

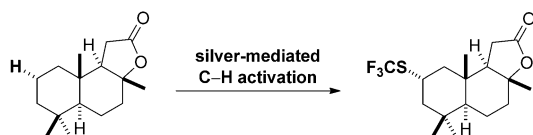
# Silver-Mediated Oxidative Aliphatic C–H Trifluoromethylthiolation\*\*

Shuo Guo, Xiaofei Zhang, and Pingping Tang\*

Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

**Abstract:** The first example of a practical and direct trifluoromethylthiolation reaction of unactivated aliphatic C–H bonds employs a silver-based reagent. The reaction is operationally simple, scalable, and proceeds under aqueous conditions in air. Furthermore, its broad scope and good functional-group compatibility were demonstrated by applying this method to the selective trifluoromethylthiolation of natural products and natural-product derivatives.

The growing importance of fluorinated organic compounds as pharmaceuticals, agrochemicals, and materials has driven the development of new methods for the introduction of fluorine into small molecules.<sup>[1]</sup> The incorporation of the trifluoromethylthio group (SCF<sub>3</sub>) into new drugs and agrochemicals has attracted much attention owing to its strongly electron-withdrawing nature and high lipophilicity.<sup>[2]</sup> Consequently, the development of new trifluoromethylthiolation methods is of great interest to synthetic organic chemists.<sup>[3]</sup> However, the selective trifluoromethylthiolation of unactivated C(sp<sup>3</sup>)–H bonds remains a significant challenge. Herein, we present the first example of a silver-mediated oxidative aliphatic C–H trifluoromethylthiolation. The developed method is operationally simple and scalable; the desired transformation proceeds under aqueous conditions in air and can be applied for the late-stage trifluoromethylthiolation of complex small molecules (Scheme 1).



**Scheme 1.** Silver-mediated trifluoromethylthiolation of aliphatic C(sp<sup>3</sup>)–H bonds.

Methods to indirectly access this important class of compounds include halogen–fluorine exchange reactions and the trifluoromethylation of sulfur-containing compounds.<sup>[4]</sup> However, both of these methods require the preparation of complex precursors. The trifluoromethylthiolation of substrates by the direct formation of the C–SCF<sub>3</sub> bond is a more efficient approach.<sup>[5]</sup> For example, trifluoromethylthiolation reactions of aryl Grignard reagents,<sup>[6]</sup> aryl halides,<sup>[7–10]</sup> boronic acids,<sup>[11–15]</sup> diazo compounds,<sup>[16–19]</sup> alkenes,<sup>[20]</sup> and terminal alkynes<sup>[21–22]</sup> with different trifluoromethylthiolation reagents have been developed. Moreover, the introduction of a trifluoromethylthio group has been achieved through C(sp<sup>2</sup>)–H bond functionalization and the activation of C(sp<sup>3</sup>)–H bonds adjacent to a carbonyl group.<sup>[23]</sup> For instance, the trifluoromethylthiolation of aryl C–H bonds in the presence of a directing group was studied by the groups of Daugulis,<sup>[23c]</sup> Shen,<sup>[23j]</sup> and Huang.<sup>[23k]</sup> Although progress has recently been made in the trifluoromethylthiolation of C(sp)–H and C(sp<sup>2</sup>)–H bonds, methods for the transformation of unactivated C(sp<sup>3</sup>)–H bonds into C(sp<sup>3</sup>)–SCF<sub>3</sub> bonds have hardly been reported. Traditional methods for the synthesis of alkyl trifluoromethylthioethers through the functionalization of unactivated C(sp<sup>3</sup>)–H bonds with dangerous reagents, such as trifluoromethylthiol chloride, suffer from poor selectivity.<sup>[24]</sup> Recently, Qing and co-workers reported the copper-catalyzed trifluoromethylthiolation of benzylic C(sp<sup>3</sup>)–H bonds.<sup>[25]</sup> Although the reaction provides a straightforward method for the formation of benzyl trifluoromethyl sulfides, a large excess of the methyl arene was required. To date, no examples of transition-metal-catalyzed/mediated trifluoromethylthiolation reactions of unactivated C(sp<sup>3</sup>)–H bonds have been reported. Therefore, the development of general and practical methods for the trifluoromethylthiolation of unactivated aliphatic C(sp<sup>3</sup>)–H bonds is highly desirable.

