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Synthetic Methods

Electrophilic Trifluoromethylthiolation of Carbonyl Compounds

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Abstract: A general method for the α-trifluoromethylthiolation of carbonyl compounds, without prefunctionalization, has been developed. Aldehydes, ketones, esters, amides, keto-esters, alkaloids, and steroids have been trifluoromethylthiolated with good yields. This work, proposing a new reagent for electrophilic trifluoromethylthiolation, provides a route towards the original synthesis of various trifluoromethylthiolated molecules for further applications.

Fluorinated molecules are often studied for a wide range of applications, particularly in life science.[1] However, a major problem concerns transmembrane permeation, which is crucial for the biodisponibility of therapeutic molecules and, consequently, for the administrated dose of the drug candidate.[2] The trifluoromethylthio group (CF_3S) is one of the most lipophilic substituents known[3] and, consequently, its presence in organic molecules can provide crucial physicochemical modifications.[4] Because of the growing interest in such substituents, reliable methods for their introduction into organic molecules are increasingly required.

Numerous methods to introduce this group into organic substrates have been described in the literature.[5] However, these methods are, in general, indirect methods or require specific skills to manipulate aggressive reagents. From a retrosynthetic point of view, the direct disconnection of the CF_3S group from the target molecule constitutes a more classical strategy for synthetic chemists non-specialized in fluorine chemistry. Recently, some elegant methods have emerged to propose such reactions.[5a,6]

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Carbonyl compounds constitute a large family of interesting building blocks for various syntheses.[7] Furthermore, a wide range of bioactive and natural compounds possess a carbonyl function.[8] Consequently, α-trifluoromethylthiolated carbonyl molecules could be of great interest for further applications.

To date, few α-trifluoromethylthiolation reactions of carbonyl compounds have been described in the literature. If such compounds can react with CF_3SCl,[9] the high toxicity[10] of this gaseous reagent precludes its utilization. Keto-esters (and β-diketones) are the most studied compounds. These compounds can be trifluoromethylthiolated with electrophilic reagents (Figure 1; **2**–**4**). Some asymmetric reactions have also been developed with tertiary keto-esters.[11]

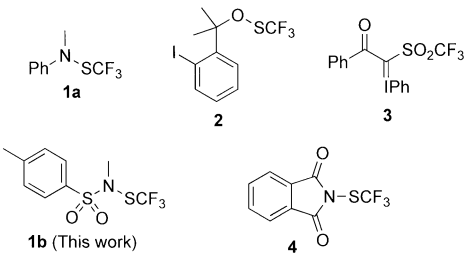

Figure 1. Reagents for electrophilic trifluoromethylthiolation.

Enantioselective trifluoromethylthiolations of oxindoles have also been performed by using **4** or CF_3SAg.[12] With the exception of the trifluoromethylthiolation of an aldehyde,[11c] no reactions of other simple carbonyl compounds have been described with electrophilic reagents. On the contrary, several esters and ketones have been trifluoromethylthiolated with nucleophilic reagents, starting from diazo compounds with CF_3SAg or CF_3SCu,[13] or from α-bromo ketones with (*S*)-trifluorothiocarbonate.[14]

These methods are interesting, but they suffer some drawbacks. For the nucleophilic method, the necessary use of the relatively unstable CF_3S^- anion confers some limitations to such a strategy. The method developed by Zard,[14] uses an (*S*)-trifluorothiocarbonate to generate this anion in situ. This method is an interesting alternative, but requires the preliminary preparation of α-bromo ketones. Electrophilic trifluoromethylthiolations, using reagents **2**–**4**, have been applied to a more restricted family of compounds. Furthermore, the reagents, **2**, developed by Shen and co-workers,[11c] and **4**, recently reintroduced by Rueping, Shen, and co-workers,[11a,15] are prepared by using the CF_3S^- anion, which requires some precautions and relevant expertise because of its instability. Reagent **3**, developed by Shibata,[11f] has circumvented this draw-

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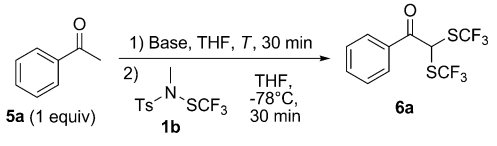
back, but the scope of reactivity is relatively restrained to only a few keto-esters.

