

Synthetic Methods

N-Trifluoromethylthiosaccharin: An Easily Accessible, Shelf-Stable, Broadly Applicable Trifluoromethylthiolating Reagent**

Chunfa Xu, Bingqing Ma, and Qilong Shen*

Abstract: A new, electrophilic trifluoromethylthiolating reagent, *N*-trifluoromethylthiosaccharin, was developed and can be synthesized in two steps from saccharin within 30 minutes. *N*-trifluoromethylthiosaccharin is a powerful trifluoromethylthiolating reagent and allows the trifluoromethylthiolation of a variety of nucleophiles such as alcohols, amines, thiols, electron-rich arenes, aldehydes, ketones, acyclic β -ketoesters, and alkynes under mild reaction conditions.

As one of the most lipophilic structural moieties, the trifluoromethylthio group (CF_3S) has attracted special interests from both academia and the pharmaceutical industry.^[1] Incorporation of the trifluoromethylthio group into leading drug candidates has become an indispensable strategy for drug discovery, thus resulting in a growing demand which challenges chemists to provide reliable methods for the introduction of this highly valued structural component.^[2,3]

One general strategy for the formation of trifluoromethylthiolated compounds is the trifluoromethylation of thiols and their derivatives, and significant progress has been achieved previously.^[2] An alternate attractive and straightforward route for the incorporation of the CF_3S moiety is the direct introduction of this functional group at the late stage of a multistep synthetic sequence by employing an easily available yet stable CF_3S reagent.^[2] This strategy is particularly important for those nonspecialized laboratories since it does not require specific skills and use of protective clothing and/or equipment. However, until recently, the choice of electrophilic trifluoromethylthiolating reagents was undeniably limited and their access relatively difficult.

The first and simplest electrophilic trifluoromethylthiolating reagent was trifluoromethylsulfonyl chloride (CF_3SOCl).^[4] Although it reacts with a variety of nucleophiles, the gaseous and toxic nature of the reagent restricts its further utilization.^[5] *N*-Trifluoromethylthiophthalimide (**1**; Figure 1),^[6] which was originally prepared from phthalimide and CF_3SCl , now can be accessed by reactions of *N*-chloro- or *N*-bromophthalimide with CuSCF_3 or AgSCF_3 .^[6d,e] Never-

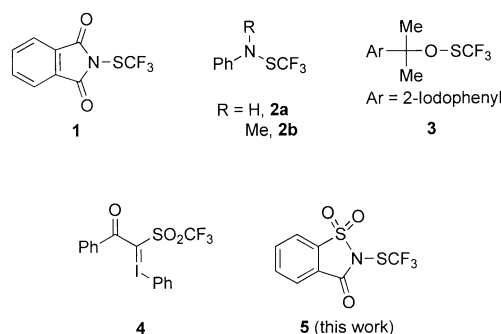


Figure 1. Electrophilic trifluoromethylthiolating reagents.

theless, its synthetic applications are rather limited. Since 2008, three different electrophilic trifluoromethylthiolating reagents emerged as a potentially valuable replacement to CF_3SCl . Billard and co-workers reported the preparation of the trifluoromethanesulfanylamides **2** from DAST, CF_3SiMe_3 , and primary amines. As one of the leading trifluoromethylthiolating reagents, **2** is effective for trifluoromethylthiolation of alkenes, alkynes, amines, indoles, and Grignard or lithium reagents,^[7] although a strong Lewis acid or Brønsted acid as activator is generally required. In early 2013, Shen and Lu reported the trifluoromethyl-substituted thioperoxide reagent **3** which could trifluoromethylthiolate a variety of substrates such as aryl and vinyl boronic acids, alkynes, aldehydes, and β -ketoesters.^[8] However, the preparation of the reagent requires a multistep sequence. Shortly after, Shibata and co-workers designed and synthesized a new electrophilic trifluoromethylthiolating reagent (**4**), a trifluoromethanesulfonyl hypervalent iodonium ylide, which reacted only with enamines, indoles, and two examples of β -ketoesters, through an in situ reduction process.^[9] Thus, development of a readily accessible, easy-to-handle, electrophilic trifluoromethylthiolating reagent, which is effective for a broad substrate scope under relatively mild reaction conditions, is highly desirable.

