CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Trifluoromethanesulfinyl Chloride for Electrophilic Trifluoromethythiolation and Bifunctional Chlorotrifluoromethythiolation

Authors: Lvqi Jiang, Qiang Yan, Rongkang Wang, Tianqi Ding, Webin Yi, and Wei Zhang

To be cited as: *Chem. Eur. J.* 10.1002/chem.201804027

Link to VoR: http://dx.doi.org/10.1002/chem.201804027

Supported by
ACES

WILEY-VCH

10.1002/chem.201804027

WILEY-VCH

FULL PAPER

Trifluoromethanesulfinyl Chloride for Electrophilic Trifluoromethythiolation and Bifunctional Chlorotrifluoromethythiolation

Lvqi Jiang‡[a], Qiang Yan‡[a], Rongkang Wang[a], Tianqi Ding[a], Wenbin Yi*[a] and Wei Zhang*[b]

Abstract: *Trifluoromethanesulfinyl chloride (CF_3SOCl) is introduced as a new reagent for C-H trifluoromethylthiolation of indoles, thiophenes, and ketones under catalyst-free conditions and in the absence of reductant. The disproportionation of CF_3SOCl to CF_3SO_2Cl and CF_3SCl provides two pathways for the trifluoromethylthiolation. Direct trifluoromethylthiolation with CF_3SCl or trifluoromethylsulfoxidation with CF_3SOCl followed by the reduction with CF_3SOCl. This reagent can be used to functionalize benzothiophenes, benzofurans and indenes under the promotion of Ag_2CO_3. It can also be used for trifluoromethylthiolation of thiols and benzeneselenols, and 1,2-bifunctional chlorotrifluoromethylthiolation of indoles, styrenes, and alkyens. The method can also be extended for difluorometylthiolation reactions using CF_2HSOCl.*

Introduction

Lipophilic trifluoromethylthio (CF_3S) group could be introduced to improve pharmacokinetic and physicochemical properties of medicinally and agrochemically interested compounds,[1,2] such as Fipronil,[3] Tiflorex,[4] Toltrazuril[5] and Cefazaflur[6] (Figure 1). Late stage direct C-H trifluoromethylthiolation is a good approach for lead optimization.[7] Over the years, highly reactive, but very toxic CF_3S-based reagents such as CF_3SCl[8] and CF_3SSCF_3[9] have been introduced as trifluoromethylthiolation reagents. Stable and use-friendly CF_3SN- and CF_3SO-based reagents **1a-g**[10-16] and CF_3SO_2-containing hypervalent idonium ylides **2a-b** have been developed for trifluoromethylthiolation of C_{sp}^2-H bonds (Figure 2).[17,18] However, they generally require several steps to prepare and involve reactions with expensive reagents such as $AgSCF_3$, (diethylamino)sulfur trifluoride (DAST), or the Ruppert−Prakash reagent (CF_3SiMe_3).

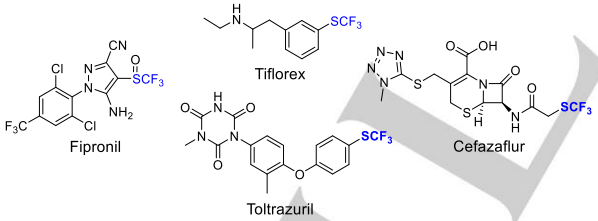


Figure 1. SCF_3-containing biologically active compounds.

Stable and readily available CF_3SO_2Na (Langlois reagent) was recently introduced to generate CF_3S^+ *in situ* under reductive and catalytic conditions for electrophilic trifluoromethylthiolation.[19] CF_3SO_2Na has also been used to generate CF_3S^- for nucleophilic, trifluoromethylthiolation of aryliodides.[20] More recently, CF_3SO_2Cl was introduced for electrophilic trifluoromethylthiolation by using Ph_3P or $(EtO)_2P(O)H$.[21] Even some progresses have been made, CF_3SO_2-based trifluoromethylthiolation still has following limitations: 1) requirement of stoichiometric amount of metal salts; 2) limited scope for electron-rich heterocycles and alkenes such as indoles, pyrroles and enamines.[19-21]

