

Direct Trifluoromethylthiolation of Unactivated C(sp³)–H Using Silver(I) Trifluoromethanethiolate and Potassium Persulfate**

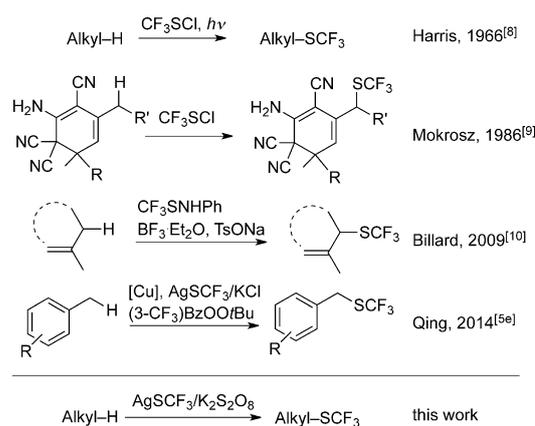
Hao Wu, Zhiwei Xiao, Junhui Wu, Yong Guo, Ji-Chang Xiao, Chao Liu,* and Qing-Yun Chen*

Abstract: A practical and efficient method for the direct trifluoromethylthiolation of unactivated C(sp³)–H bonds by AgSCF₃/K₂S₂O₈ under mild conditions is described. The reaction has a good functional-group tolerance and good selectivity. Initial mechanistic investigations indicate that the reaction may involve a radical process in which K₂S₂O₈ plays key roles in both the activation of the C(sp³)–H bond and the oxidation of AgSCF₃.

A trifluoromethylthio group (CF₃S) can significantly influence the chemical, physical, and biological properties of a parent substrate because of its strong electronegativity and high lipophilicity.^[1] Considerable efforts have thus been devoted to the development of methods to introduce this group into organic molecules. Two major strategies for the chemical introduction of trifluoromethylthio groups were developed: the direct formation of C–S bonds (R–SCF₃) and the trifluoromethylation of thiols and their derivatives (RS–CF₃).^[2] In recent years, several elegant methods have been reported for the electrophilic,^[3] nucleophilic,^[4] and oxidative direct trifluoromethylthiolation.^[5] These methods enable the fast and efficient synthesis of various CF₃S-containing compounds.

In comparison to the recent progress made in the formation of C(sp²)–SCF₃ or C(sp)–SCF₃ bonds, only few methods have been developed for the formation of C(sp³)–SCF₃ bonds. Besides the classical halogen–fluorine exchange of polyhalogenomethyl thioethers or the trifluoromethylation of sulfur-containing compounds,^[2] alkyltrifluoromethyl thioethers are mainly accessed by employing electrophilic^[3a,1,6] or nucleophilic^[7] trifluoromethylthiolation reagents. Although these methods efficiently lead to the desired alkyltrifluoro-

methylthioethers, they generally require prefunctionalized starting materials. From a preparative and atom-economical point of view, the direct trifluoromethylthiolation of an unactivated C(sp³)–H bond constitutes the most straightforward approach to alkyltrifluoromethylthioethers. However, only few synthetic methods have been reported thus far



Scheme 1. Previous reports on the direct trifluoromethylthiolation of unactivated C(sp³)–H bonds.

(Scheme 1). Harris first reported in 1966 the free-radical chain reaction of alkanes with the highly toxic gas trifluoromethanesulfonyl chloride (CF₃SCI).^[8] Although various trifluoromethylthiolated isomers were successfully obtained, the reaction showed a narrow substrate scope and poor selectivity. In 1986, Mokrosz reported the direct trifluoromethylthiolation of the allylic H atom in alkylidenemalononitrile dimers by reaction with CF₃SCI.^[9] In 2009, Billard and co-workers reported a method for the direct trifluoromethylthiolation of allylic H atoms of hindered olefins with the electrophilic reagent CF₃SNMePh.^[10] Very recently, Qing and co-workers disclosed the Cu-mediated direct trifluoromethylthiolation of a benzylic C–H bond.^[5e] Thus, the development of reagent systems that can efficiently trifluoromethylthiolate the unactivated C(sp³)–H bond under mild conditions is highly desirable.