Herein, we report the design and synthesis of the *N*-trifluoromethylthiosaccharin (**5**), which can be efficiently synthesized from commercially available *N*-chlorosaccharin or through a two-step process from saccharin, a readily available, low-cost commodity. The superior reactivity of **5** was further demonstrated by trifluoromethylthiolation a variety of nucleophiles such as alcohols, amines, thiols, and electron-rich arenes, aldehydes, ketones, and acyclic β -ketoesters under mild reaction conditions. The fast rates, broad scope, and tolerance of functionality of these trifluoromethylthiolation reactions made **5** very attractive as a general

[*] C.-F. Xu, B.-Q. Ma, Prof. Dr. Q. Shen

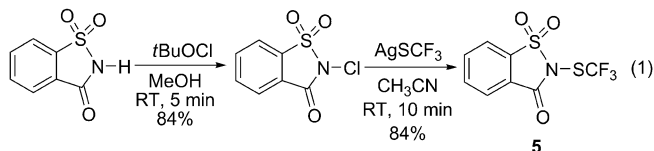
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
E-mail: shenql@sioc.ac.cn

[**] The authors gratefully acknowledge the financial support from National Basic Research Program of China (2012CB821600), the Key Program of Natural Science Foundation of China (21032006), National Natural Science Foundation of China (21172245/21172244/21372247) and SIOC for financial support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201403983>.

reagent which will allow rapid incorporation of CF_3S into small molecules.

N-trifluoromethylthiosaccharin (**5**) is easily synthesized from the reaction of *N*-chlorosaccharin with AgSCF_3 in CH_3CN for 10 minutes at room temperature, and is isolated in 84 % yield. Alternatively, it could be prepared by a two-step procedure, as shown in Equation (1). Treatment of saccharin



with *tert*-butyl hypochlorite in methanol at room temperature for 5 minutes generates *N*-chlorosaccharin,^[10] which was then reacted with AgSCF_3 in CH_3CN for 10 minutes to form **5** in 86 % yield, as determined by ^{19}F NMR spectroscopy. The reaction can be easily scaled up to 6.0 grams and **5** was isolated as a white solid in 84 % yield. The compound **5** was characterized by ^1H , ^{13}C , and ^{19}F NMR spectroscopy and elemental analysis. The structure of **5** was unambiguously confirmed by single-crystal X-ray analysis (see the Supporting Information for details).^[17]

The compound **5** is a highly stable, crystalline compound. No detectable decomposition was observed after storage for more than one month at ambient temperature. It is stable in solvents such as CH_2Cl_2 , $\text{ClCH}_2\text{CH}_2\text{Cl}$, toluene, and CH_3CN at room temperature for at least 12 hours as determined by ^{19}F NMR spectroscopy, and is less stable in THF as roughly 60 % of **5** was converted into $\text{CF}_3\text{S-SCF}_3$ after 48 hours at room temperature. The compound **5** is not stable in more polar solvents such as DMF and DMSO. It was completely decomposed after 5 minutes in DMSO and after 10 hours in DMF at room temperature as determined by ^{19}F NMR spectroscopy.

With this new reagent in hand, we then explored the reactivity of **5** with a variety of nucleophiles. Reaction of 2-(naphthalen-2-yl)ethanol with **5** in the presence of 2.3 equivalents of triethylamine gave a quantitative yield of the CF_3 -substituted thioperoxide^[11] after 5 minutes at room temperature (Figure 2). In contrast, when **1** was employed, only 12 % yield of product was detected and no improvement was observed with elongated reaction time (12 h). Three other reagents, **2–4**, which have shown to be active for electrophilic trifluoromethylthiolation for various substrates, each gave less than 2 % of the desired product. These results show that **5** displays remarkably increased reactivity compared to other trifluoromethylthiolating reagents. The increased reactivity of **5** compared to that of its analogue **1**, is likely due to the stronger electron-withdrawing property of the sulfonyl group as compared to that of a carbonyl group.

