulting in greatly enhanced heat and mass transfer as compared to common batch systems.[4] Shortened reaction times and hence prevention of undesired side reactions may contribute to higher selectivity and product purity.[5] Although well established for UV photochemistry,[6] microreactors have until now only found limited applications for visible-light photocatalytic transformations.[6−8] Likewise, there are

(1) (a) Ciamician, G. *Science* **1912**, *36*, 385. Reviews on synthetic photochemistry: (b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. (c) Hehn, J. P.; Bach, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000.

(2) (a) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (b) Teplý, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (c) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (d) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785. (e) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102.

(3) For an example where stronger light emission proved unfavorable: Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360.

(4) Recent reviews on microreactors: (a) Yoshida, J.; Kim., H.; Nagaki, A. *ChemSusChem* **2011**, *4*, 331. (b) Wiles, C.; Watts, P. *Chem. Commun.* **2011**, *47*, 6512. (c) Wegner, J; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583. (d) *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2008.

(5) Flow conditions lower products' exposure to light and hence limit degradation. Additional advantages include the possibility of both rapid analysis and fast reaction screening as well as of parallelization to allow for simple scale up; see ref 4.

(6) (a) Oelgemöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522. (b) Coyle, E: E; Oelgemöller, M. *Photochem. Photobiol. Sci.* **2008**, *7*, 1313. (c) Wiles, C.; Watts, P. *Microreaction Technology in Organic Synthesis*; Taylor and Francis Group: Boca Raton, FL, 2011; Chapter 5. (d) Fukuyama, T.; Rahman, T.; Sato, M.; Ryu, I. *Synlett* **2008**, 151.

(7) For recent examples on photocatalytic triplet sensitization, see: (a) Lévesque, F.; Seeberger, P. H. *Org. Lett.* **2011**, *13*, 5008. (b) Lévesque, F.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706.

(8) For a recent report on accelerating $[Ru(bpy)3]^{2+}$-catalyzed reactions, see: (a) Bou-Hamdan, F. R.; Seeberger, P. H. *Chem. Sci.* **2012**, *3*, 1612. Two further applications of photoredox catalysis in flow systems have been reported while this manuscript was under review: (b) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144. (c) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140.

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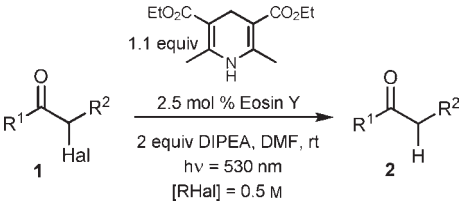
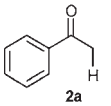
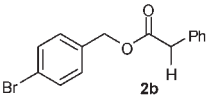
only a few reports on (homogeneous) enantioselective catalysis in microflow systems;[9,10] especially examples dealing with synergistic catalysis[11] have not yet been described. For instance, the merging of photoredox catalysis with organocatalysis as pioneered by MacMillan et al.[12,13] provides access to important chiral α-alkylated aldehyde building blocks. Proceeding under the *simultanous* activation of both the nucleophile and the electrophile (within two distinct intersecting catalytic cycles) this powerful concept poses an additional challenge for the transfer to flow systems due to the inherent low concentration of the key intermediates.[11a]

The obvious benefits of microstructured reactors known from classical photochemistry prompted us to investigate the influence of microreactors on visible-light photoredox catalysis. Herein, we disclose the successful development of flow conditions to both enhance productivity of (enantioselective) photocatalytic reactions and facilitate challenging transformations involving unstable intermediates.

We recently reported[14] that the photoredox dehalogenation[15] of activated halogenides upon irradiation with visible light can also be effected by simple organic dyes[16] and therefore chose this Eosin Y mediated transformation as a first benchmark reaction for the evaluation of flow conditions using a commercially available microreactor setup.[17] In fact, within the flow regime, by employing similar conditions as described previously,[14] we noticed a tremendous acceleration for the dehalogenation of α-bromoacetophenone **1a** (Table 1, entry 1). Full defunctionalization yielding product **2a** could be reached in less than 1 min. Similarly, the conversion of the less activated α-carbonyl chloride **1b** (entry 2) was significantly increased without loss of selectivity as the aromatic bromide remained untouched.