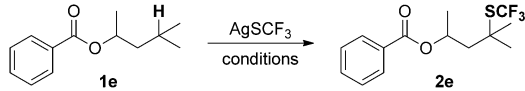
Herein, we report a practical and direct C(sp<sup>3</sup>)–H trifluoromethylthiolation method employing AgSCF<sub>3</sub> and Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> under mild conditions. AgSCF<sub>3</sub> was chosen as the trifluoromethylthiolation reagent owing to its ease of preparation and favorable stability.<sup>[26]</sup> We began our study by examining the reaction between 4-methyl-2-pentyl benzoate (**1e**) and AgSCF<sub>3</sub> as a model system to optimize the reaction conditions. After extensive screening, we found that when **1e** was subjected to AgSCF<sub>3</sub> and Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> in a mixture of acetonitrile, H<sub>2</sub>O, and DCE (6:2:1, v/v/v) at 35°C for ten hours in air, the trifluoromethylthiolated product **2e** could be isolated in 76%. As briefly illustrated in Table 1, various oxidants were evaluated, and Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> was found to give the highest yield (entries 7–9; see the Supporting Information for

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**Table 1:** Optimization of the reaction conditions.

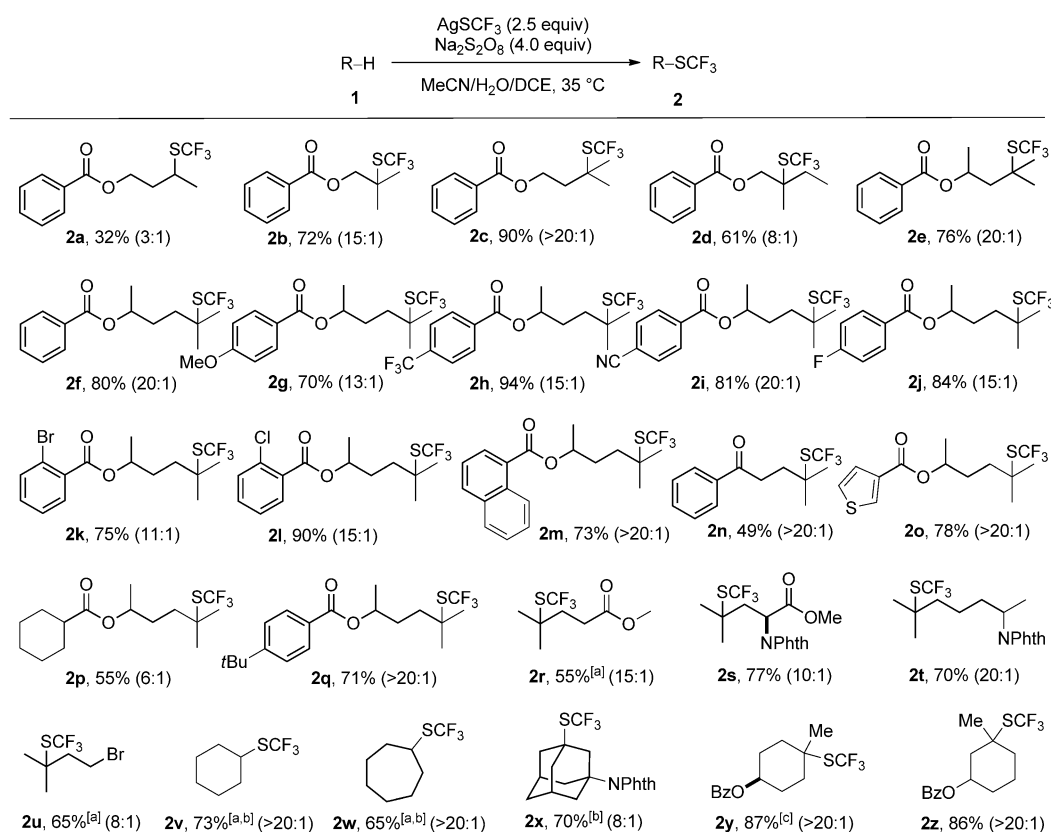
|  |                                                                                                          |                          |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------|
| Entry                                                                             | Conditions <sup>[a]</sup>                                                                                | Yield [%] <sup>[b]</sup> |
| 1                                                                                 | Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , MeCN                                                     | 22                       |
| 2                                                                                 | Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , H <sub>2</sub> O                                         | 0                        |
| 3                                                                                 | Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , DCE                                                      | 0                        |
| 4                                                                                 | Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , DMSO                                                     | 22                       |
| 5                                                                                 | Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , MeCN/H <sub>2</sub> O (3:1, v/v)                         | 74                       |
| 6                                                                                 | Na <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , DCE/H <sub>2</sub> O (3:1, v/v)                          | 0                        |
| 7                                                                                 | <b>Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, MeCN/H<sub>2</sub>O/DCE (6:2:1, v/v/v)</b>                  | <b>89</b>                |
| 8                                                                                 | (NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , MeCN/H <sub>2</sub> O/DCE (6:2:1, v/v/v) | 61                       |
| 9                                                                                 | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> , MeCN/H <sub>2</sub> O/DCE (6:2:1, v/v/v)                  | 0                        |
| 10                                                                                | MeCN/H <sub>2</sub> O/DCE (6:2:1, v/v/v)                                                                 | 0                        |