As shown in Scheme 1, **5** could trifluoromethylthiolate a variety of alcohols. Primary, secondary, and tertiary alcohols were readily converted into trifluoromethyl-substituted thioperoxides in excellent yields within 5 minutes. Functional groups such as esters, ketones, halides, and alkenes were

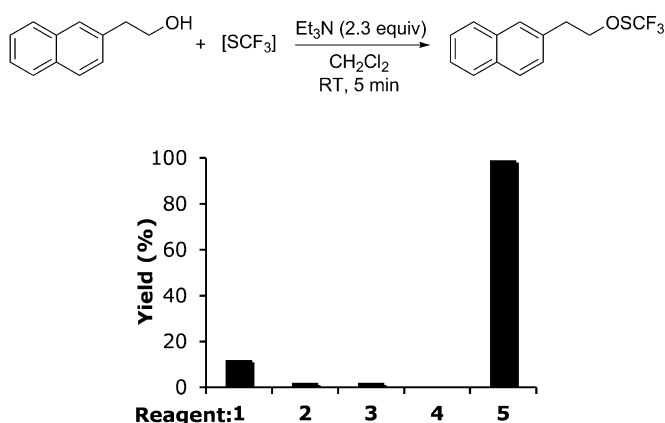
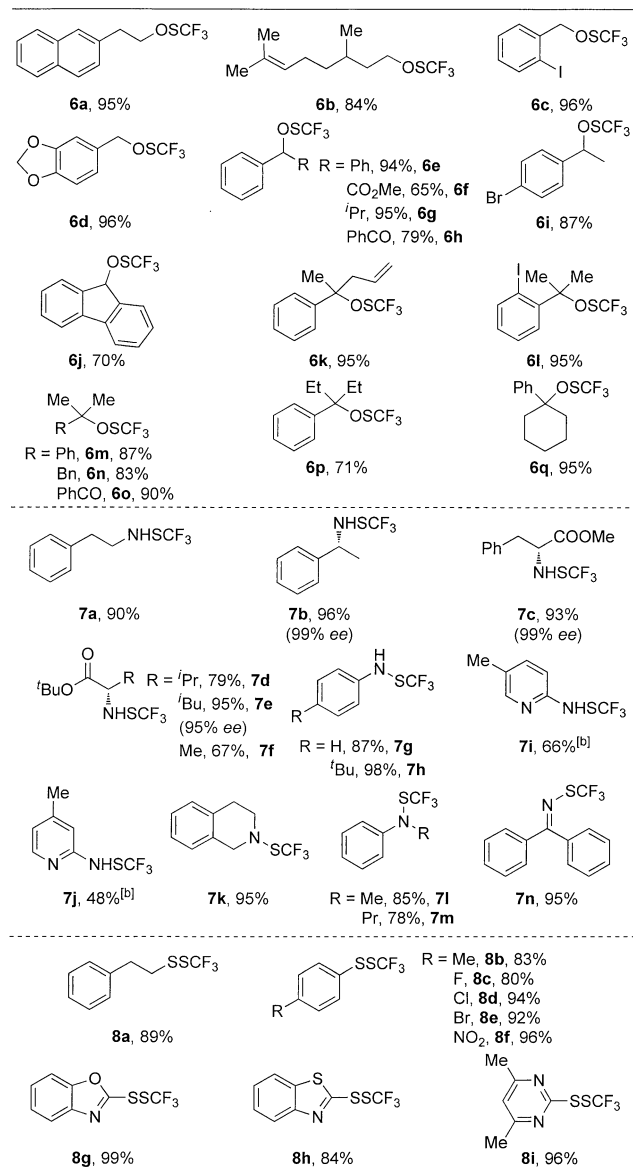


Figure 2. Results observed for reaction of 2-(naphthalen-2-yl)ethanol with the reagents **1–5**.

tolerated under standard reaction conditions (**6b–c**, **6f**, **6h–i**, **6k–l**, **6o**). Notably, **6l**, which was previously developed in our group as a trifluoromethylthiolating reagent (reagent **3** in Figure 1) in moderate yields by a multistep synthesis, can now be obtained in 95 % in one step within 5 minutes.^[8a] The structure of **3** was recently established as a trifluoromethyl-substituted thioperoxide by Buchwald and co-workers through a combination of spectroscopic techniques, derivatization experiments, and the crystal sponge method.^[8b]