On the other hand, unactivated C(sp³)–H bonds, especially those that are not adjacent to an sp²-hybridized C atom or a functional group that favors the formation of radicals or anions, exhibit the least reactivity, as they are less acidic and have no empty low-energy or filled high-energy orbitals that easily interact with orbitals of a metal center. Their selective functionalization under mild conditions represents a significant challenge and goal in modern synthetic chemistry.^[11] Recently, the direct fluorination of unactivated C(sp³)–H

[*] H. Wu, Z. Xiao, Prof. Dr. Y. Guo, Prof. Dr. J.-C. Xiao, Prof. Dr. C. Liu, Prof. Dr. Q.-Y. Chen
Key Laboratory of Organofluorine Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, 200032, Shanghai (China)
E-mail: chaoliu@sioc.ac.cn
chenqy@sioc.ac.cn

J. Wu
School of Chemical and Environmental Engineering
Shanghai Institute of Technology
100 Haiquan Road, Shanghai 201418 (China)

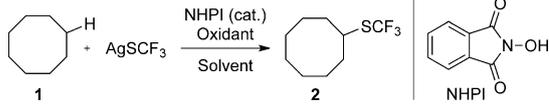
[**] The authors gratefully acknowledge the financial support from the National Basic Research Program of China (2012CB821600) and the National Natural Science Foundation of China (21032006, 21302207, 21421002).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201411953>.

bonds has received great interest and impressive progress has been made.^[12] Various C(sp³)-F bond-containing compounds were efficiently and readily produced, typically through a radical pathway involving the generation and trapping of alkyl radicals with fluorine-transfer reagents. These important advances inspired us to investigate the formation of C(sp³)-SCF₃ bonds through radical C(sp³)-H activation and functionalization.

In order to test our hypothesis, we chose cyclooctane **1** as the model substrate for the direct trifluoromethylthiolation of C(sp³)-H bonds. As radical initiator we used *N*-hydroxyphthalimide (NHPI), a precursor of the phthalimido-*N*-oxyl (PINO) radical and a well-known organocatalyst for the effective C(sp³)-H activation by hydrogen abstraction.^[13] For a CF₃S-transfer reagent system, we used AgSCF₃^[14] as the convenient CF₃S resource and K₂S₂O₈ as the oxidant.^[5 g] When a mixture of **1** (1 equiv), NHPI (0.1 equiv), AgSCF₃ (1.5 equiv), and K₂S₂O₈ (2 equiv) in CH₃CN was stirred at 60 °C under Ar atmosphere for 12 h, the desired mono-trifluoromethylthiolated product **2** was formed in 43 % yield along with some poly-trifluoromethylthiolated products, which were identified by their characteristic signals in ¹⁹F NMR spectroscopy and GC-MS mass spectrometry. Encouraged by this preliminary result, we optimized the reaction conditions (Table 1). When AgSCF₃ was used as the limiting reagent with 10 equiv of **1** under similar conditions, the desired mono-trifluoromethylthiolated product **2** was obtained in 82 % yield without the formation of any poly-trifluoromethylthiolated products (Table 1, entry 1). Later, we found that only a little excess of substrate (2 equiv) was required for the selective formation of the mono-trifluoromethylthiolated product, thus demonstrating the high efficiency of the reaction (Table 1, entry 2). The oxidant K₂S₂O₈ played an important role in the reaction, as no desired product was obtained in its absence or in the presence of other oxidants, such as NaIO₄, PhI(OAc)₂, Pb(OAc)₄ (Table 1, entries 3–5). A survey of the oxidant-to-substrate ratio showed that 2 equiv of K₂S₂O₈ gave the best yield (Table 1, entries 6 and 7). Among several common solvents that we screened, CH₃CN stood out as the best one and water was harmful for the reaction (Table 1, entries 8–13). A reaction temperature higher than 50 °C was required for an effective transformation, as no obvious conversion of AgSCF₃ was observed at lower temperatures (Table 1, entries 14–18). Interestingly, when the reaction was conducted at 50 °C, a longer reaction time (12 h) was required, as no reaction occurred within 4 h (Table 1, entry 16). Finally, the presence of the free silver cation was crucial for the reaction, because both the replacement of AgSCF₃ with CuSCF₃ and the addition of KCl (KCl/AgSCF₃ = 1:1) to the reaction mixture prevented the formation of the desired trifluoromethylthiolated product (Table 1, entries 19 and 20). To our surprise, the reaction proceeded smoothly in the absence of NHPI, which we originally considered as the key alkyl radical initiator (Table 1, entry 21). Based on these test reactions, the combination of AgSCF₃, K₂S₂O₈, and CH₃CN at 60 °C was established as the optimal conditions for the simple, mild, and efficient direct trifluoromethylthiolation of unactivated C(sp³)-H bonds.