[a] All reactions were run at 35 °C with AgSCF<sub>3</sub> (2.5 equiv) and the indicated oxidant (4.0 equiv). [b] Yields were determined by <sup>19</sup>F NMR spectroscopy with 1-fluoro-3-nitrobenzene as the internal standard.

details). The addition of water also increased the reaction yield by improving the solubility of Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (entry 5). To prevent the oxidative decomposition of the starting materials and products, we reasoned that a biphasic system could physically separate the starting materials and products from the oxidant.<sup>[5d]</sup> Therefore, nonpolar solvents were investigated

as the third solvent in the reaction mixture, and DCE was found to further improve the yield (entry 7). The reaction gave the highest yield when conducted at 35 °C whereas a yield of 68 % was achieved for the reaction at 50 °C owing to the formation of larger amounts of side products. Furthermore, in the absence of Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, trifluoromethylthiolation products were not observed (entry 10). The amounts of AgSCF<sub>3</sub> and Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> were crucial for the reaction to proceed efficiently. After thorough optimization of the reaction conditions, reactions with 2.5 equivalents of AgSCF<sub>3</sub> and 4.0 equivalents of Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> were found to give the high yields of the desired product.

With the optimized reaction conditions in hand, a variety of simple molecules with multiple unactivated C(sp<sup>3</sup>)-H bonds were successfully converted into the corresponding trifluoromethylthiolated products with yields ranging from 32 % to 94 % (Scheme 2). A wide range of functional groups, such as ketones, ethers, esters, amides, aromatic nitriles, chlorides, fluorides, and bromides, were tolerated under the standard reaction conditions. Trifluoromethylthiolation was observed to occur selectively at methine or methylene positions that are remote from electron-withdrawing groups. For instance, the trifluoromethylthiolation of butyl benzoate (**1a**) led to the formation of a mixture of regioisomers in a combined yield of 80 % (as determined by NMR spectroscopy); the major isomer, **2a**, was isolated in 32 % yield. For substrates **2b–2z**, the regioisomeric products were formed in