Not only alcohols but also amines could be expediently trifluoromethylthiolated under mild reaction conditions.^[7a,j,12] Reactions of various primary or secondary alkyl amines and arylamines with **5** proceeded in high yields after 1 hour at room temperature (Scheme 1). Billard's reagents **7g** and **7l** (reagents **2a** and **2b** in Figure 1), could also be accessed from **5** in excellent yields. Optically pure alkylamines including α -aminoesters were readily converted into the trifluoromethylthiolated amines in excellent yields without erosion of the enantioselectivity (**7b–c**, **7e**). Even an imine could be trifluoromethylthiolated in good yield under these reactions conditions (**7n**). The compound **7n** has been previously synthesized from the trifluoromethanesulfenamide **2a** under the basic conditions.^[7j] Reactions of hetaryl amines, however, were extremely slow. Billard has shown that Lewis acids such as TiCl_4 , SnCl_4 , and ClSiMe_3 could activate **2** for trifluoromethylthiolation of olefins.^[7b] Inspired by these results, we found that when Me_3SiCl was used as an activator, the reaction of hetaryl amines with **5** occurred in acceptable yields of the desired products after 8 hours at 60 °C (**7i–j**). Previously reported methods for the preparation of trifluoromethylthiolated amines required either the use of DAST,^[7a] CF_3SCl , or the presence of 1.1 equivalents of *n*BuLi as the base.^[7j]

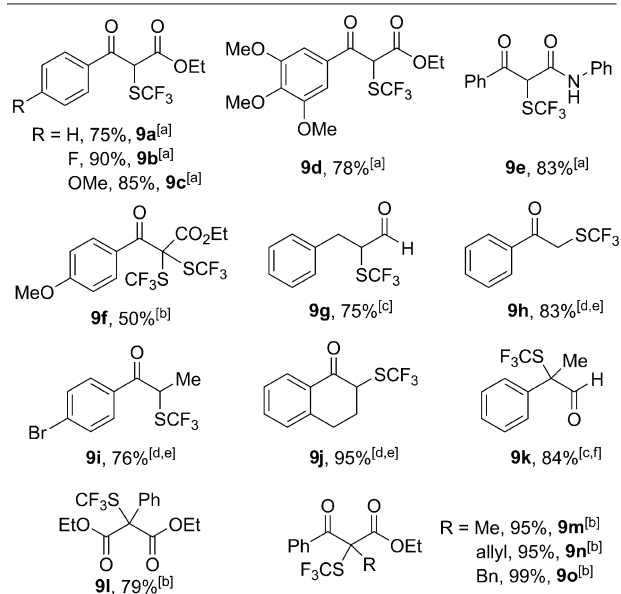
Encouraged by the superior performance of **5** compared to that of other trifluoromethylthiolating reagents, we further studied the reaction of thiols with **5**. Reactions of **5** with a variety of aryl and heteroaryl thiols occurred in excellent yields. Common functional groups such as fluoride, chloride, bromide, and nitro were tolerated under the optimized reaction conditions (Scheme 1; **8c–f**). Alkylthiol also reacted with **5** to provide the desired product in good yield (**8a**). A



Scheme 1. Trifluoromethylthiolation of alcohols, amines, and thiols with **5** under mild reaction conditions. Yields are those of the isolated products. Reaction conditions for alcohols: alcohol (0.3 mmol), **5** (0.39 mmol), Et₃N (100 μ L, 2.3 equiv), CH₂Cl₂ (6.0 mL), room temperature 5 min. Reaction conditions for amines: amine (0.30 mmol), **5** (0.30–0.39 mmol), CH₂Cl₂ (6 mL), room temperature, 0.5–1 h. Reaction conditions for thiols: thiol (0.3 mmol), **5** (0.30–0.39 mmol), CH₂Cl₂ (6.0 mL), room temperature, 1 h. [a] Me₃SiCl (1.3 equiv) was added as additive, ClCH₂CH₂Cl was used as solvent, 60 °C for 8 h.

previously known method for the preparation of aryl trifluoromethylthiolates involved the use of highly toxic CF₃SCl or CF₃SSCF₃.^[13] Thus, this method provided a straightforward route for the preparation of a family of potentially useful trifluoromethylthiolated disulfides.

