



# Metal-Free Visible-Light-Mediated Hydrotrifluoromethylation of Unactivated Alkenes and Alkynes in Continuous Flow

Anne-Laure Barthelemy, Guillaume Dagousset, Emmanuel Magnier

## ► To cite this version:

Anne-Laure Barthelemy, Guillaume Dagousset, Emmanuel Magnier. Metal-Free Visible-Light-Mediated Hydrotrifluoromethylation of Unactivated Alkenes and Alkynes in Continuous Flow. European Journal of Organic Chemistry, 2020, 2020 (10), pp.1429-1432. 10.1002/ejoc.201901252 . hal-02992749

**HAL Id: hal-02992749**

**<https://hal.science/hal-02992749>**

Submitted on 6 Nov 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Metal-Free Visible-Light-Mediated Hydrotrifluoromethylation of Unactivated Alkenes and Alkynes in Continuous Flow

Anne-Laure Barthelemy, Guillaume Dagousset,\* and Emmanuel Magnier\*

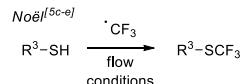
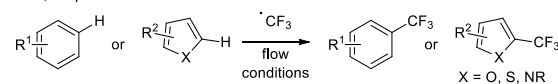
**Abstract:** We report herein a novel photoredox-catalyzed hydrotrifluoromethylation of unsaturated systems under continuous flow. This metal-free method is easily broadened to other perfluoroalkyl groups ( $R_F = CF_3, CFCF_2, CF_2Br, C_4F_9$ ) thanks to the use of sulfilimino iminiums as sources of  $\cdot R_F$  radicals. The mild reaction conditions are compatible with unactivated alkenes bearing a wide range of functionalities, as well as with alkynes for the first time.

Due to the specificities of the fluorine atom, the introduction of a trifluoromethyl group into organic compounds has a dramatic impact on the physicochemical and biological properties of these molecules. It has undoubtedly triggered the development of a wide range of efficient methods to synthesize trifluoromethylated compounds, notably via nucleophilic or electrophilic trifluoromethylations.<sup>[1]</sup> Concerning radical approaches, visible-light photoredox catalysis has recently established itself as one of the most efficient methodology to perform trifluoromethylation reactions.<sup>[2,3]</sup> However, in classical batch conditions using standard glassware, one potential drawback of such procedures is that visible light is rapidly absorbed on a millimeter scale, according to Beer-Lambert-Bouguer's law. Therefore, the desired reaction can only occur near the surface of the flask, in a very small volume compared to the total reaction mixture. As a consequence, prolonged irradiation time is needed to go until complete conversion. This may lead to the formation of undesired side-products, and this limitation is clearly amplified in the case of large-scale experiments.

To circumvent this issue, continuous flow has recently appeared as the technique of choice to perform photochemical reactions.<sup>[4]</sup> Indeed, the narrow tubing of flow reactors allows for a homogeneous and optimal irradiation of the reaction mixture, thanks to a very high surface-to-volume ratio. Regarding the trifluoromethyl group, pioneer studies were successfully reported by the groups of Noël<sup>[5]</sup> and Stephenson.<sup>[6]</sup> Efforts were mainly focused on the C–H trifluoromethylation of (hetero)arenes<sup>[5a-b,f-g,6]</sup> or thiols.<sup>[5c-e,7]</sup> Surprisingly, to the best of our knowledge, only one example of trifluoromethylation of alkenes was recently reported by Noël and coworkers.<sup>[8-10]</sup> Although good yields and high *E* selectivity were achieved, the reaction was limited to styrene derivatives and an expensive Ir-based photocatalyst was used. Therefore, the development of a general metal-free continuous-flow method that would be compatible with unactivated alkenes is highly desirable.<sup>[11]</sup> In addition, if alkynes are substrates of choice for photoredox-catalyzed trifluoromethylation in batch,<sup>[11a,11c,12]</sup> analogous reactions in flow have not been reported yet, to the best of our knowledge. We wish to report herein a new and efficient hydrotrifluoromethylation of unactivated alkenes in flow. This