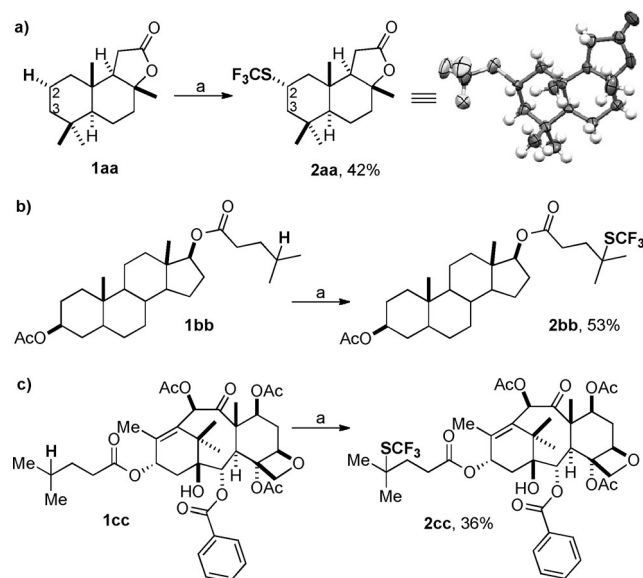
**Scheme 2.** Scope of the silver-mediated trifluoromethylthiolation. Yields of isolated products are given unless otherwise noted. The ratios of the shown products to other regioisomers were determined by <sup>19</sup>F NMR spectroscopy and are given in parentheses. [a] Yield determined by <sup>19</sup>F NMR spectroscopy with 1-fluoro-3-nitrobenzene as the internal standard. [b] Substrate (5.0 equiv). [c] 1:0.9 d.r. Bz = benzoyl, Phth = phthalimido.

less than 10% yield according to  $^{19}\text{F}$  NMR spectroscopy. In addition, a substrate with a heteroaromatic substituent (**1o**) afforded the corresponding trifluoromethylthiolated product in good yield. This method could also be applied to the trifluoromethylthiolation of an amino acid derivative and provided the corresponding product with high selectivity and in good yield (**2s**). An excess of starting material was employed for some substrates (**1v–1x**) as the polytrifluoromethylthiolation products were observed with one equivalent of substrate; the trifluoromethylthiolation yields for these substrates are based on the amount of  $\text{AgSCF}_3$  that was employed in these reactions. Moreover, the two diastereomers of **2y** were formed in a 1:0.9 ratio when *cis*-4-methyl-1-cyclohexanol benzoate (**1y**) was subjected to the standard reaction conditions, which is consistent with a reaction mechanism that involves either radical species or a carbocation. Furthermore, the reaction of **1i** could be carried out on gram scale under the standard reaction conditions and enabled the isolation of **2i** in 90% yield, which demonstrates both the scalability and practicality of this method.

Encouraged by our success with simple alkanes, more complex substrates were then investigated. To our delight, the trifluoromethylthiolation of the natural product sclareolide (**1aa**) proceeded under the standard reaction conditions to yield the corresponding product in 42% yield (yield of the major isomer, ca. 50% recovered starting material; Scheme 3a). The trifluoromethylthiolation did not occur at either of the two methine positions because of steric hindrance and the deactivation of these positions; instead, selective trifluoromethylthiolation was observed at the C2 methylene position, which is less sterically hindered.<sup>[27]</sup> Furthermore, other molecules derived from complex natural products were successfully trifluoromethylthiolated with our method. For instance, the transformation of a derivative of 5 $\alpha$ -androstan-