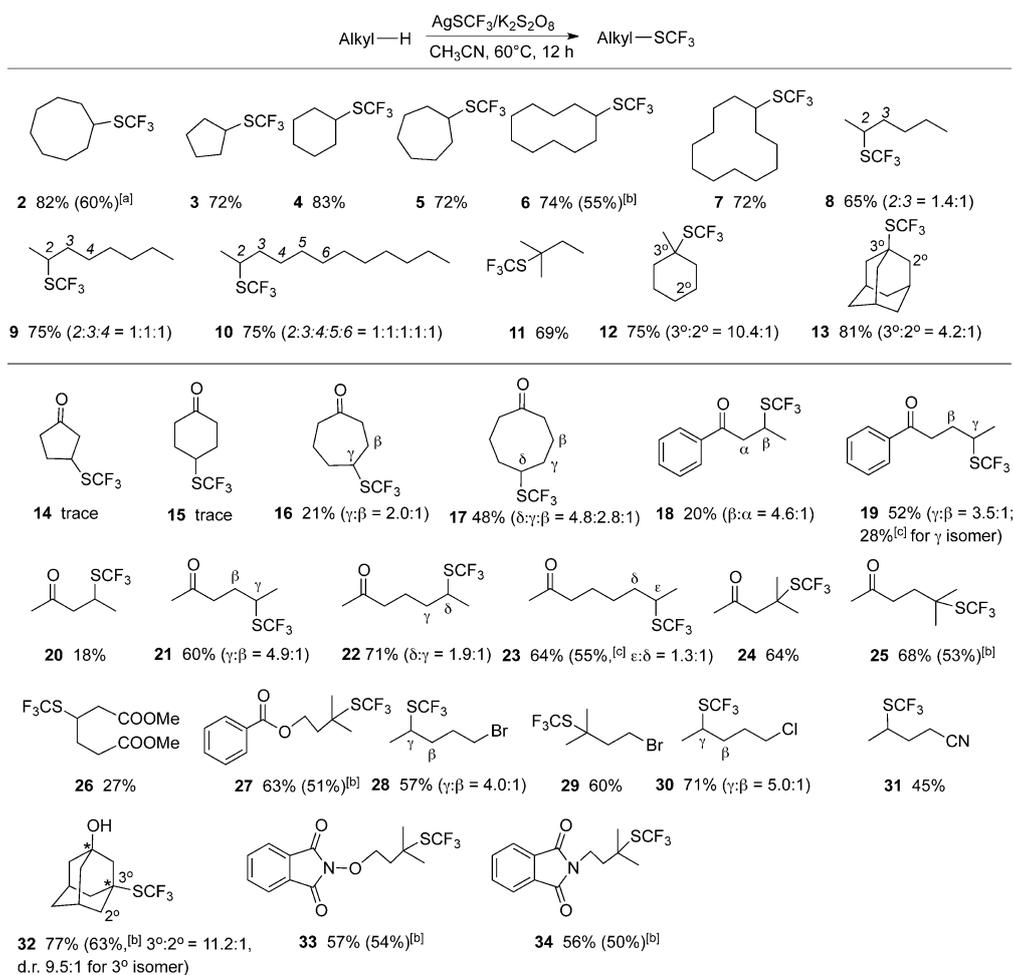
Table 1: Optimization of reaction conditions for trifluoromethylthiolation of cyclooctane.^[a]