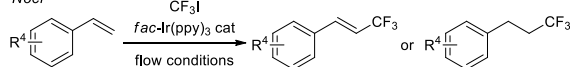
## a) With (hetero)arenes or thiols as substrates

Noël, Stephenson<sup>[5,6]</sup>

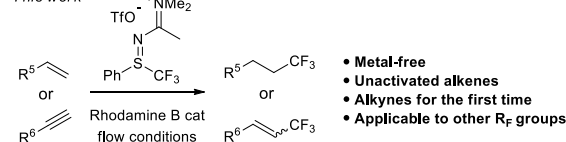


## b) With alkenes as substrates

Noël<sup>[8]</sup>



This work



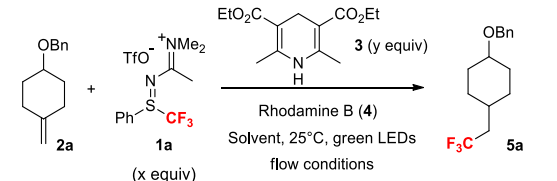
- Metal-free
- Unactivated alkenes
- Alkynes for the first time
- Applicable to other  $R_F$  groups

**Scheme 1.** Main developments in continuous-flow photoredox-catalyzed trifluoromethylation reactions.

metal-free process has been successfully extended to other perfluoroalkyl groups, and for the first time to alkynes as substrates.

We recently disclosed the use of fluorinated sulfilimino iminiums **1** as new sources of perfluoroalkyl radicals under photoredox catalysis.<sup>[13]</sup> Based on this experience and on our recent work on continuous-flow photocatalyzed reactions,<sup>[14]</sup> we envisioned that these reagents, easily prepared in one step from the corresponding sulfoxide at a multi-gram scale, would be suitable partners to perform hydroperfluoroalkylation of alkenes. Indeed, when alkene **2a** was treated with 1 equiv of  $CF_3$ -sulfilimino iminium **1a**, 2 equiv of Hantzsch ester **3** (HE) as H atom source, and Rhodamine **4** as photocatalyst (5 mol%) with a flow rate of  $0.5 \text{ mL} \cdot \text{min}^{-1}$  under green LEDs irradiation, the corresponding adduct **5a** was obtained in 50% yield (Table 1, entry 1). Encouraged by this result, the reaction parameters were then optimized, including the flow rate (entries 3-4), the solvent (entry 5), the stoichiometry of reagents and catalyst (entries 6-7,10), and the concentration of the reaction mixture (entries 8-9). Finally, the best conditions were found by dissolving alkene **2a** with 1.5 equiv of **1a**, 2.7 equiv of **3** and 5 mol% of photocatalyst **4** in  $CH_2Cl_2$  (0.025 M), with a flow rate of  $1 \text{ mL} \cdot \text{min}^{-1}$  (entry 7).<sup>[15]</sup> With these mild reaction conditions in hand, the scope of this hydrotrifluoromethylation was next investigated, and the results are summarized in Scheme 2. First, sulfilimino iminiums **1b-1d** with other perfluoroalkyl groups ( $R_F = CF_2Br, CFCF_2$  and  $C_4F_9$ , respectively) were also suitable partners for this reaction, giving access to the expected monofluoromethyl, difluoromethyl and perfluoroalkyl adducts **5ab-5ad** in up to 60% yield. Pleasingly, a wide number of mono-substituted or 1,1-disubstituted alkenes **2b-2g** bearing a variety of functional groups (ether, carbamate,