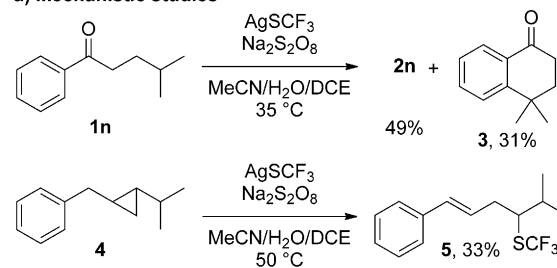
3 $\beta$ ,17 $\beta$ -diol gave the trifluoromethylthiolated product **2bb** in 53% yield (Scheme 3b). A derivative (**1cc**) of the anticancer drug taxol provided the corresponding trifluoromethylthiolated product **2cc** in 36% yield (ca. 50% recovered starting material; Scheme 3c). Trifluoromethylthiolation occurred selectively at the methine position on the side chain owing to steric hindrance and the deactivation of the available tertiary C–H bonds on the rings of these substrates (**1bb**, **1cc**).

To gain mechanistic insights into the trifluoromethylthiolation process, some preliminary studies were conducted. The trifluoromethylthiolated product was formed in less than 5% yield when a radical inhibitor, namely 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; 1 equiv each), was added. Whereas similar yields were achieved when the reaction was performed in air or under inert atmosphere in a 2 mL sealed vial, the yield decreased under  $\text{O}_2$  atmosphere, which is consistent with a free radical mechanism. Furthermore, trifluoromethylthiolated products were not observed when  $\text{CsSCF}_3$  or  $n\text{Bu}_4\text{NSCF}_3$  were used as the trifluoromethylthiolation reagents in the presence of silver salts (see the Supporting Information for details), which indicates that the reaction may not proceed through a carbocationic intermediate. Finally, cyclized product **3** was observed when ketone **1n** was used as the substrate under the standard reaction conditions, whereas cyclized products were not observed with esters **1b** and **1d**. Cyclopropane **4** was designed as a radical probe, and the ring-opening product **5** was indeed formed under the reaction conditions (Scheme 4a), which provides solid evidence for the intermediacy of carbon-centered radicals in the reaction. All of these observations support the hypothesis that a radical-chain mechanism or single-electron transfer (SET) may be involved in this transformation. Furthermore, monitoring of the reaction by  $^{19}\text{F}$  NMR spectroscopy showed that  $\text{CF}_3\text{SSCF}_3$  was generated in the reaction.<sup>[20b,28]</sup> When  $\text{CF}_3\text{SSCF}_3$  was used

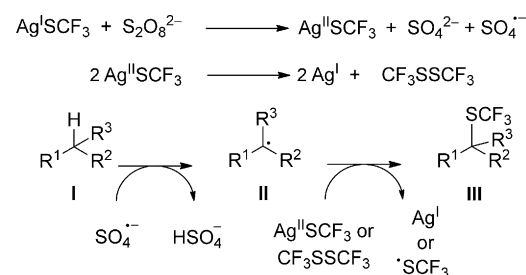


**Scheme 3.** Silver-mediated C(sp<sup>3</sup>)-H trifluoromethylthiolation reactions of natural products and natural-product derivatives. Reaction conditions: a)  $\text{AgSCF}_3$  (2.5 equiv),  $\text{Na}_2\text{S}_2\text{O}_8$  (4.0 equiv),  $\text{MeCN}/\text{H}_2\text{O}/\text{DCE}$ , 35 °C.

#### a) Mechanistic studies



#### b) Proposed mechanism



**Scheme 4.** a) Mechanistic studies. b) Proposed mechanism.

as the trifluoromethylthiolation reagent, the trifluoromethylthiolation product was formed in 38% yield in the presence of silver salts whereas no product was formed in the absence of silver salts (see the Supporting Information for details). To gain further insights into the reaction mechanism, the intermolecular kinetic isotope effect (KIE) was determined. A significant KIE ( $k_H/k_D = 3.8$ ) was observed in competition experiments using an excess amount of a 1:1 mixture of cyclohexane and  $[D_{12}]$ cyclohexane under the standard reaction conditions, which suggests that C–H bond cleavage might be involved in the rate-limiting step of this transformation.<sup>[29]</sup>