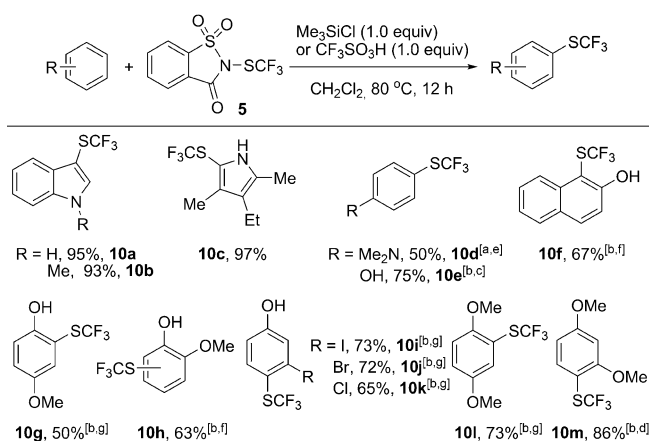
The incorporation of a CF₃S moiety through the mono-trifluoromethylthiolation of acyclic β -keto esters using trifluoromethylthiolating reagents other than CF₃SCl is quite challenging.^[14] The reaction of acyclic β -keto esters with **3** in



Scheme 2. Trifluoromethylthiolation of β -keto esters, aldehydes and ketones with **5** under mild reaction conditions. Yields are those of the isolated products. [a] Reaction conditions: β -keto ester (0.3 mmol), NaH (0.33 mmol), **5** (0.39 mmol), THF (2.0 mL), 0 °C, 30 min. [b] Reaction conditions: β -keto ester (0.3 mmol), **5** (0.66 mmol), DMAP (1.26 mmol), toluene (6.0 mL), room temperature, 8 h. [c] Reaction conditions: Aldehyde (0.3 mmol), **5** (0.36 mmol), morpholine hydrochloride (30 mol %), CH₂Cl₂ (6.0 mL), 30 °C, 12 h. [d] Reaction conditions: Ketone (0.3 mmol), **5** (0.45 mmol), morpholine hydrochloride (30 mol %), CH₂CN (6.0 mL), 80 °C, 12 h. [e] Me₃SiCl (0.45 mmol) was added. [f] 60 °C, 12 h.

the presence of 4-dimethylaminopyridine (DMAP) as a base results in a complex mixture.^[8a] One example of mono-trifluoromethylthiolation of acyclic β -keto esters was reported recently by Shibata and co-workers. However, the reaction occurred only in 48 % yield.^[9] It was found that reactions of acyclic β -keto esters with **5** occurred to afford the mono-trifluoromethylthiolated β -keto esters after 0.5 hours at 0 °C when NaH was used as the base (Scheme 2; **9a–d**). Likewise, acyclic β -ketoamide also underwent mono-trifluoromethylthiolation in good yield (**9e**). Interestingly, a ditrifluoromethylthiolated β -keto ester was formed when DMAP was used as the base (**9f**). Reactions of α -substituted acyclic β -keto esters or malonates with **5** occurred smoothly at room temperature to give the trifluoromethylthiolated products in excellent yields (**9i–o**). Reactions of aldehydes and ketones were much less effective when the reactions were conducted using NaH as the base. Only 23 % yield of the corresponding trifluoromethylthiolated aldehyde was observed for reaction of 2-phenylpropanal using DMAP as the base. Interestingly, reactions of aldehydes and ketones with **5** generated monotrifluoromethylthiolated products when morpholine hydrochloride was used as the catalyst (**9g–k**).

Since **5** was effective for trifluoromethylthiolation of different nucleophiles, we next evaluated the direct electrophilic trifluoromethylthiolation of arenes.^[7c,13c,15] As shown in Scheme 3, a variety of electron-rich arenes reacted with **5** to