Entry	Oxidant	Solvent	T [°C]	Yield [%] ^[b]
1 ^[c]	K ₂ S ₂ O ₈	CH ₃ CN	60	82
2	K ₂ S ₂ O ₈	CH ₃ CN	60	82
3	NaIO ₄	CH ₃ CN	60	0
4	PhI(OAc) ₂	CH ₃ CN	60	< 5
5	Pb(OAc) ₄	CH ₃ CN	60	0
6	K ₂ S ₂ O ₈ ^[d]	CH ₃ CN	60	74
7	K ₂ S ₂ O ₈ ^[e]	CH ₃ CN	60	48
8	K ₂ S ₂ O ₈	DMF	60	trace
9	K ₂ S ₂ O ₈	DMSO	60	8
10	K ₂ S ₂ O ₈	acetone	60	10
11	K ₂ S ₂ O ₈	ClCH ₂ CH ₂ Cl	60	0
12	K ₂ S ₂ O ₈	MeOH	60	0
13	K ₂ S ₂ O ₈	CH ₃ CN/H ₂ O ^[f]	60	< 5
14	K ₂ S ₂ O ₈	CH ₃ CN	40	0
15	K ₂ S ₂ O ₈	CH ₃ CN	50	80
16 ^[g]	K ₂ S ₂ O ₈	CH ₃ CN	50	0
17	K ₂ S ₂ O ₈	CH ₃ CN	70	81
18	K ₂ S ₂ O ₈	CH ₃ CN	80	79
19 ^[h]	K ₂ S ₂ O ₈	CH ₃ CN	60	0
20 ^[i]	K ₂ S ₂ O ₈	CH ₃ CN	60	0
21^[j]	K₂S₂O₈	CH₃CN	60	82

[a] Reaction conditions: cyclooctane (2.0 equiv), AgSCF₃ (0.2 mmol, 1.0 equiv), oxidant (2.0 equiv) and NHPI (0.1 equiv) in solvent (2 mL) under Ar atmosphere for 12 h. [b] Yields were determined by ¹⁹F NMR spectroscopy with trifluorotoluene as an internal standard. [c] Cyclooctane (10 equiv) was used. [d] K₂S₂O₈ (3.0 equiv) was used. [e] K₂S₂O₈ (1.0 equiv) was used. [f] The reaction was conducted in CH₃CN/H₂O (1:0.1 v/v). [g] Reaction time: 4 h. [h] CuSCF₃ (1.0 equiv) was used instead of AgSCF₃. [i] KCl (1.0 equiv) was added to the reaction. [j] No NHPI was used. The entry in bold marks optimized reaction conditions.