Table 1. Acceleration of the Photocatalytic Reductive Dehalogenation within a Microreactor[a]



entry	R-Hal	product	$t_{reaction}$ batch	$t_{residence}$ microreactor (yield [%])
1	**1a** R^1 = Ph R^2 = H Hal = Br	 **2a**	12 h	40 s (97[b])
2	**1b** R^1 = (*p*-Br)BnO R^2 = Ph Hal = Cl	 **2b**	18 h	20 min (89[b])

[a] Reaction conditions according to ref 14, $c_{RHal} = 0.5$ M. [b] Isolated yield.

We assume that in the presence of sacrificial electron donors (such as diisopropylethylamine (DIPEA) and/or Hantzsch ester) the strongly improved light penetration results in the efficient formation of the excited ^{1}EY* and subsequent intersystem crossing to the corresponding triplet state ^{3}EY* and hence in a higher concentration of the strong reductant Eosin Y radical anion $EY^{\bullet -}$ being capable of reducing the α-halogen carbonyl compounds. The observed temporary decolorization of the usually orange reaction mixture during irradiation might also indicate the accumulation of this active catalyst species.[18]

Encouraged by these initial results we turned our attention to aza-Henry reactions, representing an example for oxidative α-amino C−H functionalizations *via* visible-light photoredox catalysis.[19] Quite a number of related transformations employing different nucleophiles[20] and also "follow-up" reactions[21] with the help of various photoredox catalysts[22] have been published recently. Upon irradiation, initial formation of an α-amino radical cation by

(9) (a) Rasheed, M; Elmore, S. C.; Wirth, T. In *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques and Applications*; Gruttadauria, M., Giacalone, F., Eds.; Wiley: Hoboken, NJ, 2011; p 345. (b) Mak, X. Y.; Laurino, P.; Seeberger, P. H. *Beilstein J. Org. Chem.* **2009**, *5*, No. 19, DOI: 10.3762/bjoc.5.19. Selected recent examples of enantioselective flow chemistry: (c) Odedra, A.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2699. (d) Fritzsche, S.; Ohla, S.; Glaser, P.; Giera, D. S.; Sickert, M.; Schneider, C.; Belder, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 9467.

(10) For a seminal example of enantioselective photochemistry in a micoreactor (≈ 2% ee), see: Maeda, H.; Mukae, H.; Mizuno, K. *Chem. Lett.* **2005**, *34*, 36.

(11) For recent reviews, see: (a) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (b) Wende, R. C.; Schreiner, P. *Green Chem.* **2012**, DOI: 10.1039/C2GC35160A.

(12) (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (c) Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600.

(13) For another example of synergistic photoredox organocatalysis (albeit with only poor enantioselectivity), see ref 3.

(14) Neumann, M.; Füldner, S.; König, B.; Zeitler, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 951.

(15) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. J. R. *J. Am. Chem. Soc.* **2009**, *131*, 8756.

(16) For selected recent applications using organic photoredox catalysts, see: (a) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682. (b) Pan, Y.; Wang, S.; Kee, C. W.; Dubuisson, E.; Yang, Y.; Loh, K. P.; Tan, C.-H. *Green Chem.* **2011**, *13*, 3341. (c) Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958. (d) Hari, D. P.; B. König, B. *Org. Lett.* **2011**, *13*, 3852. (e) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K. A.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784. For a review, see: (f) Ravelli, D.; Fagnoni, M. *ChemCatChem* **2012**, *4*, 169. (g) Pandey, G.; Ghorai, M. K.; Hajra, S. *Pure Appl. Chem.* **1996**, *68*, 653.

(17) For details see Supporting Information.

(18) (a) Neckers, D. C.; Valdes-Aguilera, O. M. *Adv. Photochem.* **1993**, *18*, 315. For recent spectroelectrochemical studies on redox reactions of Eosin Y, see: (b) Zhang, J.; Sun, L.; Yoshida, T. *J. Electroanal. Chem.* **2011**, *662*, 384.