**Table 1.** Survey of reaction conditions for the photoredox-catalyzed hydrotrifluoromethylation of alkene **1a**.



Entry	x ; y	Solvent	Flow rate (mL.min <sup>-1</sup> )	Residence time (t <sub>R</sub> )	Yield [%] <sup>[a,b,c]</sup>
1	1 ; 2	DCE	0.5	20 min	50
2	1.5 ; 3	DCE	0.5	20 min	60
3	1.5 ; 3	DCE	1.0	10 min	66
4	1.5 ; 3	DCE	2.0	5 min	62
5	1.5 ; 3	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	75
6	1.5 ; 2.5	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	71
7	1.5 ; 2.7	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	87 (76) <sup>[d]</sup>
8 <sup>[e]</sup>	1.5 ; 2.7	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	47
9 <sup>[f]</sup>	1.5 ; 2.7	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	63
10 <sup>[g]</sup>	1.5 ; 2.7	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	72
11 <sup>[h]</sup>	1.5 ; 2.7	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	0
12 <sup>[i]</sup>	1.5 ; 2.7	CH <sub>2</sub> Cl <sub>2</sub>	1.0	10 min	0

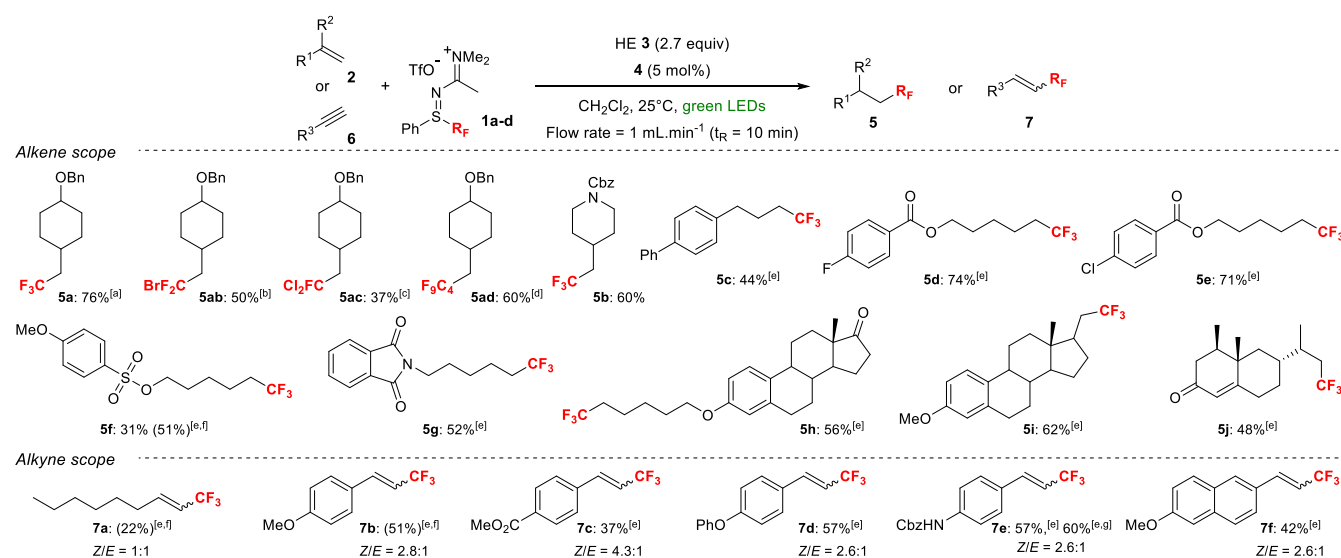
[a] General conditions: **2a** (0.20 mmol), **1a** (x equiv), **3** (y equiv), and **4** (5 mol%) in 8 mL of MeCN irradiated with green LEDs (525 nm) at 25°C inside a 10 mL reactor of a E-series Vapourtec flow system. See ESI for more details. [b] Yields determined by <sup>19</sup>F NMR spectroscopy using PhOCF<sub>3</sub> as an internal standard. [c] d.r. = 1.1:1 in all cases. [d] Yield into brackets referred to chromatographically pure product. [e] With 20 mL of CH<sub>2</sub>Cl<sub>2</sub>. [f] With 4 mL of CH<sub>2</sub>Cl<sub>2</sub>. [g] With 2.5 mol% of **4**. [h] Without **4**. [i] In the dark.

ester, halogen, sulfonic ester, phthalimide, ketone) were smoothly trifluoromethylated by this continuous-flow process, affording the corresponding CF<sub>3</sub>-adducts **5b-5g** in good yields. Importantly, this photocatalyzed reaction was also readily performed with steroid derivatives **2h-2i** and with natural compound (+)-Nootkatone **2j**, showing that it is easily applicable to the late-stage functionalization of small complex molecules.

