Chemical Science

EDGE ARTICLE

View Article Online
View Journal



Cite this: DOI: 10.1039/c4sc01982b

# A mild and fast photocatalytic trifluoromethylation of thiols in batch and continuous-flow†

Natan J. W. Straathof,[a] Bart J. P. Tegelbeckers,[a] Volker Hessel,[a] Xiao Wang*[b] and Timothy Noël*[ac]

Received 3rd July 2014
Accepted 7th August 2014

DOI: 10.1039/c4sc01982b

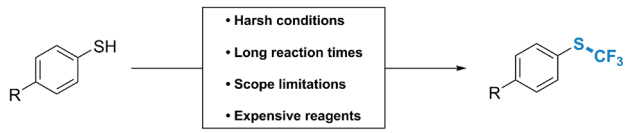
www.rsc.org/chemicalscience

$S–CF_3$ bonds are important structural motifs in various pharmaceutical and agrochemical compounds. However, their preparation remains a major challenge in synthetic organic chemistry. Here, we report the development of a mild and fast photocatalytic trifluoromethylation of thiols. The combination of commercially available $Ru(bpy)_3Cl_2$, visible light and inexpensive $CF_3I$ gas proved to be an efficient method for the direct trifluoromethylation of thiols. The protocol is demonstrated on a wide range of aromatic, hetero-aromatic and aliphatic substrates in both batch and continuous microflow (32 examples, 52–98% yield). Process intensification through continuous microflow application resulted in a 15-fold increase in production rate (0.25 mmol $min^{-1}$) due to improved gas–liquid mass transfer, enhanced irradiation as well as convenient handling of the gaseous $CF_3$ source. Furthermore, the efficiency of the flow process allowed to reduce the amount of $CF_3I$ (1.1 equivalent) to reach full conversion.

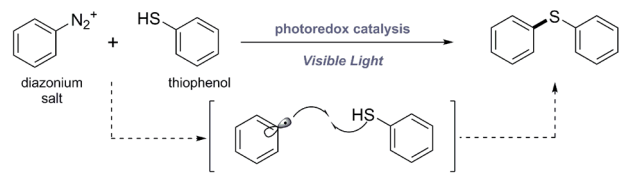
## Introduction

The development of mild methods regarding the incorporation of fluorine-containing functional groups has gained increasing attention.[1] This is undoubtedly driven by the growing demand in the pharmaceutical and agrochemical industry, as well as its increasing need for the development of $^{18}F$-labeled organic compounds for positron emission tomography (PET) imaging.[2] In particular, the incorporation of trifluoromethyl moieties ($CF_3$) has been widely investigated on *e.g.* alkenes, arenes and hetero-arenes.[3] In contrast, the trifluoromethylation of thiols ($S–CF_3$) is much less developed.[4] The incorporation of a trifluoromethylthio ($S–CF_3$) motif in a drug molecule results in an extremely high lipophilicity (Hansch parameter, $\pi_R = 1.44$) and improves the stability of the molecule in acidic media. Access to such compounds is crucial since they constitute a key intermediate for the synthesis of biologically active (trifluoromethyl)-sulfoxides and sulfones.

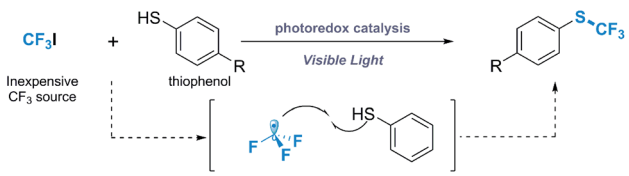
**Reported Direct Trifluoromethylation of Benzenethiols Methods (Eq. 1)**




**Construction of Thioethers via Photocatalytic Aryl Radical Generation (Eq. 2)**




**Direct Trifluoromethylation of Thiols via Photocatalytic $CF_3^{\bullet}$ Generation (This work) (Eq. 3)**




To date, a number of methods have been developed for the construction of $S–CF_3$ bonds *via* direct trifluoromethylation of readily accessible aryl and alkyl thiols.[5] These bonds can be constructed *via* an ion-radical mechanism employing inexpensive $CF_3$ sources such as $CF_3I$ or $CF_3Br$.[6,7] However, most of these methods, if not all, suffer from limited substrate scope, prolonged reaction times and require harsh conditions, such as the use of liquid ammonia as a solvent system, elevated pressure and the use of UV light (eqn (1)). A more convenient