(19) Condie, A. G.; González-Gómez, J.-C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464.

(20) For selected examples using Ir- or Ru-based catalysts, see: (a) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94. (b) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 12709. (c) Xuan, J.; Cheng, Y.; An, J.; Lu, L.-Q.; Zhang, X.-X.; Xiao, W.-J. *Chem. Commun.* **2011**, *47*, 8337. See also ref 3.

(21) (a) Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615. (b) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171.

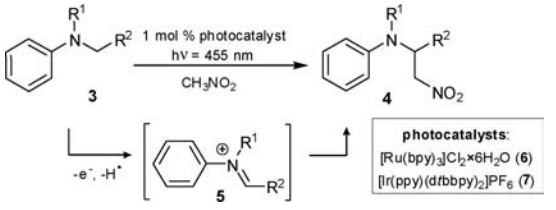
(22) Examples with organic photocatalysts, see refs 16a, 16b, 16d, and 23a. For solid inorganic catalysts, see: (a) Rueping, M.; Zoller, J.; Fabry, D. C.; Poscharny, K.; Koenigs, R. M.; Weirich, T. E.; Mayer, J. *Chem.—Eur. J.* **2012**, *18*, 3478. (b) Cherevatskaya, M.; Neumann, M.; Füldner, S.; Harlander, C.; Kümmel, S.; Dankesreiter, S.; Pfitzner, A.; Zeitler, K.; König, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 4062. (c) Xie, Z.; Wang, C.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc.* **2011**, *133*, 2056.

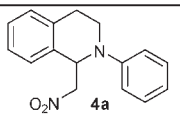
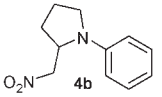
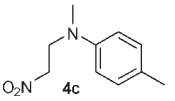
reductive quenching of the photoexcited catalyst is commonly proposed to be the starting point for a subsequent generation of a electrophilic iminium intermediate **5**.[23] This can then be trapped by different nucleophiles[20] such as nitromethane in the case of aza-Henry reactions. Despite known side reactions such as the undesired amide formation in nondegassed reaction mixtures,[21a] these transformations only work well for stabilized iminium ions, i.e. those stemming from benzylic amines such as *N*-aryl tetrahydroisoquinolines (THIQs).[24] Other tertiary amines, such as *N*-phenyl pyrrolidine **3b** or dimethylaniline **3c**, are known to be difficult substrates that require long reaction times (Table 2, entries 3 and 4) and often fail to reach full conversion.[25] We envisioned our microflow conditions to be beneficial for these critical transformations as the improved mass transfer (in combination with effective irradiation) could ensure a fast reaction of the unstable iminium intermediates with their corresponding reaction partner.[26]

To test our hypothesis, we launched aza-Henry reactions of different substrates under microflow conditions with conditions reported by Stephenson[19] using both $[Ru(bpy)_3]Cl_2$ **6** and $[Ir(ppy)_2(d\mathit{t}bbpy)]PF_6$ **7** as catalysts.

Having established an amine concentration of c = 0.25 M as optimal, we started to compare our results regarding conversion, time, and yield with the literature data of the optimized batch conditions.[19] With THIQ **3a** as the "iminium precursor" we could solely identifiy the generation of the corresponding aza-Henry product **4a** with an approximate 20−30-fold acceleration without formation of any side products.[27] Unlike the batch conditions[19] the choice of Ru or Ir catalyst indeed slightly altered the reaction time, but did not influence the isolated yield of the product (see Table 2, entries 1 and 2). Remarkably, using 2 mol % of the Ir catalyst **7**, the more challenging substrate *N*-phenyl pyrrolidine **3b** could smoothly be converted to the desired nitromethane addition product **4b** (entry 3). This clearly demonstrates the superiority of the flow conditions for aza-Henry reactions as compared to batch transformations. Likewise, we also noticed a considerable enhancement in reaction rate. Even substrates requiring the intermediate formation of a nonstabilized iminium ion containing a primary carbon atom such as aniline **3c** (which completely failed to react under batch conditions)[19] could be successfully converted to the corresponding product **4c** (entry 4) in good yield within the microreactor. However, we still could not achieve full conversion, as further prolonged reaction times led to degradation of the Ir photocatalyst.