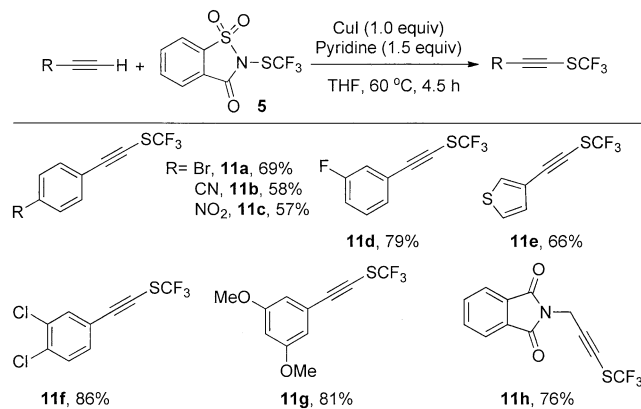


Scheme 3. Trifluoromethylthiolation of electron-rich arenes with **5** [a] Reaction conditions: arene (0.3 mmol), **5** (0.36–0.45 mmol), Me₃SiCl (36 μ L, 0.30 mmol), CH₂Cl₂ (6.0 mL), room temperature, 30 min. Yields are those of the isolated products. [b] CF₃SO₃H (24 μ L, 0.30 mmol) was added as additive instead of Me₃SiCl. [c] 60 °C for 8 h. [d] Room temperature, 4 h. [e] **5** (0.45 mmol), Me₃SiCl (54 μ L, 0.45 mmol), CH₃CN (6.0 mL), 60 °C, 18 h. [f] 80 °C, 18 h. [g] 80 °C, 36 h.

give the corresponding trifluoromethylthiolated products in good to excellent yields when either Me₃SiCl or triflic acid was used as an activator. For example, reactions of phenol and *N,N*-dimethylaniline gave exclusively the *para*-trifluoromethylthiolated products in good yields (**10d,e**). Similarly, reaction of 2-naphthanol produced 1-trifluoromethylthiolated-2-naphthanol in 67% yield. Notably, 3-chloro-, 3-bromo-, and 3-iodophenol were also converted effectively into trifluoromethylthio-substituted arenes in reasonable yields (**10i–k**). These compounds are of interest since many transition metal catalyzed cross-coupling reactions have been reported, thus allowing additional functional-group transformations.^[16]

To further extend the synthetic utility of **5**, we studied the trifluoromethylthiolation of alkynes. After a quick screening of the reaction conditions, it was found that reaction of 1-ethynyl-3-fluorobenzene with **5**, conducted with a combination of 2.0 equivalents of CuI and 3.0 equivalents of pyridine as the catalyst in THF, resulted in full conversion into the trifluoromethylthiolated alkyne in 79% yield. A variety of the terminal alkynes with functional groups such as nitro, cyano, fluoride, chloride, bromide, and amide can be transformed into their corresponding alkynyl trifluoromethyl sulfides in good yields (Scheme 4; **11a–d**, **11f**, **11h**). The reaction conditions for the trifluoromethylthiolation of alkynes were not as efficient as those previously reported.^[3h,7f–h,8a] Nevertheless, these results demonstrated the broad reaction scope of **5**.

In summary, a new electrophilic *N*-trifluoromethylthiosaccharin (**5**) for direct trifluoromethylthiolation has been developed. The reagent **5** can be efficiently synthesized in two steps and is effective for the direct transfer of the CF₃S group to various substrates such as alcohols, amines, thiols, β -ketoesters, aldehydes, ketones, electron-rich arenes, and alkynes under mild reaction conditions. The ready availabil-



Scheme 4. Copper-mediated trifluoromethylthiolation of alkynes. Reaction conditions: alkyne (0.6 mmol), **5** (0.30 mmol), CuI (0.60 mmol), pyridine (72 μ L, 0.90 mmol), THF (2.0 mL), 60 °C, 4.5 h. Yields are those of the isolated products.

ity, ease of handling, and high activity makes **5** very attractive as a general electrophilic reagent for the synthesis of a variety of CF₃S-containing molecules. Studies on the expansion of the scope of this reagent are underway and will be reported shortly.