During the trifluoromethylthiolation reactions with CF_3SO_2Na or CF_3SO_2Cl, reactive species such as CF_3SSCF_3 and CF_3SCl were observed from the reaction process.[19-21] CF_3SOCl, which could be obtained from commercial suppliers or easily synthesiezd by the treatment of readily available CF_3SO_2Na and $SOCl_2$,[22] has been reported for direct trifluoromethylsulfoxidations.[23] It was reported that CF_3SOCl could disproportionate into CF_3SCl and CF_3SO_2Cl.[24] Thus, we believe it is possible to develop CF_3SOCl as a reagent for trifluoromethylthiolation through dismutation without using an additional reductant.

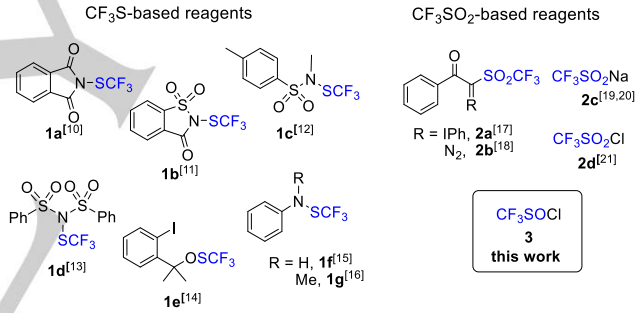


Figure 2. Electrophilic trifluoromethylthiolation reagents.

Results and Discussion

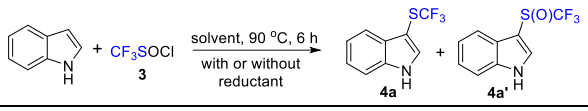
Indole is a well-studied substrate for trifluoromethylthiolation.[19,21] A reaction of 1:1.5:1.5 indole/CF_3SOCl/$(EtO)_2P(O)H$ in MeCN was carried out at 90 °C for 6 h. This condition is similar to our previous reported for the CF_3SO_2Cl/$(EtO)_2P(O)H$ system.[21b] Product **4a** was obtained in 36% yield (Table 1, entry 1), together with 9% yield of trifluoromethylsulfoxidation product **4a'**. After testing other reductants (Table 1, entries 2-4), it was found that the reaction with PPh_3 gave a good yield of 86%. Considering CF_3SOCl has disproportionation capability to generate CF_3SCl by self reduction,[24] a reaction of CF_3SOCl (1.5 equiv) without using phosphorus as a reductant was conducted (Table 1, entry 5). To our delight, 26% yield of **4a** was observed. Increased the amounts of CF_3SOCl from 1.5 to 3 equiv, the yield of **4a** steadily increased from 26% to 83% (Table 1, entries 6-8). It is worth noting that a significant amount of trifluoromethylsulfoxidation product **4a'** was observed from the reaction mixture, especially from the reactions with a low loading of CF_3SOCl. The screening of solvents revealed that MeCN is better than $ClCH_2CH_2Cl$ (DCE), PhMe and DMF for the reaction of indole (Table 1, entries 9-11).

[a] Prof. Dr. W. Yi, L. Jiang, Q. Yan, R. Wang, T. Ding
School of Chemical Engineering, Nanjing University of Science and Technology
200 Xiao Ling Wei Street, Nanjing 210094 (China)
E-mail: yiwb@njust.edu.cn
[b] Prof. Dr. W. Zhang
Department of Chemistry, University of Massachusetts Boston
100 Morrissey Boulevard, Boston, MA 02125 (USA)
E-mail: wei2.zhang@umb.edu

Supporting information for this article is given via a link at the end of the document.

