CHEMSUSCHEM
COMMUNICATIONS

ChemPubSoc Europe

DOI: 10.1002/cssc.201301282

Rapid Trifluoromethylation and Perfluoroalkylation of Five-Membered Heterocycles by Photoredox Catalysis in Continuous Flow

Natan J. W. Straathof,[a] Hannes P. L. Gemoets,[a] Xiao Wang,[b] Jaap C. Schouten,[c] Volker Hessel,[a] and Timothy Noël*[a, d]

Trifluoromethylated and perfluoroalkylated heterocycles are important building blocks for the synthesis of numerous pharmaceutical products, agrochemicals and are widely applied in material sciences. To date, trifluoromethylated and perfluoroalkylated hetero-aromatic systems can be prepared utilizing visible light photoredox catalysis methodologies in batch. While several limitations are associated with these batch protocols, the application of microflow technology could greatly enhance and intensify these reactions. A simple and straightforward photocatalytic trifluoromethylation and perfluoroalkylation method has been developed in continuous microflow, using commercially available photocatalysts and microflow components. A selection of five-membered hetero-aromatics were successfully trifluoromethylated (12 examples) and perfluoroalkylated (5 examples) within several minutes (8–20 min).

The incorporation of fluorinated functional groups, such as the trifluoromethyl (CF_3) group, into chemical compounds has numerous advantages, including improved chemical stability, elevated lipophilicity, and increased binding selectivity.[1,2] The presence of CF_3 in a drug structure has a diminishing effect on the metabolic oxidation by cytochrome P450 oxidase and increases the bioactivity by affecting the compound's distribution and absorption. In particular, the establishment of methodologies for the incorporation of trifluoromethyl or perfluoroalkyl moieties to five-membered heterocycles is of great value in pharmaceutical manufacturing, as well as agrochemistry and material science (Figure 1).[3,4] This has stimulated the development and improvement of novel trifluoromethylation methodologies, which are of great importance for the production of compounds with trifluoromethyl groups.[5–7]

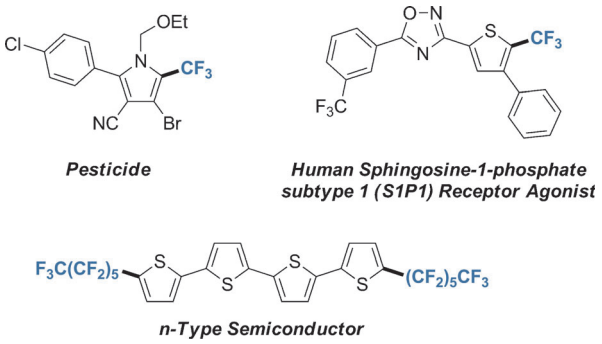


Figure 1. Perfluoroalkylation of five-membered hetereocycles as an important strategy for the preparation of drug candidates and advanced materials.

Historically, the construction of the Ar–CF_3 bond was performed by means of metal-catalyzed cross-coupling methods,[8,9] using different CF_3 sources such as Ruppert–Prakash reagents or the more recent Umemoto's reagents[10,11] and Togni's reagents.[12] However, these methods often involve stoichiometric amounts of metal salts and/or require the presence of functional groups,[13–18] such as boronic acids, amides, or halides and pseudohalides, to establish the CF_3 linkage. Moreover, several synthetic methodologies have been reported which employ radical trifluoromethylation ($[CF_3]^{\bullet}$) to functionalize unactivated C–H bonds.[19] One of the most potent strategies involves the use of photoredox catalysis to generate electrophilic radicals.[20–27] Hereby, polypyridyl organometallic complexes, such as $[Ru(bpy)_3Cl_2]$, are activated by visible light and have proven to be mild and more sustainable alternatives for traditional photochemistry utilizing UV energy.[28–31] Recently, the MacMillan group reported a photocatalytic trifluoromethylation of heterocycles using triflyl chloride (CF_3SO_2Cl, **1b**) as a $[CF_3]^{\bullet}$ source (Scheme 1a).[21,22] Later, another approach based on inexpensive gaseous trifluoroiodomethane (CF_3I, **1a**) was developed by Cho and co-workers.[23,24] However, decisive limitations are associated with these batch protocols, such as: i) limited scale-up potential; ii) inefficient light transmission in the batch reactor according to the Lambert–Beer law, especially when there is significant scattering of the incident light in a heterogeneous mixture; iii) prolonged reaction times; and