In this context, trifluoromethanesulfenamide **1a** can be easily prepared, starting from commercially available reagents, which can be used without any specific experimental expertise.[16] This substrate has proved to be an efficient electrophilic trifluoromethylthiolating reagent.[17]

Consequently, to extend the reactivity of **1a**, and to expand the availability of α-trifluoromethylthiolated carbonyl compounds, reactions between **1a** and enolizable carbonyl compounds have been envisaged. Unfortunately, no attempts have succeeded to form the expected α-trifluoromethylthiolated acetophenone starting from **1a**. Hypothesizing that **1a** is not electrophilic enough to react with enolates, a more reactive derivative has been targeted. Therefore, an amine bearing a stronger electron-withdrawing group has been used to synthesize new reagent **1b**.[16] This compound can be prepared on a 20 g scale with an overall yield of 80%. This new reagent has been used for the α-trifluoromethylthiolation of the enolate of acetophenone (**5a**) (Table 1).

Table 1. Reaction of **1b** with enolate of **5a**.



Entry	Base [(equiv)]	T [°C]	**1b** [(equiv)]	**6a** [%][a]
1	*t*BuOLi (1.1)	0	1.2	60
2	*t*BuONa (1.1)	0	1.2	55
3	LiHMDS (1.1)	−78	1.2	50
4	LDA (1.1)	−78	1.2	60
5	LDA (1.2)	−78	2.2	88
6	*t*BuOLi (1.2)	0	2.4	64

[a] Yield of products, as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. LiHMDS = lithium hexamethyl disilazide.

Regardless of the base used, only the product of bistrifluoromethylthiolation, **6a**, is observed. By using 2.2 equivalents of **1b**, compound **6a** is formed in good yield (entries 5 and 6). Such results suggest that the monoadduct, **7a**, could also be deprotonated to react with **1b**. However, if diisopropylamine, generated from lithium diisopropylamide (LDA), can, eventually, deprotonate **7a**, in the case of *t*BuOLi or *t*BuONa, no base is generated apart from the lithium sulfonamide **8-Li**, arising from the reaction of **1b**. Such species are known to be very weak bases, therefore, the potential role of **8-Li** in this reaction must be elucidated.[18]

Consequently, monoadduct **7a** has been prepared by decarboxylation of **8n** (see Figure 2) and then engaged in a α-trifluoromethylthiolation reaction by using only **8-Li** as a base (Scheme 1). The formation of **6a** was observed with good yield, confirming the ability of **8-Li** to deprotonate **7a**. It should be noted that these conditions did not work when

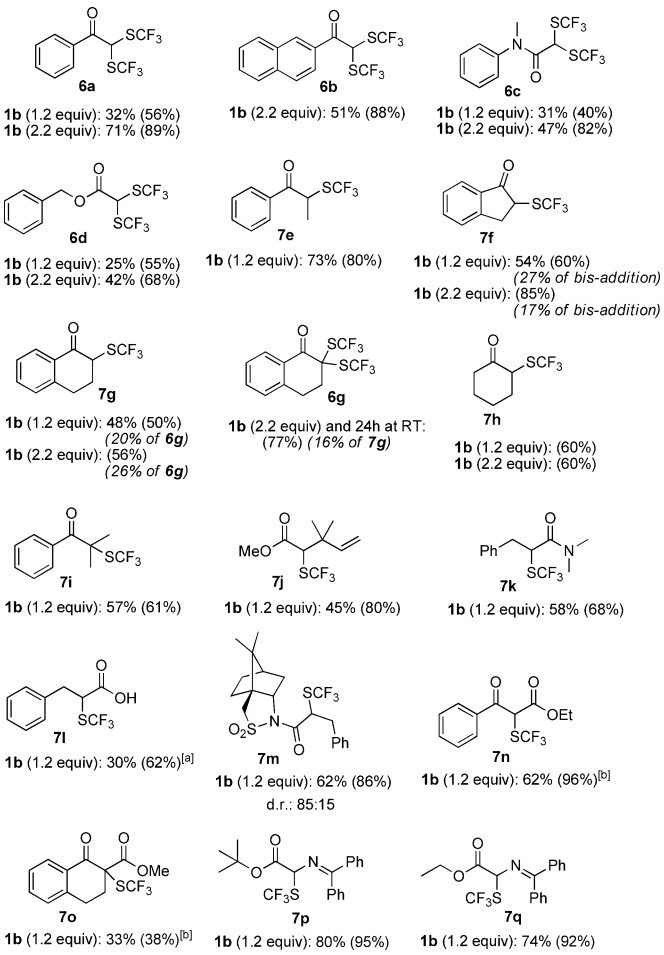
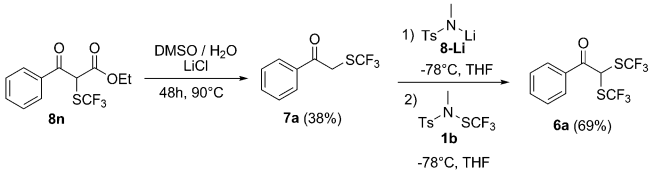