Received: April 3, 2014

Revised: May 26, 2014

Published online: July 7, 2014

Keywords: electrophilic substitution · fluorine · NMR spectroscopy · sulfur · synthetic methods

- a) A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525; b) R. Filler, *Biomedical Aspects of Fluorine Chemistry*, Kodansha, Tokyo, **1982**; c) L. M. Yagupolskii, A. Y. Ilchenko, N. V. Kondratenko, *Russ. Chem. Rev.* **1974**, *43*, 32; d) C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165.
- a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; b) B. Manteau, S. Pazenok, J.-P. Vors, F. R. Leroux, *J. Fluorine Chem.* **2010**, *131*, 140; c) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880, and references therein; d) B. Manteau, S. Pazenok, J.-P. Vors, F. R. Leroux, *J. Fluorine Chem.* **2010**, *131*, 140; e) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors, F. R. Leroux, *Beilstein J. Org. Chem.* **2013**, *9*, 2476; f) A. Tili, T. Billard, *Angew. Chem.* **2013**, *125*, 6952; *Angew. Chem. Int. Ed.* **2013**, *52*, 6818; g) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; h) W.-M. He, Z.-Q. Weng, *Prog. Chem.* **2013**, *25*, 1071; i) F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415; j) I. Kietlsch, P. Eisenberger, A. Togni, *Angew. Chem.* **2007**, *119*, 768; *Angew. Chem. Int. Ed.* **2007**, *46*, 754.
- Selected methods for the introduction of the trifluoromethylthio group: a) Q.-Y. Chen, J.-X. Duan, *Chem. Commun.* **1993**, 918; b) D. J. Adams, J. H. Clark, *J. Org. Chem.* **2000**, *65*, 1456; c) D. J. Adams, A. Goddard, J. H. Clark, D. J. Macquarrie, *Chem. Commun.* **2000**, 987; d) W. Tyrre, D. Naumann, B. Hoge, Y. L. Yagupolskii, *J. Fluorine Chem.* **2003**, *119*, 101; e) I. Kietlsch, P. Eisenberger, A. Togni, *Angew. Chem.* **2007**, *119*, 768; *Angew. Chem. Int. Ed.* **2007**, *46*, 754; f) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312; g) C.-P. Zhang, D. A. Vacic, *J. Am. Chem. Soc.*