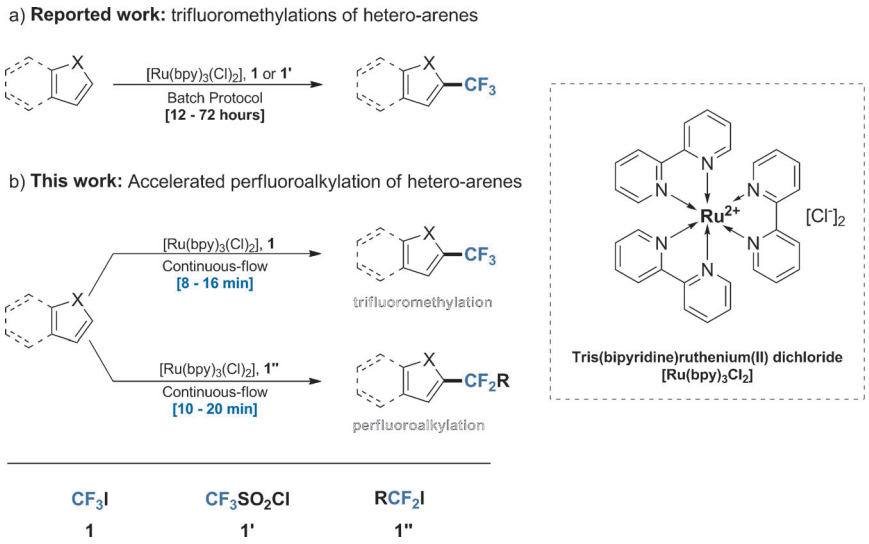
[a] N. J. W. Straathof, H. P. L. Gemoets, Prof. Dr. V. Hessel, Dr. T. Noël
Department of Chemical Engineering and Chemistry
Micro Flow Chemistry & Process Technology
Eindhoven University of Technology
Den Dolech 2, 5612 AZ Eindhoven (The Netherlands)
E-mail: t.noel@tue.nl

[b] Dr. X. Wang
Harvard NeuroDiscovery Center
Harvard Medical School and Brigham & Women's Hospital
65 Landsdowne Street, Cambridge, MA 02139 (USA)

[c] Prof. Dr. J. C. Schouten
Department of Chemical Engineering and Chemistry
Chemical Reactor Engineering
Eindhoven University of Technology
Den Dolech 2, 5612 AZ Eindhoven (The Netherlands)

[d] Dr. T. Noël
Ghent University
Department of Organic Chemistry
Krijgslaan 281 (S4), 9000 Ghent (Belgium)

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/cssc.201301282.



Scheme 1. a) Reported trifluoromethylation batch protocols [Refs. [21,23]]. b) Accelerated trifluoromethylation and perfluoroalkylation, enabled by continuous-flow.

iv) the complicated handling of gaseous reagents and insufficient interfacial contact area which leads to limited gas–liquid mass transfer rate.

To overcome these limitations, we reasoned that the use of continuous-flow processing would significantly enhance the utility for the trifluoromethylation and perfluoroalkylation of five-membered heterocycles. Due to their high surface-to-volume ratios, microreactors offer the advantage of an increased control over different process parameters (e.g., heat- and mass-transfer, gas-liquid characteristics, residence time control), which leads to a safer handling of hazardous compounds.[32–36] In addition, the small dimensions in microreactor technology allow for homogeneous irradiation of the entire reaction mixture.[37,38] As a consequence of the relatively high extinction coefficient of photoredox catalysts, a considerable amount of light is absorbed within the first few hundreds of micrometers of the light path, which makes the use of microreactor technology vital for successful scale-up by a numbering-up strategy.[39–44] Moreover, owing to the improved irradiation of the reaction mixture, microflow chemistry also allows to decrease the amount of photocatalyst without significant loss of efficiency.[39] Herein, we report the first photocatalytic trifluoromethylation and perfluoroalkylation of five-membered heteroarenes in continuous microflow, which renders an extra rapid and up-scalable, industrially relevant method to construct the Ar–CF_3 bond.

Based on our experience with continuous-flow chemistry,[45–47] we also felt that the presence of a gaseous reagent (such as CF_3I) would not obstruct our investigations and could be perfectly dosed to the reaction mixture by means of a mass flow controller. Furthermore, the presence of a gas phase leads to segmented flow which in fact provides fast mixing (internal circulation in the liquid phase), a large and well-defined interfacial area, intensified mass- and heat-transfer, and a reduced axial dispersion.[48,49] Notwithstanding, a continuous-flow protocol also allowed for an accelerated reaction protocol, enabling a fast and robust approach to trifluoromethyl- or perfluoroalkyl-functionalized five-membered heteroarenes (Scheme 1b).