Encouraged by these results, we next thought to extend the scope of this reaction to alkynes. While aliphatic alkynes such as 1-octyne (**6a**) gave only poor yield of the corresponding trifluoromethylated alkene (22% NMR yield for **7a**), we were pleased to see that aromatic alkynes **6b-6f** bearing electron-donating (OMe, OPh, NHCbz) or –withdrawing groups (CO<sub>2</sub>Me) were efficiently trifluoromethylated under the same reaction conditions (flow rate of 1 mL.min<sup>-1</sup>, t<sub>R</sub> = 10 min). This difference of reactivity between aliphatic and aromatic alkynes could not be rationalized. However, it is worth to note that similar reactions in batch are carried out with aliphatic alkynes, while aromatic alkynes are usually unreactive substrates.<sup>[11a,11c,12b-d]</sup>

Importantly, the reaction with alkyne **7e** could be carried out on a ten-fold higher scale (2 mmol) without any decrease in yield. This demonstrated the practicality and efficiency of continuous-flow photocatalysis to perform large-scale experiments with a significant throughput (1.5 mmol.h<sup>-1</sup>).

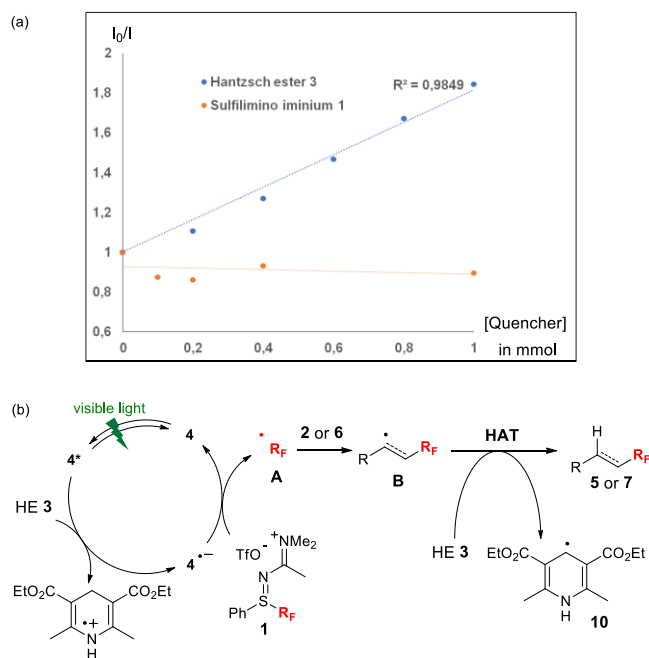
In order to gain some insight into the mechanism of this hydroperfluoroalkylation process, some control experiments were performed. Both the light and the photocatalyst **4** were essential parameters for the reaction to proceed (Table 1, entries 11-12), which suggested that a radical pathway was involved. Moreover, some luminescence quenching experiments were carried out (Scheme 3a). The rate of quenching determined using Stern-Volmer plots showed that a reductive quenching cycle involving the oxidation of Hantzsch ester **3** by the excited state **4\*** of Rhodamine B was favoured over an



**Scheme 2.** Scope of hydroperfluoroalkylation of alkenes and alkynes in flow. General Conditions: alkene **2** or alkyne **6** (0.2 mmol), **1** (0.3 mmol), Hantzsch ester **3** (HE, 0.54 mmol), **4** (5 mol%) in 8 mL of CH<sub>2</sub>Cl<sub>2</sub> at 25°C. Flow rate of 1 mL.min<sup>-1</sup> (t<sub>R</sub> = 10 min) under green LED irradiation. Yield refer to chromatographically pure product. [a] d.r. = 1.1:1. [b] d.r. = 1:1. [c] d.r. = 1:1. [d] d.r. = 2:1. [e] With 3 equiv of **1a** and 3 equiv of **3**. [f] Yields into brackets determined by <sup>19</sup>F NMR spectroscopy using PhOCF<sub>3</sub> as an internal standard. [g] Reaction performed on a 2 mmol scale. d.r. = diastereomeric ratio.

oxidative quenching cycle (i.e. direct reduction of **1** by **4\***).