Figure 2. α-trifluoromethylthiolation of various carbonyl compounds. [a] 2.4 equiv of LDA, 0 °C. [b] 24 h at 0 °C. Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

starting from acetophenone (**5a**). These results confirm that the CF_3S group is a strong electron-withdrawing group.

These conditions for α-trifluoromethylthiolation (Table 1, entries 4 or 5) have also been extended to carbonyl compounds (Figure 2).

In general, the reaction gives good results, for example, for the acetophenone, only bis-addition is observed with primary compounds (**6a–d**). These bistrifluoromethylthiolated products were obtained with good yields when using 2.2 equivalents of **1b**. With secondary compounds, the monotrifluoromethylthiolated products, **7**, are generally the major, or often, the only compounds formed. This result can be rationalized by the



Scheme 1. α-trifluoromethylthiolation of **7a** with **8-Li** as a base. Ts = tosyl.

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steric hindrance of **7** preventing the approach of the hindered base (**8-Li** or diisopropylamine) for the second deprotonation. In the case of tetralone, the bis-adduct, **6g**, can be obtained after a longer reaction time, at room temperature, whereas no bis-addition is observed with cyclohexanone (**7h**). This reaction also provides good results with amides (**6c** and **7k**), esters (**6d** and **7j**), and a free carboxylic acid (**7l**). With an Oppolzer's reagent, the mono α-trifluoromethylthiolated product (**7m**) is obtained with good yields and with a diastereoisomeric ratio of 85:15. As previously described in the literature with other reagents,[11] keto-esters can also be α-trifluoromethylthiolated (**7n**–**o**). For **7o**, the moderate yield observed could be rationalized by the steric hindrance of the tertiary starting material. Schiff bases of glycine have also been α-trifluoromethylthiolated with good yields (**7p**–**q**). It should be noted that the obtained compounds are occasionally difficult to purify because of their volatilities, and especially because some of the obtained compounds are in equilibrium with their enol forms (due to the high acidity of the α hydrogen atom), which are difficult to elute from silica. This can explain the variations observed between the crude and isolated yields.

This methodology has been applied, as follows, to more elaborate compounds, possessing some biological activities (Figure 3).

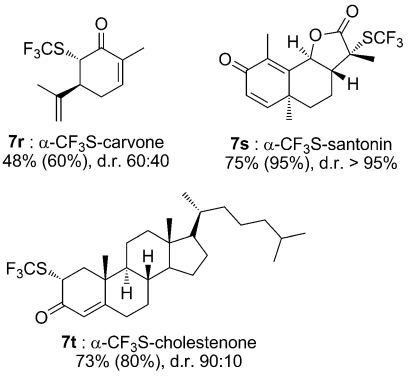
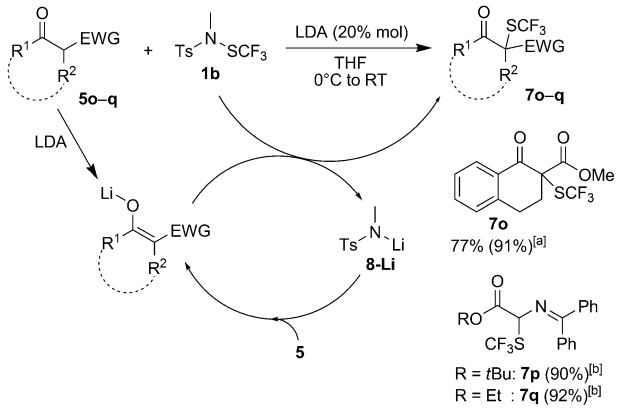


Figure 3. α-trifluoromethylthiolation of bioactive molecules. Yields shown are of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Good yields were obtained, despite the presence of other functionalities in the molecules. To our knowledge, the example of the santonin, **7s**, constitutes the first α-trifluoromethylthiolation of a lactone. For santonin and cholestenone, good diastereomeric ratios have also been observed. The configuration of each major diastereomer (drawn in Figure 3) could be determined by NOESY and HOESY (H–F) experiments.