[a]*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; Tel: +31-40-247-3623*

[b]*Harvard NeuroDiscovery Center, Harvard Medical School and Brigham & Women's Hospital, 65 Landsdowne Street, Cambridge, Massachusetts 02139, USA. E-mail: xwang21@partners.org*

[c]*Department of Organic Chemistry, Ghent University, Krijgslaan 281 (S4), 9000 Ghent, Belgium*

† Electronic supplementary information (ESI) available: Detailed $^1H$, $^{13}C$ and $^{19}F$ NMR. See DOI: 10.1039/c4sc01982b

radical-chain approach *via* a single electron transfer (SET) was reported by Koshechko and coworkers but still rendered a very limited scope and relative long reaction times.[8] More recently, great effort was conducted in the development of shelf-stable $CF_3$-electrophilic ($CF_3^+$) reagents, such as Umemoto's reagent[9] and Togni's reagent.[10] These reagents are well-known and easy-to-handle trifluoromethylating agents and demonstrate good selectivity and broad substrate scope. However, commercial sources of these reagents are expensive, and the preparation requires multiple synthetic steps, making them less attractive for scale-up.[11] In contrast, radical $CF_3$ sources, such as $CF_3I$ (bulk chemical) or triflyl chloride ($CF_3SO_2Cl$), would be more advantageous to use given their low cost price and availability. In search of a mild and broadly applicable method for the trifluoromethylation of thiols, we turned our attention to the use of visible-light photoredox catalysis.[12] Visible-light photoredox catalysis has emerged as a mild and efficient method to functionalize molecules and is tolerant to a broad range of functional groups. Recently, we have established the efficient and mild formation of C–S bonds *via* a photocatalytic Stadler–Ziegler reaction.[13] Hereby, aryl radicals are generated from *in situ* prepared diazonium salts which subsequently react with thiols to generate the required C–S linkage (eqn (2)).[14] We anticipated that a similar strategy could be exploited for the trifluoromethylation of thiols, thereby rendering a more general and practical approach to the formation of RS–$CF_3$ compounds (eqn (3)). Furthermore, the use of $CF_3I$, as an inexpensive, stable and widely available $CF_3$ source, makes our method cost-efficient.[15] Taking advantage of continuous-flow photochemistry, we were able to accelerate the developed S–$CF_3$ protocol significantly to increase its throughput and scalability.[16]

## Results and discussion

The proposed trifluoromethylation strategy was first evaluated with thiophenol, $Ru(bpy)_3Cl_2$, and a 24 W fluorescent lamp (Table 1). Both $CF_3I$ and $CF_3SO_2Cl$ were used as a $CF_3$ source (Table 1, entries 1–3). In the absence of any additive, only a trace amount of the desired compound (**1b**) could be observed, while the major reaction was the formation of diphenyl disulfide (**1c**). A high selectivity for the disulfide product was found when $CF_3SO_2Cl$ was used, which also occurred in the absence of a photocatalyst. The use of an organic base effectively suppressed by-product formation (Table 1, entries 4–8).[17] Optimal conditions were obtained when 2.0 equivalents of triethylamine (TEA) was introduced to the reaction, resulting in the selective trifluoromethylation of thiophenol within one hour. Further, only a slight excess (1.1 equiv.) of TEA was required to obtain full conversion of thiophenol (Table 1, entries 9–10). Control experiments established the necessity of both the photoredox catalyst and the presence of visible light (Table 1, entries 11–12), as a high degree of disulfide formation or no reaction was observed in both these cases. The formation of the $SCF_3$-product in the absence of a photocatalyst occurs through homolysis of $CF_3I$ upon irradiation.[18]