To develop a successful continuous flow procedure, we designed an operationally simple microflow setup from commercially available components (Figure 2a). The microreactor was constructed by using transparent PFA capillary tubing (500 μm ID, 1/16" OD, 200 μL V_{max}) coiled around a large transparent disposable syringe. Next, the capillary microreactor assembly was placed inside a beaker in which an array of blue light-emitting diodes (LEDs) (3.12 W blue LED stripe, 78 Lm, 39 LED, 97 cm length, λ_{max} = 450–460 nm) was coiled in a spiral fashion. The CF_3I gas flow rate was monitored and controlled utilizing a mass flow controller (MFC) (mL min^{-1}). The liquid flow rate was regulated by a syringe pump, which introduces the liquid reagents (photocatalyst, substrate, base and solvent) (mL min^{-1}). A T-shaped micromixer was used to combine the gas and liquid phase prior to irradiation inside the photomicroreactor (see the Supporting Information for more detailed information regarding the microfluidic setup).

We began our studies with the trifluoromethylation of *N*-methylpyrrole **2** utilizing gaseous CF_3I in the presence of a base and $[Ru(bpy)_3Cl_2]$ (1 mol%).[50] Initially, a residence time of approximately 4 min was applied by combining a liquid flow rate of 100 μL min^{-1} and a gas flow rate of 2 mL min^{-1}. Various organic nitrogen bases (2 equiv) were investigated, such as DBU, TEA, DIPEA, and TMEDA (respectively 1,8-diazabicyclo[5.4.0]undec-7-en, triethylamine, diisopropylethylamine, and *N,N,N′,N′*-tetramethyl-1,2-diaminoethylene) (Figure 2b, entries 1–4). TMEDA proved to be the most effective for this trifluoromethylation protocol, providing 81% conversion within 4 min residence time (Figure 2b, entry 4). Next, the flow rate of the liquid phase or the reactor length were adjusted until a satisfactory residence time (t_R) was obtained to achieve full conversion of the starting material (Figure 2b, entries 5 and 6). With a residence time of 8 min, we were able to achieve up to 99% conversion and the corresponding product was obtained in 95% yield as judged by ^{19}F NMR (Figure 2b, entry 6). Subsequently, we also investigated different CF_3I gas flow rates (Figure 2b, entries 7 and 8). The optimal gas flow rate was found to be 2 mL min^{-1} (4 equiv CF_3I) (Figure 2b, entry 6), as decreasing the CF_3I flow gave lower conversions (44–62%).

With the optimal conditions in hand, we conducted a series of experiments to evaluate the scope of our continuous-microflow trifluoromethylation method (Scheme 2). *N*-methylpyrrole **2a** and a selection of indole derivatives **2b**–**2f** were efficiently

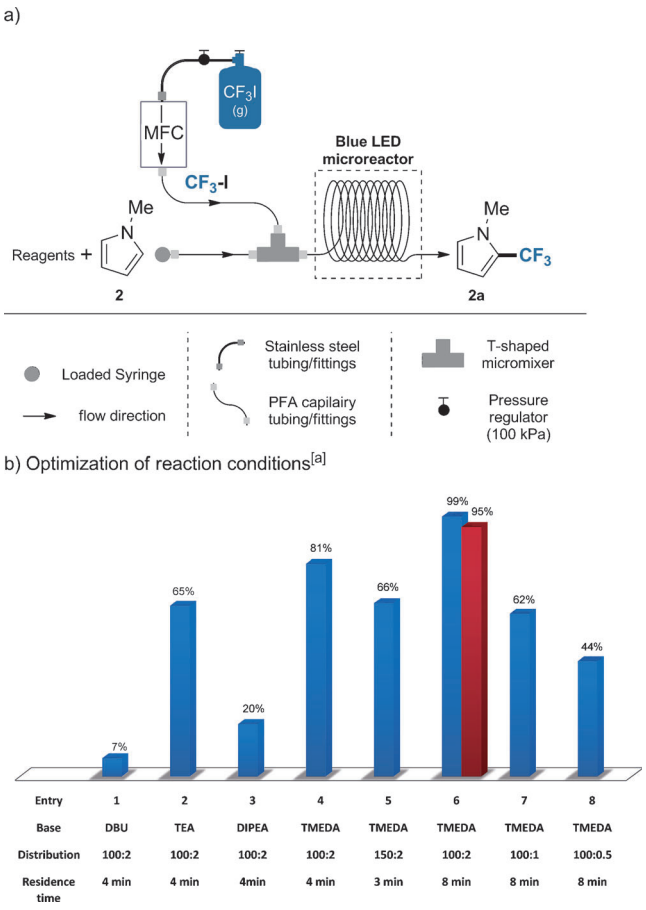
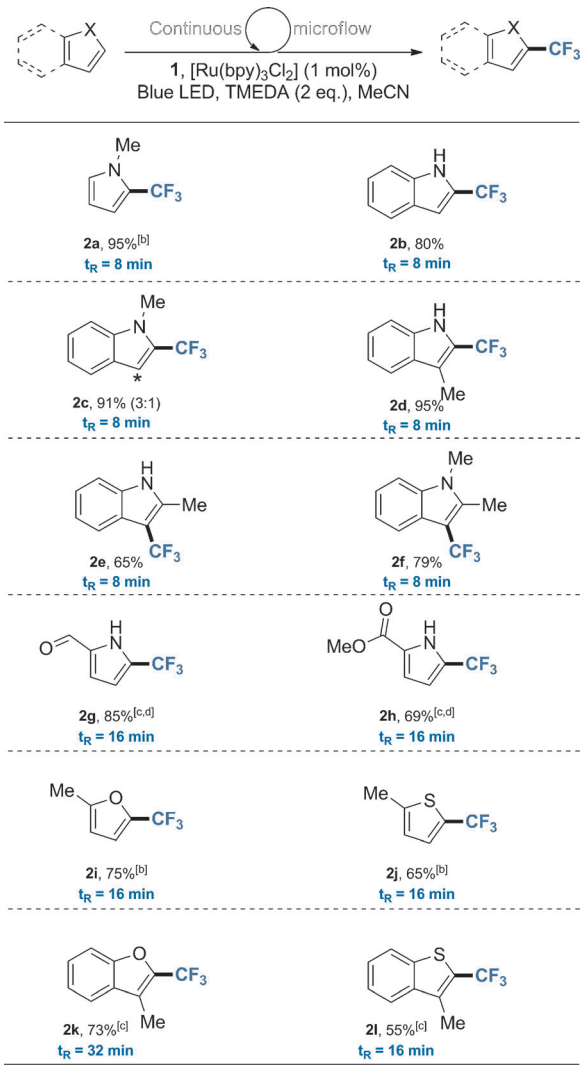