Table 2. Comparison of Visible Light Photoredox Aza-Henry Reactions Conducted in Batch and Flow Reactor[a]



entry	product	rxn time[b] batch	yield[b] (conversion) [%]	residence time microreactor	yield[c] (conversion)[d] [%]
1	 4a	10 h	92 (100)	30 min	93 (100)
2		20 h[e]	81 (100)	40 min	93 (100)
3	 4b	72 h	27 (40)	60 min	59[f] (100)
4	 4c	72 h	0 (0)	130 min	77 (85[g])

[a] Conditions: 1 mol % Ir catalyst **7**, nitromethane, c_{amine} = 0.25 M. [b] According to ref 19. [c] Yield of isolated product. [d] Determined by GC analysis using an internal standard. [e] Conducted using 1 mol % of Ru catalyst **6**. [f] Volatile compound. [g] Longer residence times could not improve conversion due to photocatalyst bleaching.

We then sought to further investigate the full potential of the microflow approach. While in the previous examples the photocatalytically generated electrophiles were reacted with an excess of (pro)nucleophile, we wondered whether an extension to a more challenging enantioselective, synergistic catalytic system, such as the aminocatalyzed α-alkylation of aldehydes,[12a,14] would be possible. Here, it is critical to match the photoredox catalytic generation of the electron-deficient stabilized α-carbonyl alkyl radicals from the corresponding halides with the aminocatalyzed formation of the nucleophilic enamine intermediate; too low enamine concentrations would promote dehalogenation as a side reaction. Additionally, one must ensure the sufficiently fast oxidation of the intermediary aminoradical to both allow for regeneration of the imidazolidinone catalyst **10** and ensure the availability of the reductive species of the photocatalyst. We were pleased to find that the synergistic catalysis using previously established Eosin Y catalyzed conditions[14] indeed performed extremely well within the microreactor flow regime (Table 3). While no erosion of yield or enantiomeric excess was noticed, we could significantly shorten the reaction time. In an effort to lower the amount of organocatalyst[28] we investigated the influence of the microflow conditions on the enamine formation by a stepwise reduction of the loading of catalyst **10**, monitoring both yield and

(23) For selected recent mechanistic studies, see: (a) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem.—Eur. J.* **2012**, *18*, 620. (b) See ref 20a.

(24) Successful photoredox reactions of nonbenzylic amines often follow a different α-amino radical mechanism: (a) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (b) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672. (c) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338.

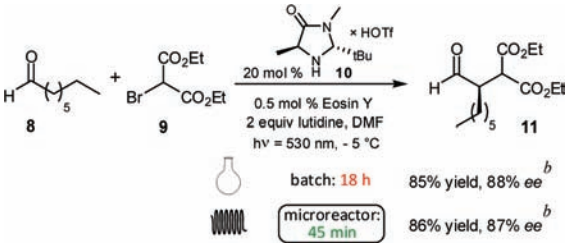
(25) For other documented examples (rxn time up to 96 h) please refer to refs 16a and 16d.

(26) The transformation of unstable intermediates under flow conditions is known: Yoshida, J. *Flash chemistry: fast organic synthesis in microsystems*; Wiley: Hoboken, NJ, 2008. For the recent transformation of unstable silyl enolethers, see: Kurahashi, K.; Takemoto, Y.; Takasu, K. *ChemSusChem* **2012**, *5*, 270.

(27) Flow conditions additionally allow for advantageous in-line workup and purification. For the possibility to conduct these aza-Henry reactions with in-line purification through connection to a SiO_2 pad, please see Supporting Information.

enantiomeric excess as a function of the reaction temperature. Residence times (Table 3) were each adjusted to reach full conversion. At 20 °C reduced amounts of amino catalyst (down to 10 mol %) still allowed for full conversion and good isolated yields, albeit requiring longer reaction times (entries 1, 4, and 7). Lowering the reaction temperature to −5 °C could considerably improve the enantioselectivity (as also previously observed for our batch conditions[14]) at a catalyst loading of 20 mol % (entries 2, 3). However, this turned out to be difficult for lower catalyst amounts, as we could not detect a comparable improvement and noticed even further prolonged reaction times (entries 5 and 8).