10.1002/chem.201804027

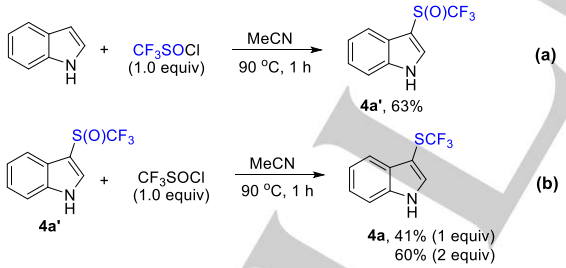
Table 1: Optimization of trifluoromethylthiolation with CF_3SOCl[a]



Entry	**3** (equiv)	Solvent	Reductant (1.5 equiv)	**4a**/**4a'** (%)[b]
1	1.5	MeCN	$(EtO)_2P(O)H$	36/9
2	1.5	MeCN	$(MeO)_2P(O)H$	31/10
3	1.5	MeCN	PPh_2Cl	66/8
4	1.5	MeCN	PPh_3	86/5
5	1.5	MeCN	-	26/40
6	2	MeCN	-	44/31
7	2.5	MeCN	-	65/20
8	3	MeCN	-	83/8
9	3	DCE	-	32/10
10	3	PhMe	-	44/21
11	3	DMF	-	trace

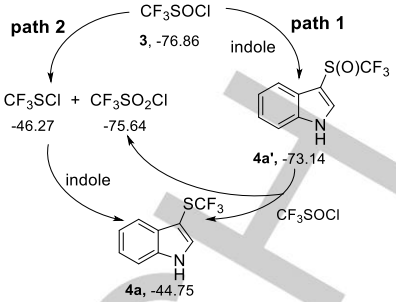
[a] Reaction conditions: indole (0.2 mmol), solvent (1 mL), under N_2 at 90 °C for 6 h; [b] Yield determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

Results in Table 1 show that reactions using CF_3SOCl (1.5 equiv)/PPh_3 (1.5 equiv) or using CF_3SOCl (3 equiv) without an additional reductant gave similar results (Table 1, entries 4 and 8). Previously reported CF_3SO_2Cl/$(EtO)_2P(O)H$[21b] and CF_3SO_2Cl/PPh_3[21a] reaction systems both generated CF_3S^+ as a reactive species for trifluoromethylthiolation. To confirm if CF_3SCl was generated from the reaction of CF_3SOCl in the absence of a reductant, a sample of CF_3SOCl in MeCN was heated at the reaction temperature of 90 °C for 1 h. ^{19}F NMR analysis of the sample gave two new signals at δ -46.27 and -75.64 ppm for CF_3SCl and CF_3SO_2Cl, respectively. A control reaction of indole using only 1.0 equiv of CF_3SOCl was also conducted (Scheme 1a). Trifluoromethylsulfoxidation product **4a'** was obtained in 63% yield. Compound **4a'** was then reacted with 1 equiv of CF_3SOCl at 90 °C for 1 h to afford trifluoromethylthiolation product **4a** in 41% yield (Scheme 1b). The yield of **4a** was increased to 60% if 2 equiv of CF_3SOCl was used.



Scheme 1. Formation of **4a'** and its reaction with CF_3SOCl for **4a**

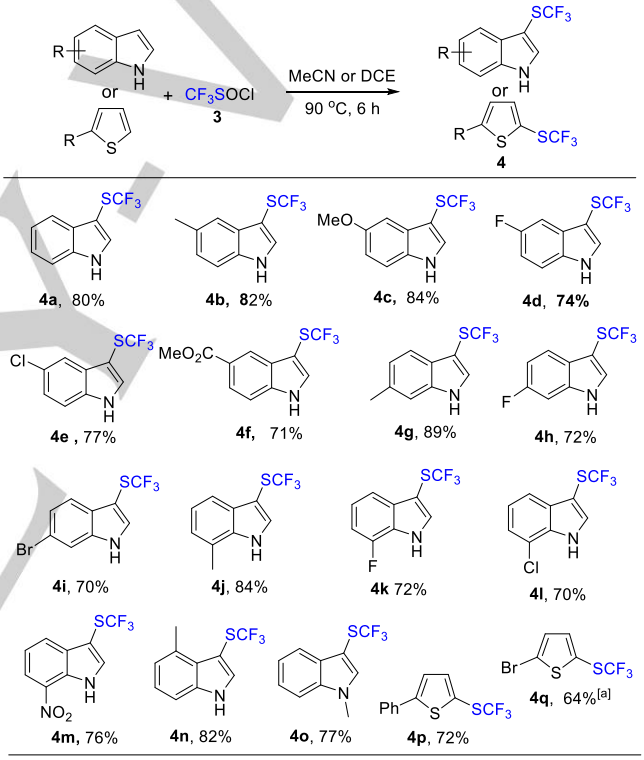
Results from the control experiment and literature[21,24] allowed us to propose two possible pathways for CF_3SOCl trifluoromethylthiolation (Scheme 2). Heating CF_3SOCl with indole at the reaction temperature of 90 °C resulted trifluoromethylsulfoxylated compound **4a'**. It is then reduced with CF_3SOCl to form product **4a.** CF_3SOCl could also undergo disproportionation to form CF_3SO_2Cl and CF_3SCl. The CF_3SCl reacts with indole to give the direct trifluoromethylthiolation product **4a**. Reactions of a series of substituted indoles under the optimized conditions were conducted (Table 2). Reactions of indoles bearing Me, MeO, halogen, or ester groups at the 5-position generated corresponding products **4b-f** in high yields. Reactions of indoles with Me or halogen groups at 6- or 7-position gave **4g-m** also in good yields. Reactions with