On the basis of these observations, a plausible mechanism is proposed (Scheme 4b). It is known<sup>[30]</sup> that peroxydisulfate anions disproportionate into sulfate dianions and sulfate radical anions in the presence of silver(I) salts. We hypothesized that carbon radical **II** is formed by oxidation with a sulfate radical anion.  $Ag^II$ SCF<sub>3</sub> or CF<sub>3</sub>SSCF<sub>3</sub>, which may be formed from  $Ag^II$ SCF<sub>3</sub> through single electron transfer,<sup>[20b]</sup> can then readily react with the generated carbon radical **II** to provide the desired trifluoromethylthiolated product **III**.<sup>[31]</sup>

In conclusion, we have reported the first silver-mediated trifluoromethylthiolation of unactivated aliphatic C–H bonds, which proceeds under mild conditions. The new method enables the functionalization of a variety of substrates, including natural products and amino acid derivatives. Furthermore, the reaction tolerates a wide range of functional groups and can be run on gram scale. Owing to its operational simplicity, this method could find wide applications in the synthesis of pharmaceutical and agrochemical compounds.

**Keywords:** C–H activation · fluorine · radicals · synthetic methods · trifluoromethylthiolation

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- [1] a) P. Jeschke, *ChemBioChem* **2004**, *5*, 570; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; c) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; e) R. Berger, G. Resnati, P. Metrangola, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496.
- [2] a) A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525; b) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; c) B. Manteau, S. Pazenok, J. P. Vors, F. R. Leroux, *J. Fluorine Chem.* **2010**, *131*, 140.
- [3] For selected reviews, see: a) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880; b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; *Angew. Chem.* **2013**, *125*, 8372; c) H. Liu, X. Jiang, *Chem. Asian J.* **2013**, *8*, 2546; d) X. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731.
- [4] For selected examples, see: a) F. Swarts, *Bull. Acad. R. Belg.* **1892**, *24*, 309; b) E. A. Nodiff, S. Lipschutz, P. N. Craig, M. Gordon, *J. Org. Chem.* **1960**, *25*, 60; c) T. Umemoto, S. Ishihara, *J. Am. Chem. Soc.* **1993**, *115*, 2156; d) I. Kietlsch, P. Eisenberger, A. Togni, *Angew. Chem. Int. Ed.* **2007**, *46*, 754; *Angew. Chem.* **2007**, *119*, 768; e) J. M. Kremsner, M. Rack, C. Pilger, C. O. Kappe, *Tetrahedron Lett.* **2009**, *50*, 3665; f) N. J. W. Straathof, B. J. P. Tegelbeckers, V. Hessel, X. Wang, T. Noël, *Chem. Sci.* **2014**, *5*, 4768.
- [5] For reviews, see: F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415; for selected examples, see: a) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem. Int. Ed.* **2009**, *48*, 8551; *Angew. Chem.* **2009**, *121*, 8703; b) K. P. Wang, S. Y. Yun, P. Mamidipalli, D. Lee, *Chem. Sci.* **2013**, *4*, 3205; c) M. Rueping, N. Tolstoluzhsky, P. Nikolaienko, *Chem. Eur. J.* **2013**, *19*, 14043; d) Q. Xiao, J. Sheng, Z. Chen, J. Wu, *Chem. Commun.* **2013**, *49*, 8647; e) F. Hu, X. Shao, D. Zhu, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 6105; *Angew. Chem.* **2014**, *126*, 6219; f) P. Nikolaienko, R. Pluta, M. Rueping, *Chem. Eur. J.* **2014**, *20*, 9867; g) Y. Huang, X. He, X. Lin, M. Rong, Z. Weng, *Org. Lett.* **2014**, *16*, 3284; h) K. Y. Ye, X. Zhang, L. X. Dai, S. L. You, *J. Org. Chem.* **2014**, *79*, 12106; i) J. B. Liu, X. H. Xu, Z. H. Chen, F. L. Qing, *Angew. Chem. Int. Ed.* **2015**, *54*, 897; *Angew. Chem.* **2015**, *127*, 911.