Figure 2. a) Schematic representation of the continuous-flow setup for trifluoromethylation of hetero-arenes. b) Optimization of the continuous-flow reaction conditions. [a] Reactions were carried out using $[Ru(bpy)_3Cl_2]$ (1.0 mol%), base (2.0 equiv) in MeCN (0.2 M), and irradiated by blue LEDs. [b] Distribution; liquid flow rate, and gas flow rate are given in $\mu L\,min^{-1}$ and $mL\,min^{-1}$, respectively. Residence time of 4 min and 3 min are performed in a 200 μL Vmax microreactor, 8 min residence time was performed in a 400 μL Vmax microreactor. (blue bars) Conversion, analyzed by GC with α,α,α-trifluorotoluene as internal standard. (red bars) ^{19}F NMR yield of the product.



Scheme 2. Trifluoromethylation of five-membered hetero-arenes. [a] Reactions were carried out using $[Ru(bpy)_3Cl_2]$ (1.0 mol%), TMEDA (2.0 equiv), CF_3I (4.0 equiv) in MeCN (0.2 M), and irradiated with blue LED, [b] Yield determined with ^{19}F NMR with α,α,α-trifluorotoluene as an internal standard, [c] An increased catalyst loading (4 mol%) was used. [d] MeCN:DMSO (9:1) was used as solvent system.

trifluoromethylated within a residence time of 8 min and were obtained in sufficiently pure form to allow for a simple purification (65–95%). A slightly lower yield was obtained for 2-methylindole **2e** (65%), while 1,2-dimethylindole **2f** could be smoothly trifluoromethylated in 79% yield. Trifluoromethylation of 1H-pyrrole-2-carboaldehyde **2g** and methyl-1H-pyrrole-2-carboxylate **2h** resulted in the formation of a small amount of precipitation, clogging the microreactor. This could be efficiently prevented by using a slightly different solvent mixture of DMSO/MeCN (1:9), which increased the solubility of the precipitate. However, an increased catalyst loading (4 mol%) was required to compensate the lower rate of the photocatalytic transformation in DMSO. The same method was applied to 2-methylfuran and 2-methylthiophene, which were both successfully trifluoromethylated within 16 min of residence time (**2i** and **2j**). Likewise, 3-methylbenzofuran and 3-methylbenzothiophene were also trifluoromethylated and isolated in good yield (73% and 55%, **2k** and **2l**).