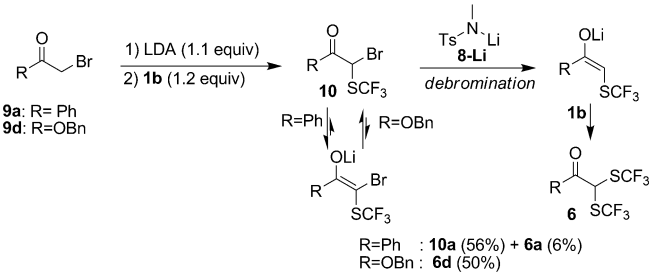
Because the ability of sulfonamide **8-Li** to deprotonate strong acidic hydrogen atoms has been previously underlined, base-catalyzed conditions with strong acidic starting materials, such as keto-esters or Schiff base of glycine have been tested (Scheme 2).

Good yields were obtained under these conditions. Surprisingly, in the case of the keto-esters (**5o**) better results are obtained than with the stoichiometric conditions. In the case of Schiff bases (**7p**–**q**) the reaction is very rapid and only 5 min was required for the completion of the reaction.



Scheme 2. Base-catalyzed α-trifluoromethylthiolation. [a] 24 h. [b] 5 min. Yields shown are those of isolated products; values in parentheses are yields as determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. EWG = electron-withdrawing group.

To extend such strategies to the synthesis of various valuable building blocks, α-bromo carbonyl compounds have also been engaged in the trifluoromethylthiolation reaction (Scheme 3).



Scheme 3. α-trifluoromethylthiolation of α-bromo compounds. Yields shown were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

Depending on the starting compounds (ketone **9a** or ester **9d**), different products are formed. With bromoacetophenone **9a**, expected product **10a** is obtained with a small amount of bistrifluoromethylthiolated compound **6a**. On the contrary, with ester **9d**, only the unexpected bistrifluoromethylthiolated compound **6d** is formed. The only conceivable explanation is to envisage the debromination of **10** by **8-Li**, generated during the formation of **10**, to form an enolate that is able to react with **1b** to give **6**. The debromination of **10** can only be performed with the non-enol form, which predominates in ester **10d**, whereas ketone **10a** is mainly in the enol form under the reaction conditions and, consequently, is "protected" against the side debromination. This debromination step has been proven by the successful formation of product **6a** by mixing **10a** and **1b** in the presence of **8-Li**.

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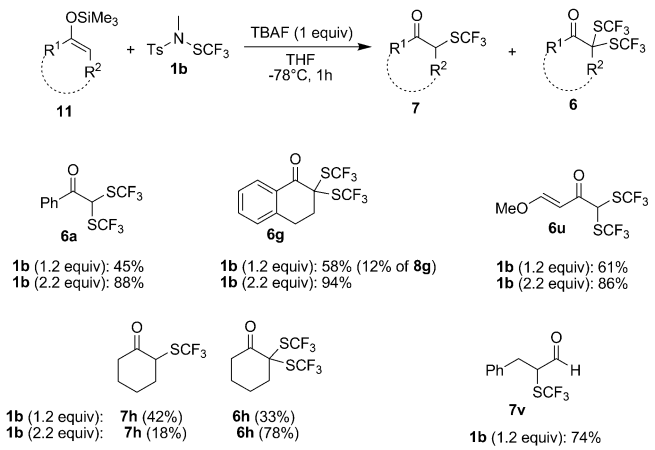
Finally, since silyl enol ethers are well-known stabilized forms of enolate, their reactivity with **1b** has also been examined (Scheme 4).



Scheme 4. α-trifluoromethylthiolation of silyl enol ethers. Yields shown were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. TBAF = tetrabutylammonium fluoride.

With silyl enol ethers of ketones, the bistrifluoromethylthiolated products, **6**, are always formed. In particular, with tetralone or cyclohexanone the bis-adducts, **6g** and **6h**, can be predominantly, or exclusively, obtained, whereas under the previous basic conditions, specific conditions were required for the formation of **6g**, and **6h** was never formed. Such results could be explained by the generation, during the reaction, of a tetrabutylammonium sulfonamide (**8-NBu$_4$**), which should be more basic than **8-Li**, generated during the previous reactions, and should consequently favor the second deprotonation of the mono-adducts (**7**). Danishefsky's diene can also react under these conditions to furnish bistrifluoromethylthiolated product **6u**. The silyl enol ether of an aldehyde was successfully trifluoromethylthiolated, whereas the more reactive enolate failed under previous conditions, allowing the formation of α-CF_3S aldehyde **7v**.