- [6] F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382; *Angew. Chem.* **2012**, *124*, 10528.
- [7] G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 7312; *Angew. Chem.* **2011**, *123*, 7450.
- [8] C. Zhang, D. A. Vicić, *J. Am. Chem. Soc.* **2012**, *134*, 183.
- [9] Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K. W. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1548; *Angew. Chem.* **2013**, *125*, 1588.
- [10] J. Xu, X. Mu, P. Chen, J. Ye, G. Liu, *Org. Lett.* **2014**, *16*, 3942.
- [11] C. Chen, Y. Xie, L. Chu, R. W. Wang, X. Zhang, F. L. Qing, *Angew. Chem. Int. Ed.* **2012**, *51*, 2492; *Angew. Chem.* **2012**, *124*, 2542.
- [12] C. P. Zhang, D. A. Vicić, *Chem. Asian J.* **2012**, *7*, 1756.
- [13] L. Zhai, Y. Li, J. Yin, K. Jin, R. Zhang, X. Fu, C. Duan, *Tetrahedron* **2013**, *69*, 10262.
- [14] a) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457; *Angew. Chem.* **2013**, *125*, 3541; b) X. Shao, T. Liu, L. Lu, Q. Shen, *Org. Lett.* **2014**, *16*, 4738.
- [15] R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 1650; *Angew. Chem.* **2014**, *126*, 1676.
- [16] G. Danoun, B. Bayarmagnai, M. F. Gruenberg, L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312.
- [17] M. Hu, J. Rong, W. Miao, C. Ni, Y. Han, J. Hu, *Org. Lett.* **2014**, *16*, 2030.
- [18] X. Wang, Y. Zhou, G. Ji, G. Wu, M. Li, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2014**, 3093.
- [19] Q. Lefebvre, E. Fava, P. Nikolaienko, M. Rueping, *Chem. Commun.* **2014**, *50*, 6617.
- [20] a) Y. Yang, X. Jiang, F. L. Qing, *J. Org. Chem.* **2012**, *77*, 7538; b) F. Yin, X. S. Wang, *Org. Lett.* **2014**, *16*, 1128; c) K. Zhang, J. B. Liu, F. L. Qing, *Chem. Commun.* **2014**, *50*, 14157.
- [21] C. Chen, L. Chu, F. L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454.
- [22] S. Alazet, L. Zimmer, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 10814; *Angew. Chem.* **2013**, *125*, 11014.
- [23] For selected examples, see: a) H. Bayreuther, A. Haas, *Chem. Ber.* **1973**, *106*, 1418; b) A. Kolasa, *J. Fluorine Chem.* **1987**, *36*, 29; c) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237; d) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160; e) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856; *Angew. Chem.* **2013**, *125*, 13093; f) X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 12860; *Angew. Chem.* **2013**, *125*, 13098; g) Y. D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782; h) C. Xu, Q. Shen, *Org. Lett.* **2014**, *16*, 2046; i) E. Vinogradova, P. Müller, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 3125; *Angew. Chem.* **2014**, *126*, 3189; j) W. Yin, Z. Wang, Y. Huang, *Adv. Synth. Catal.* **2014**, *356*, 2998; k) X. L. Zhu, J. H. Xu, D. J. Cheng, L. J. Zhao, X. Y. Liu, B. Tan, *Org. Lett.* **2014**, *16*, 2192; l) S. Alazet, L. Zimmer, T. Billard, *J. Fluorine Chem.* **2015**, *171*, 78; m) B. Ma, X. Shao, Q. Shen, J.