Next, we extended our focus by developing a continuous-flow method for the photocatalytic perfluoroalkylation of hetero-arenes using iodoperfluoroalkyl **1c** (RCF_2I). Perfluoroalkylation offers, besides the profound effects of the presence of fluorine substituents for pharmaceuticals and materials, a straightforward pathway to introduce other functional groups such as esters, ethers or other halogens. The continuous-flow setup for the perfluoroalkylation was a simplified version of the one used for the trifluoromethylation (Figure 3a). Instead of a biphasic gas–liquid phase reaction, homogeneous reaction conditions were used for perfluoroalkylation. More detailed explanation regarding the micro flow setup construction can be found in the Supporting Information.

Preliminary optimization studies were carried out to acquire the optimal perfluoroalkylation conditions. A number of soluble organic bases were tested (Figure 3). In contrast with the

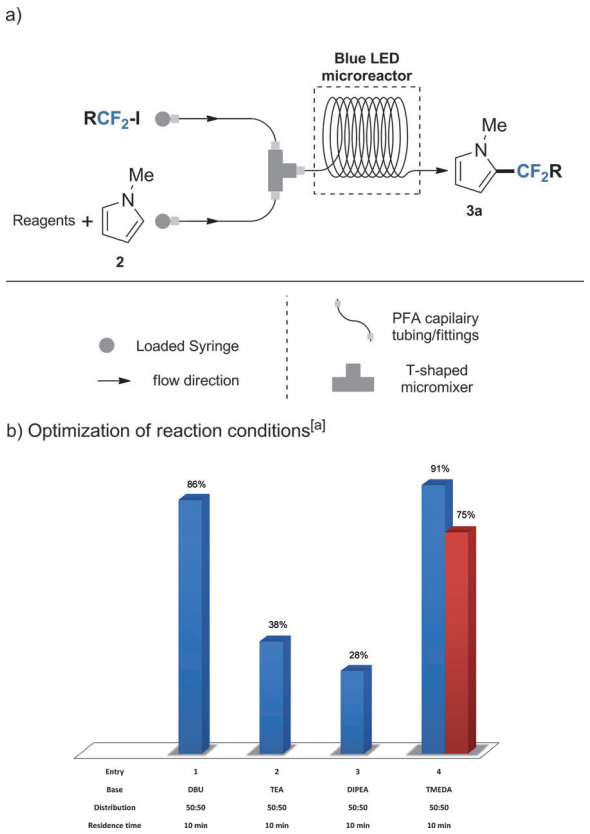
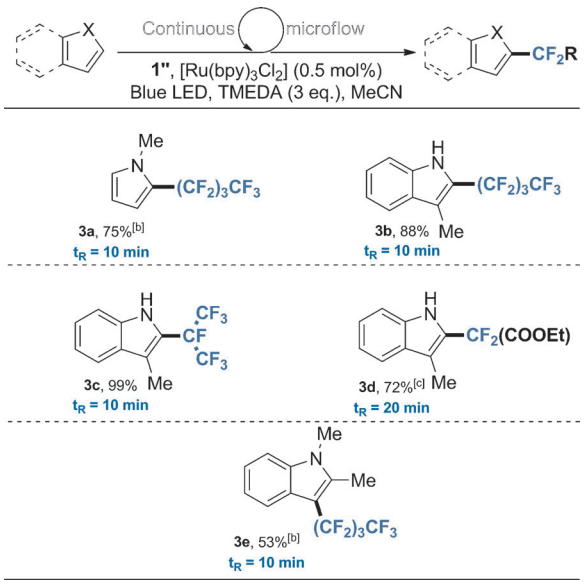
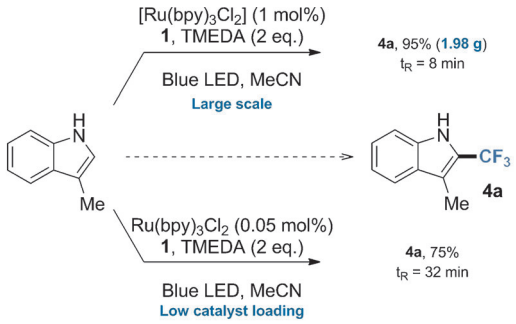


Figure 3. a) Schematic representation of the continuous-flow setup for the perfluoroalkylation of hetero-arenes. b) Optimization of the reaction conditions. [a] Reactions were carried out using $[Ru(bpy)_3Cl_2]$ (0.5 mol%), base (3 equiv) nonafluoro-1-iodobutane (2 equiv) in MeCN, and irradiated by blue LEDs. [b] Distribution; liquid/liquid flow rate are given in $\mu L\,min^{-1}$ and $\mu L\,min^{-1}$, respectively. (blue bars) Conversion, analyzed by GC with α,α,α-trifluorotoluene as internal standard. (red bar) ^{19}F NMR yield of the product.