- 2012**, 134, 183; h) C. Chen, L.-L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, 134, 12454; i) C. Chen, Y. Xie, L.-L. Chu, R.-W. Wang, X.-G. Zhang, F.-L. Qing, *Angew. Chem.* **2012**, 124, 2542; *Angew. Chem. Int. Ed.* **2012**, 51, 2492; j) C.-P. Zhang, D. A. Vicić, *Chem. Asian J.* **2012**, 7, 1756; k) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, 134, 18237; l) Z. Weng, W. He, C. Chen, R. Lee, D. Dan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem.* **2013**, 125, 1588; *Angew. Chem. Int. Ed.* **2013**, 52, 1548; m) K.-P. Wang, S. Y. Yun, P. Mamidipalli, D. Lee, *Chem. Sci.* **2013**, 4, 3205; n) L. Zhai, Y. Li, J. Yin, K. Jin, R. Zhang, X. Fu, C. Duan, *Tetrahedron* **2013**, 69, 10262; o) M. Rueping, N. Tolstoluzhsky, P. Nikolaienko, *Chem. Eur. J.* **2013**, 19, 14043; p) G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Chem. Sci.* **2014**, 5, 1312.
- [4] Selected examples for electrophilic trifluoromethylthiolation using CF_3SCl : a) L. M. Yagupolskii, N. V. Kondratenko, G. N. Timofeeva, *J. Org. Chem. USSR* **1984**, 20, 103; b) T. Umemoto, S. Ishihara, *Tetrahedron Lett.* **1990**, 31, 3579; c) S. Munavalli, D. K. Rohrbaugh, F. R. Longo, H. D. Durst, *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, 177, 1073; d) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, W. G. Wagner, H. D. Durst, *Phosphorus Sulfur Silicon Relat. Elem.* **2002**, 177, 1021.
- [5] CF_3SCl was reported to have an $L(\text{ct})50$ of between 440 and 880 ppm min^{-1} . *Chem. Eng. News* **1967**, 45, 44.
- [6] a) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, *Synth. Commun.* **2000**, 30, 2847; b) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem.* **2013**, 125, 13093; *Angew. Chem. Int. Ed.* **2013**, 52, 12856; c) M. Rueping, X. Liu, T. Bootwicha, R. Pluta, C. Merckens, *Chem. Commun.* **2014**, 50, 2508; d) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem.* **2014**, 126, 1676; *Angew. Chem. Int. Ed.* **2014**, 53, 1650; e) K. Kang, C.-F. Xu, Q. Shen, *Org. Chem. Front.* **2014**, 1, 294.
- [7] a) A. L. Ferry, T. Billard, B. R. Langlois, E. Bacque, *J. Org. Chem.* **2008**, 73, 9362; b) A. Ferry, T. Billard, B. R. Langlois, E. Bacque, *Angew. Chem.* **2009**, 121, 8703; *Angew. Chem. Int. Ed.* **2009**, 48, 8551; c) A. Ferry, T. Billard, E. Bacque, B. R. Langlois, *J. Fluorine Chem.* **2012**, 134, 160; d) Y. Yang, X.-L. Jang, F.-L. Qing, *J. Org. Chem.* **2012**, 77, 7538; e) J. Liu, L. L. Chu, F.-L. Qing, *Org. Lett.* **2013**, 15, 894; f) F. Baert, J. Colomb, T. Billard, *Angew. Chem.* **2012**, 124, 10528; *Angew. Chem. Int. Ed.* **2012**, 51, 10382; g) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem.* **2013**, 125, 11014; *Angew. Chem. Int. Ed.* **2013**, 52, 10814; h) Q. Xiao, J. Sheng, Z. Chen, J. Wu, *Chem. Commun.* **2013**, 49, 8647; i) J. Sheng, S. Li, J. Wu, *Chem. Commun.* **2014**, 50, 578; j) S. Alazet, K. Ollivier, T. Billard, *Beistein J. Org. Chem.* **2013**, 9, 2354.
- [8] a) X.-X. Shao, X.-Q. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem.* **2013**, 125, 3541; *Angew. Chem. Int. Ed.* **2013**, 52, 3457; b) E. V. Vinogradova, P. Müller, S. L. Buchwald, *Angew. Chem.* **2014**, 126, 3189; *Angew. Chem. Int. Ed.* **2014**, 53, 3125; c) X.-Q. Wang, T. Yang, X.-L. Cheng, Q. Shen, *Angew. Chem.* **2013**, 125, 13098; *Angew. Chem. Int. Ed.* **2013**, 52, 12860; d) Q.-H. Deng, C. Rettenmeier, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2014**, 20, 93.
- [9] Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shitaba, *J. Am. Chem. Soc.* **2013**, 135, 8782.
- [10] G. S. Borovikova, E. S. Levchenko, E. I. Kaminskaya, *Zh. Org. Khim.* **1986**, 22, 100.
- [11] a) S. Andreades, US3081350, **1963**; b) D. Ceacareanu, M. R. C. Gerstenberger, A. Haas, *Chem. Ber.* **1983**, 116, 3325.
- [12] A. Kolasa, M. Lieb, *J. Fluorine Chem.* **1995**, 70, 45.
- [13] a) S. Munavalli, *J. Fluorine Chem.* **1993**, 60, 85; b) J. F. Harris, *J. Org. Chem.* **1981**, 46, 268; c) S. Andreades, J. F. Harris, W. A. Sheppard, *J. Org. Chem.* **1964**, 29, 898.
- [14] Monotrifluoromethylthiolation has previously been reported by reaction of acyclic β -keto esters with CF_3SCl : a) H. Bayreuther, A. Haas, *Chem. Ber.* **1973**, 106, 1418; b) V. I. Popov, A. Haas, M. Lieb, *J. Fluorine Chem.* **1990**, 47, 131.
- [15] a) H. Richert, Belg. Patent 624397, **1963**; b) H.-S. Lee, L. Geng, T. Skotheim, WO Patent 96/29,753, **1996**; c) T. S. Croft, *Phosphorus Sulfur Relat. Elem.* **1976**, 2, 133; d) A. Haas, V. Hellwig, *J. Fluorine Chem.* **1975**, 6, 521.
- [16] J. F. Hartwig, *Organotransition Metal Chemistry: from Bonding to Catalysis*, University Science Books, Sausalito, **2010**.
- [17] CCDC 994834 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [18] During the reviewing of the manuscript, Billard and co-workers reported a general method for mono-trifluoromethylthiolation of carbonyl compounds using a new electrophilic trifluoromethylthiolating reagent: *Chem. Eur. J.* **2014**, 20, DOI: 10.1002/chem.201403409.