Based on this analysis and on previous Electron Paramagnetic Resonance experiments with sulfilimino iminiums **1**,<sup>[13]</sup> a plausible mechanism is depicted in Scheme 4b. After irradiation with visible light, the formed excited state **4\*** oxidizes HE **3**. The highly reductive species **4<sup>-</sup>** generated reacts with **1** to form the corresponding  $\cdot R_F$  radical **A**, which subsequently adds onto alkene **2** (or alkyne **6**). Final HAT (Hydrogen atom transfer) of the formed radical intermediate **B** with HE **3** would lead to the desired perfluoroalkylated adduct **5** (or **7**).<sup>[16]</sup>



**Scheme 3.** (a) Luminescence quenching experiments. Stern Volmer plots  $I_0/I = f([\text{quencher}])$ . (b) Proposed mechanism.

In conclusion, we have successfully developed a novel photoredox-catalyzed hydroperfluoroalkylation protocol under continuous-flow conditions, which uses sulfilimino iminiums as versatile sources of perfluoroalkyl radicals. This process is quite efficient (residence time of 10 min) and tolerates a large array of functional groups. Importantly, both alkenes and alkynes were smoothly perfluoroalkylated under these mild and metal-free reaction conditions. Extension of this work to other perfluoroalkylation reactions is currently underway in our laboratory and will be reported in due course.

## Experimental Section

**General procedure:** In a dry tube under argon were added the sulfilimino iminium **1** (0.3 mmol, 1.5 equiv), Hantzsch Ester **3** (0.54 mmol, 2.7 equiv), Rhodamine B **4** (0.01 mmol, 5 mol%) and the alkene **2** (0.2 mmol, 1 equiv).  $\text{CH}_2\text{Cl}_2$  (8 mL) was added and the solution is degassed with argon and stirred at room temperature until complete dissolution of Hantzsch ester **3**. Then, using an easy-Photochem E-series system from Vapourtec with a 10 mL reactor irradiated with a green 525 nm LED

system, 8 mL of the solution (0.2 mmol) was pumped at a flow rate of  $1 \text{ mL} \cdot \text{min}^{-1}$  at  $25^\circ\text{C}$ . After collecting the reaction mixture, a solution of HCl 1M (10 mL) was added and the solution was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 20 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure. The crude was then purified by preparative TLC on silica gel to afford the corresponding pure product **5**.

## Acknowledgments

ALB thanks the French Ministry of Research for a doctoral fellowship. LabEx Charmmmat is gratefully acknowledged for the funding of the continuous flow device.