Scheme 3. Perfluoroalkylation of hetero-arenes. [a] Reactions were carried out using $Ru(bpy)_3Cl_2$ (0.5 mol%), base (3.0 equiv) in MeCN, and irradiated with blue LED. [b] ^{19}F NMR yield of the product. [c] Ethyl 2-bromo-difluoroacetate was used as the alkyl halide source.



Scheme 4. Large scale trifluoromethylation and the reaction with low catalyst loading. [a] Reactions were carried out using $Ru(bpy)_3Cl_2$ (1 or 0.05 mol%), TMEDA (2 equiv), 1 ($2\,mL\,min^{-1}$) in MeCN ($100\,\mu L\,min^{-1}$), microreactor (Vmax: 250 μL or 1000 μL), and irradiated with Blue LED.

trifluoromethylation experiments, DBU gave a good yield for the desired product (Figure 3b, entry 1). However, TMEDA provided the best results for the perfluoroalkylation in continuous flow (Figure 3b, entry 4). DBU gave a dark solution upon irradiation, leading to a less-efficient photon flux through the reaction mixture. On the contrary, TMEDA remained a clear and transparent solution even after prolonged irradiation times. To further optimize the reaction conditions, a variety of solvents were screened (see Supporting Information). The best results were obtained in acetonitrile. Other polar solvents were less efficient, while the use of nonpolar solvents resulted in an incomplete dissolution of the photoredox catalyst. With the optimal conditions in hand, we evaluated the method by perfluoroalkylating a selection of five-membered hetero-arenes with different perfluoro-1-iodoalkanes (Scheme 3). The construction of perfluoroalkylated *N*-methylpyrrole **3a** and a number of indole analogues **3b** and **3e** was easily achieved within several minutes ($t_R = 10$ min) and delivered the target compound in good yields (53–88%). In addition, 3-methylindole was also reacted with perfluoro-2-iodopropane and ethyl 2-bromo-difluoroacetate, providing products **3c** and **3d** in good yield (99% and 72%).

To exploit the advantages of our continuous-flow protocol, we also performed a long durational reaction to demonstrate its scalability and stability (Scheme 4). As such, we were able to produce a substantial amount of trifluoromethylated 3-methylindole **4a** in less than 9 h (1.98 g, 9.5 mmol). Additionally, we investigated whether it was feasible to decrease the catalyst system in flow (Scheme 4). The catalyst loading could be decreased (down to 0.05 mol%) without significant loss of efficiency (75%). Such low catalyst loadings are of great interest to the pharmaceutical industry and clearly show the process intensification in microflow reactors.

The pharmaceutical industry is always looking for more efficient strategies to introduce functional groups into drug candidates. The functionalization of hetero-aromatics with perfluoroalkyl moieties is one of the important strategies to enhance its biological, chemical and physical properties. Many, if not all,

of the current batch strategies are suffering from long reaction times, high catalyst loadings, limited scalability, and operational flexibility. We have successfully realized for the first time a continuous-flow method for the fast radical trifluoromethylation and perfluoroalkylation of five-membered hetero-arenes using inexpensive perfluoroalkyl sources (e.g., CF_3I and $CF_3(CF_2)_3I$). The trifluoromethylation of five-membered heteroarenes (Scheme 2) was achieved within several minutes (8–16 min) in continuous-flow due to the excellent light irradiation of the reaction mixture, the increased gas-liquid mass transfer of CF_3I, and the excellent mixing achieved in liquid slugs as a consequence of the Taylor flow regime.[47] In comparison, similar reactions required many hours (12–24 h) in batch to achieve full conversion. Next, the continuous-flow photocatalytic protocol was extended for homogeneous liquid perfluoroalkylation reactions and we were able to perfluoroalkylate a number of five-membered hetero-aromatics in less than 1 h of reaction time (10–20 min). The potential to use lower catalyst loadings (as low as 0.05 mol% photoredox catalyst) and to scale-up the photocatalytic process are additional features of our continuous-flow protocol that are not easy to achieve in a batch mode.

In conclusion, the continuous-flow perfluoroalkylation process could be significantly accelerated (from hours in batch to minutes in flow) making this methodology suitable for the production and scale-up of pharmaceutical compounds and agrochemicals agents. The mild reaction conditions (room temperature, visible light activation, atmospheric pressure) should allow easy implementation of this methodology into both academia and industry. Further investigations regarding accelerated incorporation of fluorine-containing functional groups are under development in our laboratory.