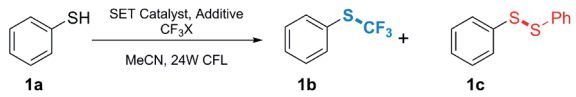
With the optimized conditions in hand, we set out to explore the scope of this photocatalytic transformation. A broad array of aromatic thiols, heteroaromatic thiols and aliphatic thiols were subjected to our optimized trifluoromethylation protocol (Scheme 1). Aromatic thiols bearing electron-withdrawing and electron-donating functional groups were all competent substrates. Notably, most examples could be finished within one hour reaction time (Scheme 1). As expected, aromatic thiols with strong electron-withdrawing functional groups reacted much slower (up to 5 hours reaction time) but were still obtained in moderate to good yields (Scheme 1, examples **6b**, **8b**, **18b**). The mildness of our protocol is exemplified by its tolerance towards aromatic thiols bearing a free carboxylic acid, an alcohol, or an amine (Scheme 1, examples **9b**, **15b**, **19b**). In addition, the presence of chlorine and bromine substituents was well tolerated providing opportunities for orthogonal selectivity with cross-coupling chemistry (Scheme 1, examples **11b** and **12b**). These representative examples illustrate the general applicability of our method to prepare S–$CF_3$ bearing aromatic compounds by photocatalytic trifluoromethylation of aromatic thiols.

Encouraged by these results, we extended our investigations towards the photocatalytic trifluoromethylation of heteroaromatic thiols (Scheme 1, examples **20–26b**). 2-Mercaptopyridine, 4-mercaptopyridine, 2-mercaptobenzoxazole, 2-mercaptobenzothiazole, unprotected and protected 2-mercaptobenzimidazole and 2-mercaptopyrimidine could be efficiently trifluoromethylated within one hour reaction time under the given conditions. It should be noted that extended reaction times resulted in lower selectivity for the desired compound through the incorporation of additional $CF_3$-groups on the aromatic ring.[19] Aliphatic thiols proved to be the most challenging substrate class (Scheme 1, examples **27–29b**). Under the established reaction conditions, the formation of the corresponding disulfides could not be prevented. This could be partially overcome by an *in situ* reduction of the formed disulfide by adding triphenylphosphine and water.[20]

During the course of our investigations, we observed that the rate of the reaction in batch is affected by the mixing efficiency. To establish a better contact between gaseous $CF_3I$ and the liquid reaction mixture in batch, $CF_3I$ was added *via* syringe pump and bubbled through the reaction mixture in 10 minutes. A further increase in interfacial area between gaseous $CF_3I$ and liquid reaction mixture can be obtained in continuous-flow microreactors.[21] In such devices, gas–liquid flow results in the formation of a segmented flow regime which provides an intense contact between liquid and gas phase. Furthermore, process intensification of photochemical transformations can be efficiently achieved in microreactors.[16,22] The observed intensification is a consequence of the improved irradiation of the reaction medium in such confined reactors, which leads to a more uniform local volumetric rate of energy absorption.[23] The microflow setup consists of a high purity perfluoroalkoxyalkane (PFA) capillary microreactor (500 μm ID, 2.5 m length, 500 μL volume) and a Tefzel cross-mixer, which was connected to a $CF_3I$ gas cylinder and two syringes containing the liquid reagents (Fig. 1). $CF_3I$ was dosed into the reactor system by means of a mass flow controller (MFC). The liquid reagents were added by syringe pump and upon