- Fluorine Chem.* **2015**, *171*, 73; n) Q. Wang, Z. Qi, F. Xie, X. Li, *Adv. Synth. Catal.* **2015**, 357, 355.
- [24] a) J. F. Harris, Jr., *J. Org. Chem.* **1966**, *31*, 931; b) A. Haas, W. Kortmann, *Z. Anorg. Allg. Chem.* **1983**, *501*, 79.
- [25] C. Chen, X. H. Xu, B. Yang, F. L. Qing, *Org. Lett.* **2014**, *16*, 3372.
- [26] a) V. V. Orda, L. M. Yagupolskii, V. F. Bystrov, A. U. Stepanyati, *Chem. Abstr.* **1965**, 63, 17861; b) J. H. Clark, C. W. Jones, A. P. Kybett, M. A. McClinton, J. M. Miller, D. Bishop, R. J. Blade, *J. Fluorine Chem.* **1990**, *48*, 249; see also Ref. [5b] and [6].
- [27] Sclareolide has recently been used as a substrate for a number of C–H functionalization methods; for selected examples, see: a) M. S. Chen, M. C. White, *Science* **2010**, 327, 566; b) W. Liu, J. T. Groves, *J. Am. Chem. Soc.* **2010**, *132*, 12847; c) W. Liu, X. Huang, M. J. Cheng, R. J. Nielsen, W. A. Goddard, J. T. Groves, *Science* **2012**, 337, 1322; d) C. W. Kee, K. M. Chan, M. W. Wong, C. H. Tan, *Asian J. Org. Chem.* **2014**, *3*, 536; e) S. Bloom, J. L. Knippel, T. Lectka, *Chem. Sci.* **2014**, *5*, 1175; f) J. B. Xia, Y. Ma, C. Chen, *Org. Chem. Front.* **2014**, *1*, 468; g) S. D. Halperin, H. Fan, S. Chang, R. E. Martin, R. Britton, *Angew. Chem. Int. Ed.* **2014**, *53*, 4690; *Angew. Chem.* **2014**, *126*, 4778; h) V. A. Schmidt, R. K. Quinn, A. T. Brusoe, E. J. Alexanian, *J. Am. Chem. Soc.* **2014**, *136*, 14389.
- [28] a) G. Haran, D. W. A. Sharp, *J. Chem. Soc. Perkin Trans. 1* **1972**, 34; b) R. E. A. Dear, E. E. J. Gilbert, *J. Fluorine Chem.* **1974**, *4*, 107.
- [29] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066; *Angew. Chem.* **2012**, *124*, 3120.
- [30] a) D. A. House, *Chem. Rev.* **1962**, *62*, 185; b) J. M. Anderson, J. K. Kochi, *J. Am. Chem. Soc.* **1970**, *92*, 1651; c) A. Kumar, P. Neta, *J. Am. Chem. Soc.* **1980**, *102*, 7284; d) S. Seo, J. B. Taylor, M. F. Greaney, *Chem. Commun.* **2012**, *48*, 8270.
- [31] It was previously suggested that Ag<sup>II</sup>X species are efficient radical halogenation reagents; for selected examples, see: a) Z. Wang, L. Zhu, F. Yin, Z. Su, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 4258; b) F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401; c) Z. Li, L. Song, C. Li, *J. Am. Chem. Soc.* **2013**, *135*, 4640; d) C. Zhang, Z. Li, L. Zhu, L. Yu, Z. Wang, C. Li, *J. Am. Chem. Soc.* **2013**, *135*, 14082; e) Z. Li, Z. Wang, L. Zhu, X. Tan, C. Li, *J. Am. Chem. Soc.* **2014**, *136*, 16439; f) Z. Li, C. Zhang, L. Zhu, C. Liu, C. Li, *Org. Chem. Front.* **2014**, *1*, 100; g) L. Zhu, H. Chen, Z. Wang, C. Li, *Org. Chem. Front.* **2014**, *1*, 1299.

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