Experimental Section

General trifluoromethylation continuous-flow procedure: An oven-dried volumetric flask (5 mL) was loaded with heterocycle (1 mmol), $[Ru(bpy)_3Cl_2]$ (1 mol%), and TMEDA (2 mmol). The flask was sealed with a septum and degassed by alternating vacuum and argon cycles (three times). Anhydrous MeCN (5 mL) was added and the mixture was loaded in a 5 mL syringe and mounted on a syringe pump. The gaseous CF_3I flow rate (2 mL min^{-1}) was established by means of a mass flow controller (MFC) and stabilized prior to the start-up of the syringe pump, which applied a liquid flow rate of 100 μL min^{-1}. After operation the reaction mixture was quenched and collected, concentrated in vacuo and purified by silica column chromatography (5% EtOAc in petroleum ether) to afford the desired product.

General perfluoroalkylation continuous-flow procedure: An oven-dried volumetric flask (10 mL) was loaded with heterocycle (2.8 mmol), $[Ru(bpy)_3Cl_2]$ (0.5 mol%), and perfluorobuthyliodide (5.6 mmol), fitted with a septum and degassed by alternating vacuum and argon backfill, and filled with MeCN. A second volumetric flask (10 mL) was loaded with TMEDA (8.4 mmol) degassed and filled with MeCN. Both mixtures were transferred to corresponding syringes and loaded in the setup. The reaction mixtures were introduced into the microreactor with a flow rate of 50 μL min^{-1}. The reaction mixture was collected, quenched, concentrated in vacuo and purified by flask chromatography over silica (5% EtOAc in petroleum ether) to yield the desired product.

Acknowledgements

T.N. acknowledged financial support from the Dutch Science Foundation for a VENI Grant (12464) and from the European Union for a Marie Curie CIG Grant. Funding by the Advanced European Research Council Grant (grant number: 267443 for V.H. and grant number: 227010 for J.C.S.) is kindly acknowledged.

Keywords: flow chemistry · heterocycles · homogeneous catalysis · photochemistry · ruthenium

[1] P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity&Applications*, Wiley-VCH, Weinheim, **2004**.
[2] J. P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medical Chemistry of Fluorine*, Wiley-VCH, Weinheim, **2008**.
[3] K. Muller, C. Feah, F. Diederich, *Science* **2007**, *317*, 1881 – 1886.
[4] S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330.
[5] T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470 – 477.
[6] Y. Macé, E. Magnier, *Eur. J. Org. Chem.* **2012**, 2479 – 2494.
[7] H. Liu, Z. Gu, X. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 617 – 626.
[8] M. Oishi, H. Kondo, H. Amii, *Chem. Commun.* **2009**, 1909 – 1911.
[9] X. Mu, T. Wu, H.-Y. Wang, Y. L. Guo, G. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 878 – 881.
[10] T. Umemoto, K. Adachi, *J. Org. Chem.* **1994**, *59*, 5692 – 5699.
[11] T. Umemoto, *Chem. Rev.* **1996**, *96*, 1757 – 1778.
[12] P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579 – 2586.
[13] K. Niedermann, N. Fruh, E. Vinogradova, M. S. Wiehn, A. Moreno, A. Togni, *Angew. Chem. Int. Ed.* **2011**, *50*, 1059 – 1063; *Angew. Chem.* **2011**, *123*, 1091 – 1095.
[14] D. J. Wilger, N. J. Gesmundo, D. A. Nicewicz, *Chem. Sci.* **2013**, *4*, 3160 – 3165.
[15] E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679 – 1681.
[16] G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 7972 – 7975; *Angew. Chem.* **2013**, *125*, 8130 – 8133.
[17] S. Seo, J. B. Taylor, M. F. Greaney, *Chem. Commun.* **2013**, *49*, 6385 – 6387.
[18] X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y, Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330 – 10333.
[19] A. A. Studer, *Angew. Chem. Int. Ed.* **2012**, *51*, 8950 – 8958; *Angew. Chem.* **2012**, *124*, 9082 – 9090.
[20] D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875 – 10877.
[21] D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224 – 228.
[22] P. V. Pham, D. A. Nagib, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2011**, *50*, 6119 – 6122; *Angew. Chem.* **2011**, *123*, 6243 – 6246.
[23] N. Iqbal, S. Choi, E. Ko, E. J. Cho, *Tetrahedron Lett.* **2012**, *53*, 2005 – 2008.
[24] N. Iqbal, S. Choi, E. Kim, E. J. Cho, *J. Org. Chem.* **2012**, *77*, 11383 – 11387.
[25] Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2012**, *134*, 9034 – 9037.
[26] E. Kim, S. Choi, H. Kim, E. J. Cho, *Chem. Eur. J.* **2013**, *19*, 6209 – 6212.
[27] S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Medebielle, V. Gouverneur, *Org. Lett.* **2013**, *15*, 1250 – 1253.
[28] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322 – 5363.
[29] Y. Xi, H. Yi. A. Lei, *Org. Biomol. Chem.* **2013**, *11*, 2387 – 2403.
[30] J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617 – 1622.
[31] J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102 – 113.
[32] V. Hessel, D. Kralisch, N. Kockmann, T. Noël, Q. Wang, *ChemSusChem* **2013**, *6*, 746 – 789.
[33] J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17 – 57.
[34] T. N. Glasnov, C. O. Kappe, *Chem. Eur. J.* **2011**, *17*, 11956 – 11968.