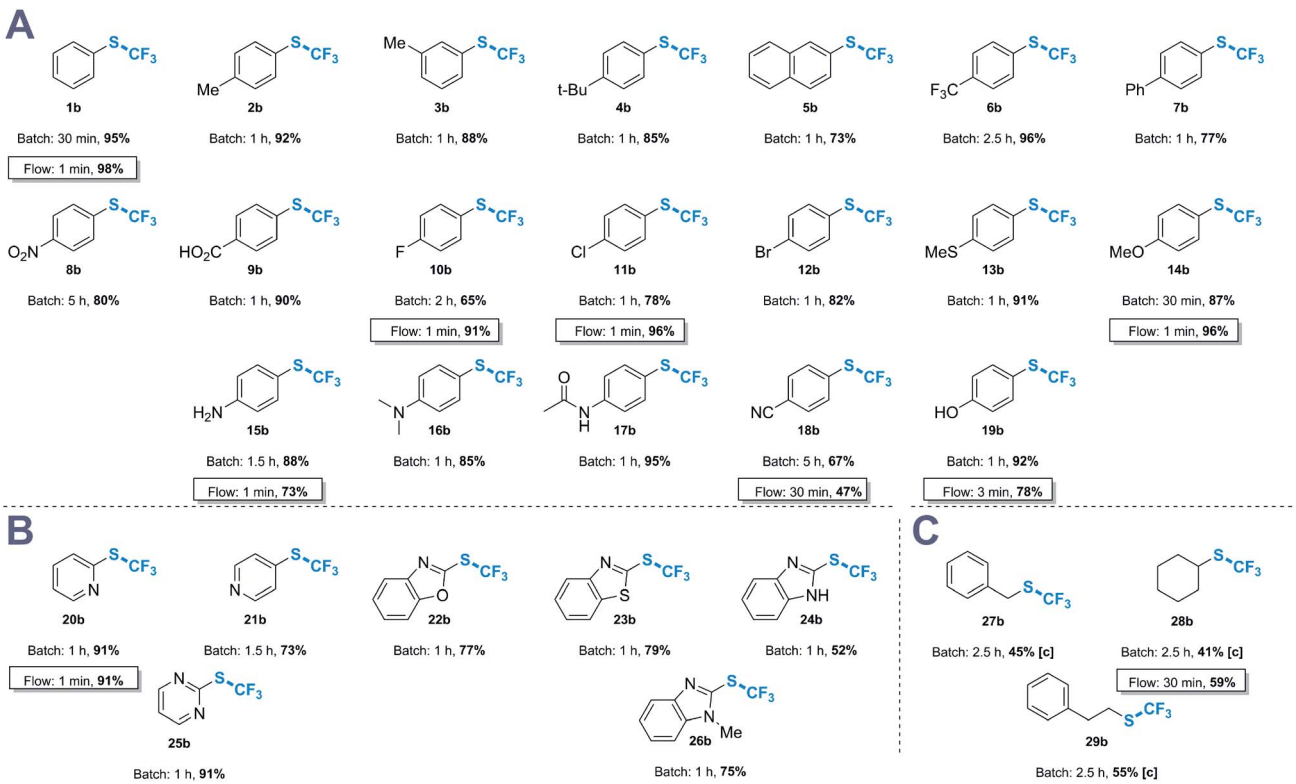
 

Table 1 Optimization of reaction conditions[e]




| | | | $CF_3I$ | | $CF_3SO_2Cl$ | |
|---|---|---|---|---|---|---|
| Entry[a] | Catalyst | Additive (equiv.) | Conv.[b] (%) | Yield [**1b** : **1c**][b] (%) | Conv. (%)[b] | Yield [**1b** : **1c**][b] (%) |
| 1 | $Ru(bpy)_3Cl_2$ | — | 35 | Trace : 33 | 98 | 0 : 98 |
| 2 | $Ir(ppy)_3$ | — | 22 | Trace : 21 | 100 | 0 : 89 |
| 3 | $Ir(F\text{-}ppy)_3$ | — | 26 | Trace : 25 | 100 | 5 : 75 |
| 4 | $Ru(bpy)_3Cl_2$ | Py (2) | 72 | 4 : 68 | — | — |
| 5 | $Ru(bpy)_3Cl_2$ | TEA (2) | 100 | 97 : 3 | — | — |
| 6 | $Ru(bpy)_3Cl_2$ | DIPEA (2) | 100 | 99 : 1 | — | — |
| 7 | $Ru(bpy)_3Cl_2$ | DBU (2) | 100 | 100 : 0 | — | — |
| 8 | $Ru(bpy)_3Cl_2$ | TMEDA (2) | 100 | 99 : 1 | — | — |
| 9 | $Ru(bpy)_3Cl_2$ | TEA (1.1) | 100 | 100 : 0 | — | — |
| 10 | $Ru(bpy)_3Cl_2$ | TEA (0.5) | 76 | 75 : 1 | — | — |
| 11[c] | none | TEA (1) | 100 | 55 : 45 | — | — |
| 12[d] | $Ru(bpy)_3Cl_2$ | TEA (1) | 0 | 0 : 0 | — | — |

[a] Reaction conditions: thiophenol (1 mmol), $CF_3I$ (4 mmol) or $CF_3SO_2Cl$ (1.2 mmol), photoredox catalyst (1 mol%), MeCN (5 mL), CFL (24 W), room temperature, 1 hour. [b] Conversion and yield of **1b** and **1c** are determined by GC and $^{19}$F-NMR. [c] Absence of photocatalyst showed rapid disulfide formation. [d] Reaction carried out in the dark. [e] *Abbreviations*: bpy: bipyridine, ppy: phenylpyridine, F-ppy: 3,5-difluorophenylpyridine, Py: pyridine, TEA: triethylamine, DIPEA: (diisopropyl)ethylamine, DBU: 1,8-diazobicyclo[5.4.0]undec-7-ene, TMEDA: tetramethylethane-1,2-diamine.