Table 3. Comparison of Batch and Microflow for Synergistic Organocatalytic Photoredox α-Alkylation and Survey of Microflow Experiments with Catalyst **10** and Eosin Y[a]



entry	mol % of catalyst **10**	*t* [°C]	residence time [min]	yield[c] [%]	*ee* [%]
1	20	20	45	87	76
2	20	0	45	88	81
3	**20**	**-5**	**45**	**86**	**87**
4	15	20	60	86	75
5	15	0	90	85	72
6	15	-5	120	82	n. d.
7	10	20	90	81	75
8	10	0	120	84	73
9	5	20	120	15[d]	n.d.

[a] Reactions conducted at $c_{\text{bromoalkyl}} = 0.5$ M; yields refer to isolated product. [b] Determined *via* NMR after acetalization with (2*S*,4*S*)-2,4-pentanediol.[12a] [c] Isolated yields. [d] Determined by GC analysis.

Using 15 mol % of catalyst **10** at −5 °C, full conversion was not reached even after 2 h (entry 6), indicating the limitations of reducing the applied catalyst amounts. We finally investigated the scalability of this approach. As microstructured flow reactors with their low flow rates and small internal volumes (ca. 100 μL) are ideally suited for reaction optimization, greater amounts of product are only available on "numbering up". In order to increase the material throughput we decided to construct a modified Booker–Milburn system[29] as a microphotoreactor. Using the highly transparent, solvent-resistant, and flexible FEP polymer (ID 0.8 mm) we coiled the tubing around a glass beaker which was equipped with an internal household fluorescent bulb (23 W);[17] the whole system was then placed in a cooling bath for temperature regulation. Our initial approach to directly transfer the optimized microreactor conditions to this first generation reactor (tubing length 8.5 m, $V_{\text{int}} \approx 4.3$ mL) failed due to clogging by 2,6-lutidine hydrobromide which precipitates from the reaction mixture. Higher flow rates in combination with ultrasonic treatment[30] and a slightly higher dilution ($c = 0.4$ mmol/mL) prevented precipitation, but full conversion could still not be attained.

Table 4. Comparison of the Performance of Different Reactors[a]

entry	reactor type	yield[b] [%]	ee [%]	productivity [mmol/h]	relative factor
1	batch	85	88	0.018	1
2	micro reactor	86	87	0.037	2
3	tube reactor	92	82	1.92	107

[a] Conditions as described in Table 3, but performed with $c_{\text{bromoalkyl}} = 0.4$ M. [b] Isolated yield.

The second generation setup with an enlarged irradiation zone by coiling the tubing around the beaker in two layers (length 21 m, $V_{\text{int}} \approx 10.5$ mL) allows for full conversion at high flow rates and low temperature (maintaining the previously optimized residence time). Comparing the performance of the three examined reactor types (Table 4) clearly demonstrates the advantage of the tube flow system with respect to productivity.

In conclusion, we have developed microflow conditions for visible light photoredox processes, which can be significantly accelerated. Especially transformations involving the conversion of unstable intermediates can be improved. Applying our simple, inexpensive tube reactor, enantioselective, synergistic photocatalytic reactions can be easily scaled up, thereby generating useful amounts of enantiopure products. We expect the merging of flow chemistry and photoredox catalysis to be of broad utility for future applications.

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Supporting Information Available. Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

The authors declare no competing financial interest.

(28) All attempts to lower the catalyst loading under batch conditions proved unsuccessful due to further increasing reaction times and associated dehalogenation as an unproductive side reaction.

(29) Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558.

(30) For representative examples for application of ultrasound in continuous flow reactions, see: (a) Shu, W.; Pellegatti, L.; Oberli, M. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 10665. (b) Hartman, R. L.; Naber, J. R.; Zaborenko, N.; Buchwald, S. L.; Jensen, K. F. *Org. Process Res. Dev.* **2010**, *14*, 347. (c) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J. *Org. Process Res. Dev.* **2010**, *14*, 405.