To conclude, we have described a general method to obtain a large variety of α-trifluoromethylthiolated carbonyl compounds by using a second generation of trifluoromethanesulfenamide (**1b**). This method allows the synthesis of valuable building blocks for further syntheses, and can be also applied to more elaborate substrates for a late trifluoromethylthiolation (see **7r–t**). Although in some cases, bistrifluoromethylthiolated compounds have been formed, such relatively unknown compounds can also present some interest for further applications. The study of the reactivity of the new reagent (**1b**) is underway and will be published in due course.

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Keywords: carbonyl compounds · enols · fluorine · trifluoromethanesulfenamide · trifluoromethylthiolation

[1] a) M. Hird, *Chem. Soc. Rev.* **2007**, *36*, 2070 – 2095; b) T. Hiyama, *Organofluorine Compounds: Chemistry and Applications,* Springer, Berlin, **2000**; c) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications,* Wiley-VCH, Weinheim, **2013**; d) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3 – 11; e) A. Becker, *Inventory of Industrial Fluoro-biochemicals,* Eyrolles, Paris, **1996**; f) S. C. Cherkofsky (du Pont de Nemours, E. I., and Co., USA), US4267184 A, **1981** [Chem. Abstr. 95:61982]; g) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369; h) P. Jeschke, *ChemBioChem* **2004**, *5*, 570 – 589; i) B. R. Langlois, T. Billard, S. Large, N. Roques, in *Fluorinated Bioactive Compounds in the Agricultural & Medical Fields,* Chemical & Polymer, **1999**, pp. 24, 21 – 24, 28; j) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; k) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; l) J. Szmuszkovicz, E. M. Glenn, R. V. Heinzelman, J. B. Hester, Jr., G. A. Youngdale, *J. Med. Chem.* **1966**, *9*, 527 – 536.

[2] a) D. E. Clark, *Drug Discovery Today* **2003**, *8*, 927 – 933; b) J. Kelder, P. D. J. Grootenhuis, D. M. Bayada, L. P. C. Delbressine, J.-P. Ploemen, *Pharm. Res.* **1999**, *16*, 1514 – 1519; c) U. Norinder, M. Haeberlein, *Adv. Drug Delivery Rev.* **2002**, *54*, 291 – 313; d) A. Avdeef, *Absorption and Drug Development: Solubility, Permeability, and Charge State*, Wiley, Hoboken, **2012**; e) D. A. Smith, C. Allerton, H. Kubinyi, H. Walker, D. K. Walker, R. Mannhold, G. Folkers, *Pharmacokinetics and Metabolism in Drug Design*, Wiley-VCH, Weinheim, **2012**.

[3] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165 – 195.

[4] a) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley, Chichester, **2009**; b) J.-P. Begue, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, Hoboken, **2008**.

[5] a) F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415 – 2428; b) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880 – 921; c) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827 – 856.

[6] a) A. Tlili, T. Billard, *Angew. Chem.* **2013**, *125*, 6952 – 6954; *Angew. Chem. Int. Ed.* **2013**, *52*, 6818 – 6819; b) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors, F. R. Leroux, *Beilstein J. Org. Chem.* **2013**, *9*, 2476 – 2536.

[7] a) J. Alvarez-Builla, J. J. Vaquero, J. Barluenga, *Modern Heterocyclic Chemistry,* Wiley-VCH, Weinheim, **2011**; b) F. A. Carey, R. J. Sundberg, *Advanced Organic Chemistry*, Springer, New York, **2000**, pp. 449 – 508.

[8] a) E. Fattorusso, W. H. Gerwick, O. Taglialatela-Scafati, *Handbook of Marine Natural Products.*, Springer-Verlag GmbH, Berlin, **2012**; b) G. Eisenbrand, W. Tang, *Handbook of Chinese Medicinal Plants: Chemistry, Pharmacology, Toxicology*, Wiley-VCH, Weinheim, **2010**; c) J. M. Kornprobst, *Encyclopedia of Marine Natural Products*, Wiley-VCH, Weinheim, **2010**; d) G. Brahmachari, *Handbook of Pharmaceutical Natural Products*, Wiley-VCH, Weinheim, **2010**; e) S. C. Sweetman, *Martindale: The Complete Drug Reference*, Pharmaceutical Press, London, **2011**.