Scheme 1 Substrate scope for photocatalytic direct trifluoromethylation. [Section A] Aryl thiols (compounds **1b–19b**), [Section B] heteroaryl thiols (compounds **20b–26b**) and [Section C] aliphatic thiols (**27b–29b**). [a] Batch protocol: thiol (1 mmol), $Ru(bpy)_3Cl_2$ (0.01 mmol), $CF_3I$ (4 mmol) in MeCN (5 mL). Then add TEA (1.1 mmol) and irradiate with a 24 W CFL household light bulb at room temperature. Reported yields are those of isolated compounds or calculated with 19F-NMR with internal standard for volatile compounds. See ESI† for more details. [b] Flow protocol: thiol (1 mmol), $Ru(bpy)_3Cl_2$ (0.01 mmol), $CF_3I$ (1.1 mmol), TEA (1.1 mmol) in MeCN are mixed *via* a cross-mixer and irradiated with an array of 3.12 W Blue LED's. [c] Additives $Ph_3P/H_2O$ (1 : 1, 1 equiv.) were added.

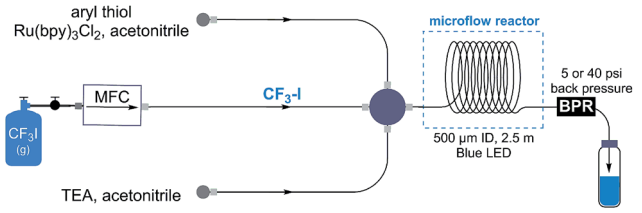



Fig. 1 Continuous-flow setup for the visible-light photocatalytic trifluoro-methylation of thiols.

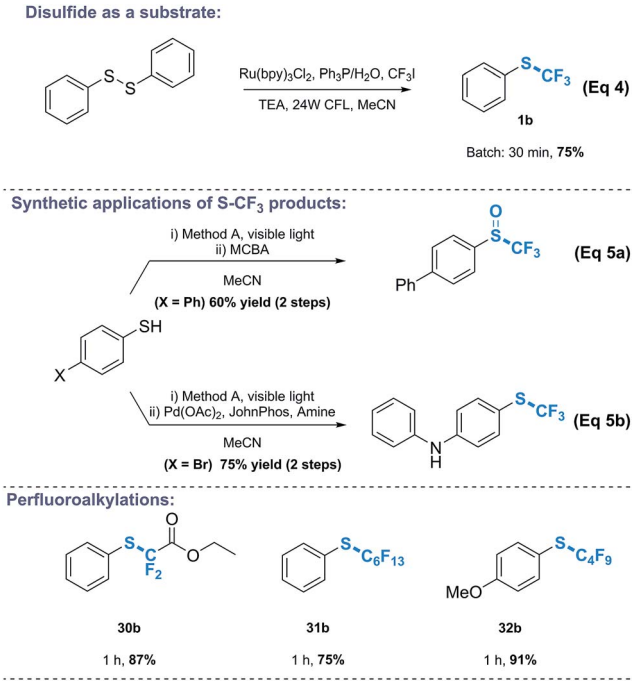
merging with gaseous $CF_3I$, a segmented gas–liquid flow was established. The reaction mixture was exposed to blue LED irradiation which matches the absorption maximum of the photocatalyst. Nine different thiols, including aryl, heteroaryl and alkyl thiols, were evaluated in our continuous-flow system (Scheme 1).

A significant acceleration could be observed in all cases; several examples could be completed within one minute residence time (Scheme 1, examples **1b**, **10b**, **11b**, **14b**, **15b**, **20b**). Thiophenols bearing electron-withdrawing functional groups could be accelerated, however, it was difficult to reach complete conversion within 30 minutes residence time (Scheme 1, example **18b**). A substantial increase was observed for cyclohexylthiol (Scheme 1, example **28b**). Importantly, it should be noted that the required amount of $CF_3I$ gas could be drastically reduced in flow to 1.1 equivalents (4 equivalents in batch) due to the improved contact between the gas and liquid reactants in the photomicroreactor.