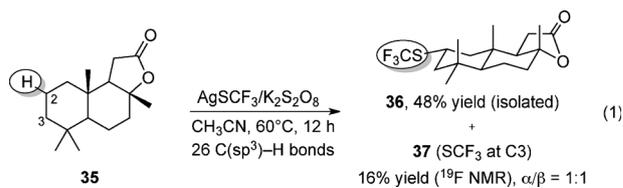
Various unactivated saturated hydrocarbons were then subjected to the optimized reaction conditions. All examined substrates were effectively transformed to the desired products in good yields (Scheme 2, **2–13**). The reaction also showed good site selectivity with preference for tertiary C-H bonds over secondary ones (**11–13**). The substrate scope of the reaction was investigated next. A variety of functional groups, such as ketones, esters, bromides, chlorides, alcohols, cyanates, and phthalimides, were well tolerated under the reaction conditions (**14–34**). Similarly, the direct C(sp³)-H trifluoromethylthiolation occurred predominantly at tertiary C-H bonds. Cyclopentanone and cyclohexanone were not suitable substrates for the reaction, as only trace amounts of the desired products were observed, however, the reaction of cycloheptanone and cyclooctanone successfully resulted in the desired products (**14–17**). Various acyclic ketones underwent the trifluoromethylthiolation to give the desired products in acceptable yields (**18–25**). Notably, although the α position of the carbonyl group is generally the most reactive site in ketones, α-CF₃S products were not the major products and were commonly formed in negligible yields, which might be ascribed to the strong polar effect exerted by the carbonyl group in the C(sp³)-H bond cleavage step in this reac-



Scheme 2. Scope of the direct trifluoromethylthiolation of various unactivated C(sp³)-H bonds. Reaction conditions: substrate (2.0 equiv), AgSCF₃ (0.2 mmol, 1.0 equiv), oxidant (2.0 equiv) in acetonitrile (2 mL) under Ar atmosphere for 12 h. Yields were determined by ¹⁹F NMR spectroscopy with trifluorotoluene as internal standard. The ratio of isomers was determined by ¹⁹F NMR spectroscopy or GC-MS. Yields of isolated products are given in parentheses. [a] 5.0 mmol scale. [b] 1.0 mmol scale. 2° = secondary carbon center, 3° = tertiary carbon center.

tion.^[13b,15] It should be mentioned that primary and secondary aliphatic alcohols could not be transformed in the reaction and no desired trifluoromethylthiolated products were observed, which might be due to the thermodynamically weaker C-H bond adjacent to the OH group. Indeed, when 1-adamantanol was used as the substrate, the trifluoromethylthiolation reaction proceeded smoothly to produce the desired trifluoromethylthiolated product in good yield (**32**). However, the reaction was not compatible with alkene and alkyne groups and a complicated reaction mixture was formed.

The possible scalability of the direct trifluoromethylthiolation of unactivated C(sp³)-H bonds was demonstrated by the reaction of cyclooctane on a 5 mmol scale. The reaction proceeded smoothly and led to the isolated product in 60% yield (Scheme 2, **2**). Furthermore, to show the potential of the reaction in late-stage synthetic planning, (+)-sclareolide (**35**), a terpenoid natural product with antifungal and cytotoxic properties, was subjected to the direct C(sp³)-H trifluoromethylthiolation [Eq. (1)]. Although **35** contains 26 aliphatic C(sp³)-H bonds, the C2-equatorial trifluoromethylthiolated



product **36** was isolated as the major product in 48% yield with minor amounts of product **37** (SCF₃ at C3). The structure of **36** was unambiguously determined by various analytical techniques, including X-ray single-crystal analysis (see the Supporting Information for details).

Some preliminary mechanistic studies on the direct trifluoromethylthiolation of C(sp³)-H bonds were conducted in order to gain some insights into the reaction pathway. First, kinetic isotope effects (KIE) were measured by using cyclooctane and [D₁₆]cyclooctane (1:1) as the substrates under the standard reaction conditions [Eq. (2)], affording an intermolecular competitive KIE of 3.3. This large KIE suggested that