**Keywords:** flow chemistry • sulfilimino iminium • trifluoromethylation • photoredox catalysis • radicals

- [1] a) P. Kirsch in *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2<sup>nd</sup>, Completely Revised and Enlarged edition, Wiley: New-York, **2013**; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, 317, 1881; c) *Bioorganic and Medicinal Chemistry of Fluorine* (Eds.: J.-P. Begue, D. Bonnet-Delpon), Wiley, Hoboken, **2008**; d) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, 114, 2432.
- [2] For recent reviews on photoredox catalysis, see: a) K. Zeitler, *Angew. Chem.* **2009**, 121, 9969; *Angew. Chem. Int. Ed.* **2009**, 48, 9785; b) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, 2, 527; c) J. M. R. Narayanan, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, 40, 102; d) F. Teplý, *Collect. Czech. Chem. Commun.* **2011**, 76, 859; e) J. Xuan, W.-J. Xiao, *Angew. Chem.* **2012**, 124, 6934. *Angew. Chem. Int. Ed.* **2012**, 51, 6828; f) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, 113, 5322; g) T. Koike, M. Akita, *Synlett* **2013**, 24, 2492; h) D. M. Schultz, T. P. Yoon, *Science* **2014**, 343, 1239176; i) M. D. Kärkäs, B. S. Matsuura, C. R. J. Stephenson, *Science* **2015**, 349, 1285.
- [3] Selected reviews on photocatalyzed perfluoroalkylations, see: a) T. Koike, M. Akita, *Top. Catal.* **2014**, 57, 967; b) H. Egami, M. Sodeoka, *Angew. Chem.* **2014**, 126, 8434; *Angew. Chem. Int. Ed.* **2014**, 53, 8294; c) S. Barata-Vallejo, S. M. Bonesi, A. Postigo, *Org. Biomol. Chem.* **2015**, 13, 11153; d) G. Dagousset, A. Carboni, G. Masson, E. Magnier, in *Modern Synthesis Processes and Reactivity of Fluorinated Compounds* (Eds.: H. Groult, F. Leroux, A. Tressaud), Elsevier, **2016**; e) X. Pan, H. Xia, J. Wu, *Org. Chem. Front.* **2016**, 3, 1163; f) E. H. Oh, H. J. Kim, S. B. Han, *Synthesis* **2018**, 50, 3346.
- [4] *Selected reviews:* a) J. P. Knowles, L. D. Elliott, K. I. Booker-Milburn, *Beilstein J. Org. Chem.* **2012**, 8, 2025; b) Y. Su, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Eur. J.* **2014**, 20, 10562; c) Z. J. Garlets, J. D. Nguyen, C. R. J. Stephenson, *Isr. J. Chem.* **2014**, 54, 351; d) M. B. Plutschack, C. A. Correia, P. H. Seeberger, K. Gilmore, *Top. Organomet. Chem.* **2016**, 57, 43; e) D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, 116, 10276.
- [5] a) 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**, 4, 12; b) N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. Schouten, V. Hessel, T. Noël, *ChemSusChem* **2014**, 7, 1612; c) N. J. W. Straathof, B. J. P. Tegelbeckers, V. Hessel, X. Wang, T. Noël, *Chem. Sci.* **2014**, 5, 4768; d) N. J. W. Straathof, Y. Su, V. Hessel, T. Noël, *Nat. Protoc.* **2016**, 11, 10; e) C. Bottecchia, X.-J. Wei, K. P. L. Kuijpers, V. Hessel, T. Noël, *J. Org. Chem.* **2016**, 81, 7301; f) Y. Su, K. P. L. Kuijpers, N. König, M. Shang, V. Hessel, T. Noël, *Chem. Eur. J.* **2016**, 22, 12295; g) I. Abdiaj, C. Bottecchia, J. Alcazar, T. Noël, *Synthesis* **2017**, 4, 4978; h) X. Zhang, Y. Li, X. Hao, K. Jin, R. Zhang, C. Duan, *Tetrahedron* **2018**, 74, 1742.