So far, we only used thiols as substrates for the formation of trifluormethylthio compounds. As was demonstrated with aliphatic thiols, disulfide by-products can be *in situ* reduced by the triphenylphosphine/water system and allowed to produce the desired S–$CF_3$ products. Utilizing this protocol, disulfides could be directly used as substrates for the trifluoromethylation protocol (see Scheme 2, eqn (4)).

The products of this photocatalytic trifluoromethylation of thiols may serve as useful synthetic intermediates towards interesting biologically active compounds. To demonstrate this, compound **7b** was oxidized to yield the corresponding sulfoxide (Scheme 2, eqn (5a)). Furthermore, as demonstrated above, reductive dehalogenation was not observed under the current reaction conditions. This feature allows to further decorate the molecule by *e.g.* cross-coupling chemistry (Scheme 2, eqn (5b)).

We next examined the structural diversity of the perfluoroalkyl halide coupling partner in this photocatalytic protocol. Efficient coupling could be achieved with ethyl 2-bromo-difluoroacetate, perfluorohexyliodide and perfluorobutyliodide as representative examples (Scheme 2, below). The coupling with ethyl 2-bromo-difluoroacetate gives rise to a versatile intermediate (**30b**) which can be used to introduce $^{18}F$ *via* a Ag-catalyzed decarboxylative fluorination.[24] The possibility to prepare perfluoroalkyl analogues represents a significant advantage of our method compared to the use of perfluoroalkyl electrophilic reagents, which are either expensive, not commercially available, or difficult to synthesize.




Scheme 2 Synthetic applications of the photocatalytic trifluoromethylation protocol. (i) Use of disulfides as a substrate (eqn (4)); (ii) formation of sulfoxides *via* a one-pot photocatalytic trifluoromethylation/oxidation sequence (eqn (5a)), and exploitation of the orthogonal selectivity between photoredox catalysis and cross-coupling chemistry (eqn (5b)); (iii) photocatalytic perfluoroalkylation of aryl thiols.

A plausible mechanism for the photocatalytic trifluoromethylation of thiols is depicted in Fig. 2. Reductive quenching of the exited state of $Ru(bpy)_3^{2+}$* occurs *via* a nitrogen base. Replacing the nitrogen base by an inorganic base, *i.e.* $K_2HPO_4$, resulted in the exclusive formation of disulfide with no S–$CF_3$ bond formation (see ESI†).[25] This observation supports the necessity of a reductive quencher to obtain the desired product.[26] Next, oxidizing the $[Ru(bpy)_3]^+$ species to its ground state generates an electrophilic $CF_3$ radical.[15] This $CF_3$ radical can subsequently react with the thiol substrate to yield the desired S–$CF_3$ product.

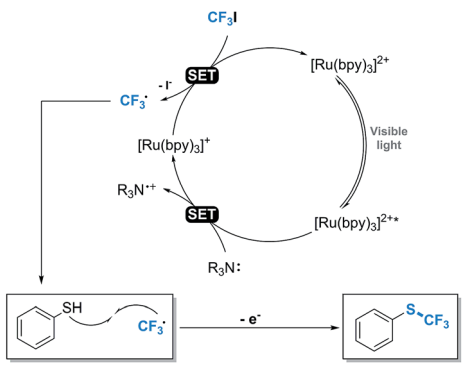



Fig. 2 Proposed mechanism for the photocatalytic trifluoromethylation of thiols.

## Conclusions

In conclusion, we have developed a mild and fast photocatalytic approach to the direct trifluoromethylation of thiols. The method was shown to have a broad substrate scope allowing for the preparation of aryl, heteroaryl and alkyl S–$CF_3$ compounds in good-to-excellent yields. Furthermore, our protocol allows for variation of the perfluoroalkyl halide coupling partner giving rise to perfluoroalkylated thiophenols. Acceleration of the photocatalytic protocol was achieved in a continuous-flow photomicroreactor (reaction times can be reduced to the minute range). Most notably, only a slight excess of $CF_3I$ (1.1 equivalents) was required in the continuous-flow experiments due to excellent gas–liquid mass transfer characteristics. Given the operational simplicity of both batch and flow protocols, we anticipate that our photocatalytic method for the trifluoromethylation of thiols will find broad application in academia and industry.

## Acknowledgements

TN. would like to acknowledge financial support from the Dutch Science Foundation for a VENI Grant (no. 12464) and from the European Union for a Marie Curie CIG Grant. XW. thanks the Harvard NeuroDiscovery Center for financial support. Funding by the Advanced European Research Council Grant (Grant number: 267443 for VH.) is kindly acknowledged.