- Chem.* **2013**, *125*, 1588; e) K.-P. Wang, S. Y. Yun, P. Mamidipalli, D. Lee, *Chem. Sci.* **2013**, *4*, 3205; f) M. Rueping, N. Tolstoluzhsky, P. Nikolaienko, *Chem. Eur. J.* **2013**, *19*, 14043; g) J. Xu, X. Mu, P. Chen, J. Ye, G. Liu, *Org. Lett.* **2014**, *16*, 3942; h) Q. Xiao, J. Sheng, Q. Ding, J. Wu, *Eur. J. Org. Chem.* **2014**, 217; i) G. Danoun, B. Bayarmagnai, M. F. Gruenberg, L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312; j) B. Bayarmagnai, C. Matheis, E. Risto, L. J. Goossen, *Adv. Synth. Catal.* **2014**, *356*, 2343.
- [5] a) L. Chu, F.-L. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513; b) 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; c) C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454; d) S.-Q. Zhu, X.-H. Xu, F.-L. Qing, *Eur. J. Org. Chem.* **2014**, 4453; e) C. Chen, X.-H. Xu, B. Yang, F.-L. Qing, *Org. Lett.* **2014**, *16*, 3372; f) C.-P. Zhang, D. A. Vivic, *Chem. Asian J.* **2012**, *7*, 1756; g) F. Yin, X.-S. Wang, *Org. Lett.* **2014**, *16*, 1128; h) X.-L. Zhu, J.-H. Xu, D.-J. Cheng, L.-J. Zhao, X.-Y. Liu, B. Tan, *Org. Lett.* **2014**, *16*, 2192.
- [6] Recent and selected examples: a) S. Alazet, L. Zimmer, T. Billard, *Chem. Eur. J.* **2014**, *20*, 8589; b) F. Hu, X. Shao, D. Zhu, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 6105; *Angew. Chem.* **2014**, *126*, 6219; c) X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 12860; *Angew. Chem.* **2013**, *125*, 13098; d) X. Shao, T. Liu, L. Lu, Q. Shen, *Org. Lett.* **2014**, *16*, 4738; e) Q.-H. Deng, C. Rettenmeier, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2014**, *20*, 93; f) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856; *Angew. Chem.* **2013**, *125*, 13093; g) M. Rueping, X. Liu, T. Bootwicha, R. Pluta, C. Merckens, *Chem. Commun.* **2014**, *50*, 2508.
- [7] Recent and representative examples: a) Q. Lefebvre, E. Fava, P. Nikolaienko, M. Rueping, *Chem. Commun.* **2014**, *50*, 6617; b) M. Hu, J. Rong, W. Miao, C. Ni, Y. Han, J. Hu, *Org. Lett.* **2014**, *16*, 2030; c) X. Wang, Y. Zhou, G. Ji, G. Wu, M. Li, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2014**, 3093; d) D. Kong, Z. Jiang, S. Xin, Z. Bai, Y. Yuan, Z. Weng, *Tetrahedron* **2013**, *69*, 6046; e) J. Tan, G. Zhang, Y. Ou, Y. Yuan, Z. Weng, *Chin. J. Chem.* **2013**, *31*, 921; f) Z. Wang, Q. Tu, Z. Weng, *J. Organomet. Chem.* **2014**, *751*, 830; g) P. Zhu, X. He, X. Chen, Y. You, Y. Yuan, Z. Weng, *Tetrahedron* **2014**, *70*, 672; h) Q. Lin, L. Chen, Y. Huang, M. Rong, Y. Yuan, Z. Weng, *Org. Biomol. Chem.* **2014**, *12*, 5500; i) Y. Huang, X. He, X. Lin, M. Rong, Z. Weng, *Org. Lett.* **2014**, *16*, 3284; j) M. Rong, D. Li, R. Huang, Y. Huang, X. Han, Z. Weng, *Eur. J. Org. Chem.* **2014**, 5010; k) P. Nikolaienko, R. Pluta, M. Rueping, *Chem. Eur. J.* **2014**, *20*, 9867; l) S.-G. Li, S. Z. Zard, *Org. Lett.* **2013**, *15*, 5898; m) K. Zhang, J.-B. Liu, F.-L. Qing, *Chem. Commun.* **2014**, *50*, 14157; n) J.-B. Liu, X.-H. Xu, Z.-H. Chen, F.-L. Qing, *Angew. Chem. Int. Ed.* **2015**, *54*, 897; *Angew. Chem.* **2015**, *127*, 911.