[35] R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 7502 – 7519; *Angew. Chem.* **2011**, *123*, 7642 – 7661.
[36] T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010 – 5029.
[37] a) M. Oelgemoeller, *Chem. Eng. Technol.* **2012**, *35*, 1144 – 1152; b) T. Fukuyama, I. Ryu, in *Encyclopedia of Radicals in Chemistry, Biology and Materials* (Eds.: C. Chatgilialoglu, A. Studer), Wiley-VCH, Chichester, UK, **2012**, pp. 1243 – 1258.
[38] T. van Gerven, G. Mul, J. Moulijn, A. Stankiewicz, *Chem. Eng. Process.* **2007**, *46*, 781 – 789.
[39] T. Noël, X. Wang, V. Hessel, *Chim. Oggi* **2013**, *31*, 10 – 14.
[40] X. Wang, G. D. Cuny, T. Noël, *Angew. Chem. Int. Ed.* **2013**, *52*, 7860 – 7864; *Angew. Chem.* **2013**, *125*, 8014 – 8018.
[41] J. D. Nguyen, B. Reiß, C. Dai, C. R. J. Stephenson, *Chem. Commun.* **2013**, *49*, 4352 – 4354.
[42] M. Rueping, C. Vila, T. Bootwicha, *ACS Catal.* **2013**, *3*, 1676 – 1680.
[43] M. Neumann, K. Zeitler, *Org. Lett.* **2012**, *14*, 2658 – 2661.
[44] J. W. Tucker, Y. Zhang, T. F. Jamison, C. R. J. Stephenson, *Angew. Chem. Int. Ed.* **2012**, *51*, 4144 – 4147; *Angew. Chem.* **2012**, *124*, 4220 – 4223.
[45] T. Noël, T. J. Maimone, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 8900 – 8903; *Angew. Chem.* **2011**, *123*, 9062 – 9065.
[46] T. Noël, J. R. Naber, R. L. Hartman, J. P. McMullen, K. F. Jensen, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 287 – 290.
[47] T. Noël, V. Hessel, *ChemSusChem* **2013**, *6*, 405 – 407.
[48] G. Chen, J. Yue, Q. Yuan, *Chin. J. Chem. Eng.* **2008**, *16*, 663 – 669.
[49] A. Günther, K. F. Jensen, *Lab Chip* **2006**, *6*, 1487 – 1503.
[50] Other photocatalysts were also tested, such as *fac*-[Ir(ppy)$_3$], Eosin Y, or Rose Bengal, but no better results than with [Ru(bpy)$_3$Cl$_2$] were obtained. See also: N. J. W. Straathof, D. J. G. P. van Osch, A. Schouten, X. Wang, J. C. Schouten, V. Hessel, T. Noël, *J. Flow Chem.* **2014**, DOI: 10.1556/JFC-D-13-00032.

Received: November 29, 2013
Revised: February 23, 2014
Published online on ■■ ■■, 0000

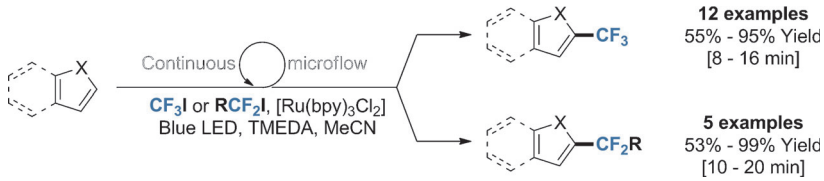


Photo workflow: A simple and straightforward photocatalytic method for perfluoroalkylation in continuous flow is developed. A photo-microreactor, constructed from commercially available components, enables accelerated photocatalysis employing $[Ru(bpy)_3Cl_2]$ as photocatalyst under irradiation by blue LED light. A series of electron-rich hetero-aromatics is successfully trifluoromethylated within 8–16 min. Also, a selection of hetero-aromatics is perfluoroalkylated within 10–20 min.

*N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. Schouten, V. Hessel, T. Noël**

■■ – ■■

Rapid Trifluoromethylation and Perfluoroalkylation of Five-Membered Heterocycles by Photoredox Catalysis in Continuous Flow