## Notes and references

1 (*a*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity & Applications*, Wiley-VCH, Weinheim, 2004; (*b*) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medical Chemistry of Fluorine*, Wiley-VCH, Hoboken, 2008.

2 (*a*) K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*c*) P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem., Int. Ed.*, 2008, **47**, 8998–9033; (*d*) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.

3 For recent reviews regarding trifluoromethylation or perfluoroalkylation, see: (*a*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477; (*b*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475–4521; (*c*) Y. Macé and E. Magnier, *Eur. J. Org. Chem.*, 2012, 2479–2494; (*d*) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950–8958; (*e*) H. Liu, Z. Gu and X. Jiang, *Adv. Synth. Catal.*, 2013, **355**, 617–626; (*f*) X. Liu, M. Wang and Q. Liu, *Chem. Rev.*, 2014, DOI: 10.1021/cr400473a.

4 L. Chu and F.-L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513–1522. (*a*) G. Landelle, A. Panossian, S. Pazenok, J. P. Vors and F. R. Leroux, *Beilstein J. Org. Chem.*, 2013, **9**, 2476–2536; (*b*) V. N. Boiko, *Beilstein J. Org. Chem.*, 2010, **6**, 880–921.

5 For selected reports on the direct trifluoromethylation: (*a*) R. Pluta, P. Nikolaienko and M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **53**, 1650–1653; (*b*) F. Hu, X. Shao, D. Zhu, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 6105–6109; (*c*) S. Alazet, L. Zimmer and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 10814–10817. For a mini-review on direct trifluoromethylthiolation: ; (*d*) A. Tlili and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 6818–6819.

6 (*a*) V. N. Boiko, G. M. Shchupak and L. M. Yagupolskii, *Zh. Org. Khim.*, 1977, **13**, 1057–1061; (*b*) V. N. Boiko, T. A. Dashevskaya, G. M. Shchupak and L. M. Yagupolskii, *Zh. Org. Khim.*, 1979, **15**, 396–400; (*c*) V. N. Boiko, G. M. Shchupak and L. M. Yagupolskii, *Zh. Org. Khim.*, 1985, **21**, 1470–1477.

7 T. Billard, N. Roques and B. R. Langlois, *J. Org. Chem.*, 1999, **64**, 3813–3820.

8 (*a*) V. G. Koshechko, L. A. Kiprianova and L. I. Fileleeva, *Tetrahedron Lett.*, 1992, **33**, 6677–6678; (*b*) V. G. Koshechko, L. A. Kiprianova, L. I. Fileleeva and Z. Z. Rozhkova, *J. Fluorine Chem.*, 1995, **70**, 277–278; (*c*) V. G. Koshechko, L. A. Kiprianova, L. I. Fileleeva and K. G. Tsanov, *J. Fluorine Chem.*, 1999, **96**, 163–166.

9 T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156–2164.

10 (*a*) P. Eisenberger, S. Gischig and A. Togni, *Chem.–Eur. J.*, 2006, **12**, 2579–2586; (*b*) I. Kieltsch, P. Eisenberger and A. Togni, *Angew. Chem., Int. Ed.*, 2007, **46**, 754–757.

11 T. Umemoto, *Chem. Rev.*, 1996, **96**, 1757–1778.

12 For selected reviews about photoredox catalysis: (*a*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2009, **48**, 9785–9789; (*b*) J. W. Tucker and C. R. J. Stephenson, *J. Org. Chem.*, 2012, **77**, 1617–1722; (*c*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (*d*) D. A. Nicewicz and T. M. Nguyen, *ACS Catal.*, 2014, **4**, 355–360.

13 X. Wang, G. D. Cuny and T. Noël, *Angew. Chem., Int. Ed.*, 2013, **52**, 7860–7864.

14 For a report with disulfides as reaction partner: M. Majek and A. J. von Wangelin, *Chem. Commun.*, 2013, **49**, 5507–5509.