[9] a) M. Bauer, A. Haas, H. Muth, *J. Fluorine Chem.* **1980**, *16*, 129 – 136; b) H. Bayreuther, A. Haas, *Chem. Ber.* **1973**, *106*, 1418 – 1422; c) K. Bogdanowicz-Szwed, B. Kawałek, M. Lieb, *J. Fluorine Chem.* **1987**, *35*, 317 – 327; d) A. Kolasa, *J. Fluorine Chem.* **1987**, *36*, 29 – 40; e) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, W. G. Wagner, H. D. Durst, *Phosphorus Sulfur and Silicon and the Related Elements* **2002**, *177*, 1021 – 1031; f) V. I. Popov, A. Haas, M. Lieb, *J. Fluorine Chem.* **1990**, *47*, 131 – 136; g) W. Zankowska-Jasinska, B. Zaleska, A. Haas, *J. Fluorine Chem.* **1984**, *24*, 363 – 368.

[10] E. C. Stump, *Chem. Eng. News* **1967**, *45*, 44.

[11] a) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem.* **2013**, *125*, 13093 – 13097; *Angew. Chem. Int. Ed.* **2013**, *52*, 12856 – 12859; b) Q.-H. Deng, C. Rettenmeier, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2014**, *20*, 93 – 97; c) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem.* **2013**, *125*, 3541 – 3544; *Angew. Chem. Int. Ed.* **2013**, *52*, 3457 – 3460; d) E. V. Vinogradova, P. Müller, S. L. Buchwald, *Angew. Chem.* **2014**, *126*, 3189 – 3192; *Angew. Chem. Int. Ed.* **2014**, *53*, 3125 – 3128; e) X. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem.* **2013**, *125*, 13098 –

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13102; *Angew. Chem. Int. Ed.* **2013**, *52*, 12860 – 12864; f) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782 – 8785.

[12] a) M. Rueping, X. Liu, T. Bootwicha, R. Pluta, C. Merkens, *Chem. Commun.* **2014**, *50*, 2508 – 2511; b) X.-L. Zhu, J.-H. Xu, D.-J. Cheng, L.-J. Zhao, X.-Y. Liu, B. Tan, *Org. Lett.* **2014**, *16*, 2192 – 2195.

[13] a) M. Hu, J. Rong, W. Miao, C. Ni, Y. Han, J. Hu, *Org. Lett.* **2014**, *16*, 2030 – 2033; b) X. Wang, Y. Zhou, G. Ji, G. Wu, M. Li, Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2014**, 3093 – 3096.

[14] S.-G. Li, S. Z. Zard, *Org. Lett.* **2013**, *15*, 5898 – 5901.

[15] a) K. Kang, C. Xu, Q. Shen, *Org. Chem. Front.* **2014**, *1*, 294 – 297; b) R. Pluta, P. Nikolaienko, M. Rueping, *Angew. Chem.* **2014**, *126*, 1676 – 1679; *Angew. Chem. Int. Ed.* **2014**, *53*, 1650 – 1653.

[16] A. Ferry, T. Billard, B. R. Langlois, E. Bacque, *J. Org. Chem.* **2008**, *73*, 9362 – 9365.

[17] a) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem.* **2009**, *121*, 8703 – 8707; *Angew. Chem. Int. Ed.* **2009**, *48*, 8551 – 8555; b) F. Baert, J. Colomb, T. Billard, *Angew. Chem.* **2012**, *124*, 10528 – 10531; *Angew. Chem. Int. Ed.* **2012**, *51*, 10382 – 10385; c) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160 – 163; d) S. Alazet, K. Ollivier, T. Billard, *Beilstein J. Org. Chem.* **2013**, *9*, 2354 – 2357; e) S. Alazet, L. Zimmer, T. Billard, *Angew. Chem.* **2013**, *125*, 11014 – 11017; *Angew. Chem. Int. Ed.* **2013**, *52*, 10814 – 10817.

[18] F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456 – 463.

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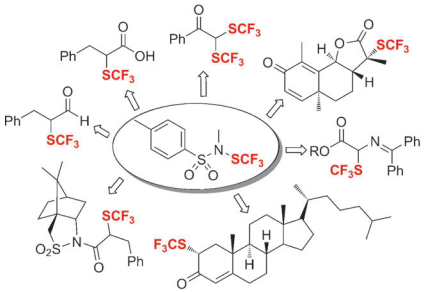
Electrophilic Trifluoromethylthiolation of Carbonyl Compounds



The next generation: A new reagent, which is more reactive than previous reagents, has been designed to perform trifluoromethylthiolation of a wide range of carbonyl compounds (see figure).

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