- [8] J. F. Harris, Jr., *J. Org. Chem.* **1966**, *31*, 931.
- [9] M. J. Mokrosz, *J. Fluorine Chem.* **1986**, *34*, 201.
- [10] A. Ferry, T. Billard, B. R. Langlois, E. Bacque, *Angew. Chem. Int. Ed.* **2009**, *48*, 8551; *Angew. Chem.* **2009**, *121*, 8703.
- [11] For selected reviews on C(sp³)-H activation, see: a) J. Schranck, A. Tlili, M. Beller, *Angew. Chem. Int. Ed.* **2014**, *53*, 9426; *Angew. Chem.* **2014**, *126*, 9580; b) M. C. White, *Science* **2012**, *335*, 807; c) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; d) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937; e) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; f) A. A. Fokin, P. R. Schreiner, *Adv. Synth. Catal.* **2003**, *345*, 1035.
- [12] For recent reviews on C(sp³)-H bond fluorination, see: a) A. Lin, C. B. Huehls, J. Yang, *Org. Chem. Front.* **2014**, *1*, 434; b) J.-A. Ma, S. Li, *Org. Chem. Front.* **2014**, *1*, 712; c) M. P. Sibi, Y. Landais, *Angew. Chem. Int. Ed.* **2013**, *52*, 3570; *Angew. Chem.* **2013**, *125*, 3654.
- [13] For selected reviews on NHPI-catalyzed reactions, see: a) Y. Ishii, S. Sakaguchi, T. Iwahama, *Adv. Synth. Catal.* **2001**, *343*, 393; b) F. Recupero, C. Punta, *Chem. Rev.* **2007**, *107*, 3800; c) S. Coseri, *Catal. Rev.* **2009**, *51*, 218–292.
- [14] Silver(I) trifluoromethanethiolate was prepared according to Ref. [4a]. Its exact molecular formula is 3 AgSCF₃·CH₃CN, and it was unambiguously characterized by X-ray crystal and elemental analysis. For simplicity, we used AgSCF₃ instead of 3 AgSCF₃·CH₃CN in the text. For details, see the Supporting Information.
- [15] R. J. O'Reilly, B. Chan, M. S. Taylor, S. Ivanic, G. B. Bacskay, C. J. Easton, L. Radom, *J. Am. Chem. Soc.* **2012**, *134*, 10401.
- [16] N. Merbouh, J. M. Bobbitt, C. Brückner, *Org. Prep. Proced. Int.* **2004**, *36*, 1–31.
- [17] N. Basicckes, T. E. Hogan, A. Sen, *J. Am. Chem. Soc.* **1996**, *118*, 13111.
- [18] F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401.

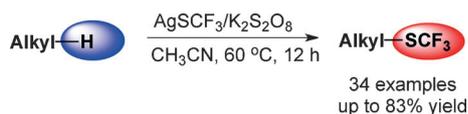
Communications



C–H Activation

H. Wu, Z. Xiao, J. Wu, Y. Guo, J.-C. Xiao,
C. Liu,* Q.-Y. Chen* ——— ■■■■–■■■■

Direct Trifluoromethylthiolation of
Unactivated C(sp³)–H Using Silver(I)
Trifluoromethanethiolate and Potassium
Persulfate



Direct and mild: A variety of alkyl-trifluoromethylthioethers were efficiently synthesized by direct trifluoromethylthiolation of unactivated C(sp³)–H bonds under mild reaction conditions. The reagent system comprises AgSCF₃

and K₂S₂O₈, the latter of which both activates the C(sp³)–H bond and oxidizes AgSCF₃. The reaction has a broad substrate scope with good functional-group tolerance and good selectivity.