15 For recent developments on C–$CF_3$ bond formations *via* photoredox catalysis utilizing $CF_3I$, see: (*a*) N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. Schouten, V. Hessel and T. Noël, *ChemSusChem*, 2014, **7**, 1612–1617; (*b*) N. J. W. Straathof, D. J. G. P. van Osch, A. Schouten, X. Wang, J. C. Schouten, V. Hessel and T. Noël, *J. Flow Chem.*, 2014, **4**, 12–17; (*c*) N. Iqbal, J. Jung, S. Park and E. J. Cho, *Angew. Chem., Int. Ed.*, 2014, **53**, 539–542; (*d*) E. Kim, S. Choi, H. Kim and E. J. Cho, *Chem.–Eur. J.*, 2013, **19**, 6209–6212; (*e*) N. Iqbal, S. Choi, E. Kim and E. J. Cho, *J. Org. Chem.*, 2012, **77**, 11383–11387; (*f*) Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034–9037; (*g*) P. V. Pham, D. A. Nagib and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2011, **50**, 6119–6122; (*h*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875–10877.

16 For reviews pertaining the combination of continuous-flow microreactors and photochemistry: (*a*) T. Noël, X. Wang and V. Hessel, *Chim. Oggi*, 2013, **31**, 10–14; (*b*)

M. Oelgemöller, *Chem. Eng. Technol.*, 2012, **35**, 1144–1152; (*c*) J. P. Knowles, L. D. Elliott and K. I. Booker-Milburn, *Beilstein J. Org. Chem.*, 2012, **8**, 2025–2052; (*d*) M. Oelgemoeller and O. Shvydkiv, *Molecules*, 2011, **16**, 7522–7550; (*e*) E. E. Coyle and M. Oelgemoeller, *Photochem. Photobiol. Sci.*, 2008, **7**, 1313–1322; (*f*) Y. Matsushita, T. Ichimura, N. Ohba, S. Kumada, K. Sakeda, T. Suzuki, H. Tanibata and T. Murata, *Pure Appl. Chem.*, 2007, **79**, 1959–1968; (*g*) Z. J. Garlets, J. D. Nguyen and C. R. J. Stephenson, *Isr. J. Chem.*, 2014, **54**, 351–360; (*h*) E. M. Schuster and P. Wipf, *Isr. J. Chem.*, 2014, **54**, 361–370.

17 It should be noted that the use of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) darkened the reaction mixture, which lengthened the reaction times due to inefficient irradiation.

18 M. R. Nyden, in *Fire suppression system performance of alternative agents in aircraft engine and dry bay laboratory systems*, ed. R. G. Gann, 1995, pp. 77–95, NIST SP 890.

19 D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224–228.

20 R. E. Humphrey and J. M. Hawkins, *Anal. Chem.*, 1964, **36**, 1812–1814.

21 T. Noël and V. Hessel, *ChemSusChem*, 2013, **6**, 405–407.

22 For selected reports on the merger of visible-light photoredox catalysis and continuous-flow microreactors: (*a*) D. Cantillo, O. de Frutos, J. A. Rincon, C. Mateos and C. O. Kappe, *Org. Lett.*, 2014, **16**, 896–899; (*b*) A. C. Hernandez-Perez and S. K. Collins, *Angew. Chem., Int. Ed.*, 2013, **125**, 12928–12932; (*c*) M. Neumann and K. Zeitler, *Org. Lett.*, 2012, **14**, 2658–2661; (*d*) J. W. Tucker, Y. Zhang, T. F. Jamison and C. R. J. Stephenson, *Angew. Chem., Int. Ed.*, 2012, **51**, 4144–4147; (*e*) See also ref. 13, 15a and b ; (*f*) For reviews on visible-light photoredox catalysis in flow, see: ref. 16a and g.

23 Y. Su, N. J. W. Straathof, V. Hessel and T. Noël, *Chem.–Eur. J.*, 2014, **20**, 10562–10589.

24 (*a*) S. Mizuta, I. S. R. Stenhagen, M. O'Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin and V. Gouverneur, *Org. Lett.*, 2013, **15**, 2648–2651; (*b*) M. Huiban, M. Tredwell, S. Mizuta, Z. Wan, X. Zhang, T. L. Collier, V. Gouverneur and J. Passchier, *Nat. Chem.*, 2013, **5**, 941–944.

25 For a comprehensive discussion of photocatalytic disulfide formation, we refer to: A. Talla, B. Driessen, N. J. W. Straathof, L.-G. Milroy, L. Brunsveld, V. Hessel, X. Wang, T. Noël, 2014, submitted for publication.

26 L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker and C. R. J. Stephenson, *Org. Lett.*, 2010, **12**, 3104–3107.