- [6] a) J. W. Beatty, J. J. Douglas, K. P. Cole, C. R. J. Stephenson, *Nat. Commun.* **2015**, *6*, 7919; b) J. W. Beatty, J. J. Douglas, R. Miller, R. C. McAtee, K. P. Cole, C. R. J. Stephenson, *Chem* **2016**, *1*, 456.
- [7] For the photocatalyzed  $\alpha$ -trifluoromethylation of ketones in flow, see: D. Cantillo, O. de Frutos, J. A. Rincón, C. Mateos, C. O. Kappe *Org. Lett.* **2014**, *16*, 896.
- [8] N. J. W. Straathof, S. E. Cramer, V. Hessel, T. Noël, *Angew. Chem.* **2016**, *128*, 15778; *Angew. Chem. Int. Ed.* **2016**, *55*, 15549.
- [9] For photocatalyzed difluoromethylation of other activated alkenes in flow, see: a) S. Sumino, M. Uno, T. Fukuyama, I. Ryu, M. Matsuura, A. Yamamoto, Y. Kishikawa, *J. Org. Chem.* **2017**, *82*, 5469; b) X.-J. Wei, W. Boon, V. Hessel, T. Noël, *ACS Catal.* **2017**, *7*, 7136; c) X.-J. Wei, T. Noël, *J. Org. Chem.* **2018**, *83*, 11377; d) Y. Nakayama, G. Ando, M. Abe, T. Koike, M. Akita, *ACS Catal.* **2019**, *9*, 6555. For photocatalyzed trifluoroethylation of styrenes in flow, see: e) L. M. Kreis, S. Krautwald, N. Pfeiffer, R. E. Martin, E. M. Carreira, *Org. Lett.* **2013**, *15*, 1634.
- [10] For a recent example of visible-light-mediated iodoperfluoroalkylation of alkenes and alkynes, see: C. Rosso, J. D. Williams, G. Filippini, M. Prato, C. O. Kappe, *Org. Lett.* **2019**, *21*, 5341.
- [11] Examples of photocatalyzed hydrotrifluoromethylation of alkenes in batch: a) S. Mizuta, S. Verhoog, K. M. Engle, T. Khotavivattana, M. O'Duill, K. Wheelhouse, G. Rassias, M. Médebielle, V. Gouverneur, *J. Am. Chem. Soc.* **2013**, *135*, 2505; b) D. J. Wilger, N. J. Gesmundo, D. A. Nicewicz, *Chem. Sci.* **2013**, *4*, 3160; c) S. P. Pitre, C. D. McTiernan, H. Ismaili, J. C. Scaiano, J. C. *ACS Catal.* **2014**, *4*, 2530; d) L. Zhu, L.-S. Wang, B. Li, B. Fu, C.-P. Zhang, W. Li, W. *Chem. Commun.* **2016**, *52*, 6371; f) Q. Lefebvre, N. Hoffmann, M. Rueping, *Chem. Commun.* **2016**, *52*, 2493; g) Y. Cheng, S. Yu, *Org. Lett.* **2016**, *18*, 2962; h) T. Yajima, S. Shigenaga, *Org. Lett.* **2019**, *21*, 138.
- [12] Examples of photocatalyzed trifluoromethylation of alkynes in batch: a) N. Iqbal, J. Jung, S. Park, E. J. Cho, *Angew. Chem.* **2014**, *126*, 549; *Angew. Chem. Int. Ed.* **2014**, *48*, 539; b) Y. Cheng, S. Yu, *Org. Lett.* **2016**, *18*, 2962; c) T. Yajima, M. Ikegami, *Eur. J. Org. Chem.* **2017**, *2126*; d) Y.-Y. Ren, X. Zheng, X. Zhang, *Synlett* **2018**, *29*, 1028.
- [13] M. Daniel, G. Dagousset, P. Diter, P.-A. Klein, B. Tuccio, B.; A.-M. Goncalves, G. Masson, E. Magnier, *Angew. Chem.* **2017**, *129*, 4055; *Angew. Chem. Int. Ed.* **2017**, *56*, 3997.
- [14] a) A.-L. Barthelemy, B. Tuccio, E. Magnier, G. Dagousset, *Angew. Chem.* **2018**, *130*, 13986; *Angew. Chem. Int. Ed.* **2018**, *57*, 13790; b) A.-L. Barthelemy, B. Tuccio, E. Magnier, G. Dagousset, *Synlett* **2019**, *10.1055/s-0037-1611785*.
- [15] The reaction was also optimized using classical batch conditions. See the Supplementary Information for more details.
- [16] As depicted in ref 13, PhS $\cdot$  radical is *in situ* generated from sulfilimino iminium **1**. An alternative mechanism involving PhSH as HAT reagent could not be ruled out. For a similar report in batch, see: W. Huang, J. Chen, D. Hong, W. Chen, X. Cheng, Y. Tian, G. Li, *J. Org. Chem.* **2018**, *83*, 578.