Scheme 2. Proposed Mechanism for trifluoromethylthiolation of indole

two thiophenes were conducted in DCE gave better results than in MeCN to afford **4p** and **4q** in 72% and 64% yields, respectively.

Table 2. Trifluoromethylthiolation of indoles and thiophenes



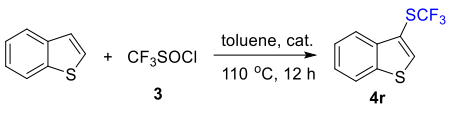
Reaction conditions: Indole (or thiophene) (0.2 mmol), **3** (0.6 mmol), in MeCN or DCE (1 mL) under N_2 at 90 °C for 6 h; isolated yields; [a] Yield was determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

A reaction of benzothiophene under the standard conditions only gave product **4r** in less than 10% yield (Table 2, entry 1). It was suggested that a catalyst may needed for a better conversion. After screening of Cu and Ag catalysts as well as solvents, it was found that the reaction with 0.2 equiv of Ag_2CO_3 in PhMe at 110 °C for 12 h resulted **4r** in 84% yield (Table 2, entry 7). We speculated that Ag_2CO_3 acts as a base to remove the trace amount of HCl which could be generated from CF_3SOCl or $SOCl_2$ by reacting with residual water in hygroscopic CF_3SO_2Na. Under the siliver-promoted conditions, reactions of halogen-substituted benzothiophenes, 2-butylbenzofuran, and indene gave the products **4s-v** in 63-78% yields (Table 3).

α-Trifluoromethylthiolated carbonyl compounds have gained growing interest in recent years due to special properties imparted by the trifluoromethylthio group.[25] Extension for the scope of CF_3SOCl reaction for ketones was attempted (Table 4). The synthesis of **5a-c** from indanone derivatives, **5d-e** from tetralone derivatives, **5f** from

10.1002/chem.201804027

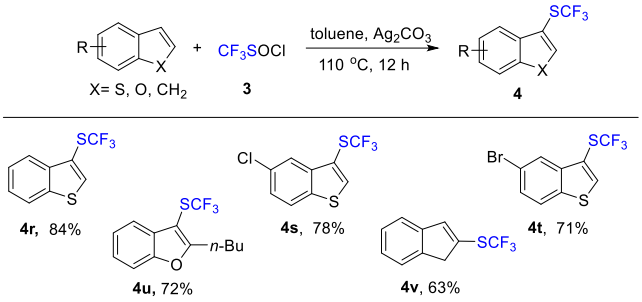
Table 2: Metal-catalyzed trifluoromethylthiolation of benzothiophene



Entry	Cat. (0.2 equiv)	Yield[a]
1	-	<10%
2	CuCl	22%
3	CuI	26%
4	Cu_2O	17%
5	$AgNO_3$	78%
6	AgF	67%
7	Ag_2CO_3	84%

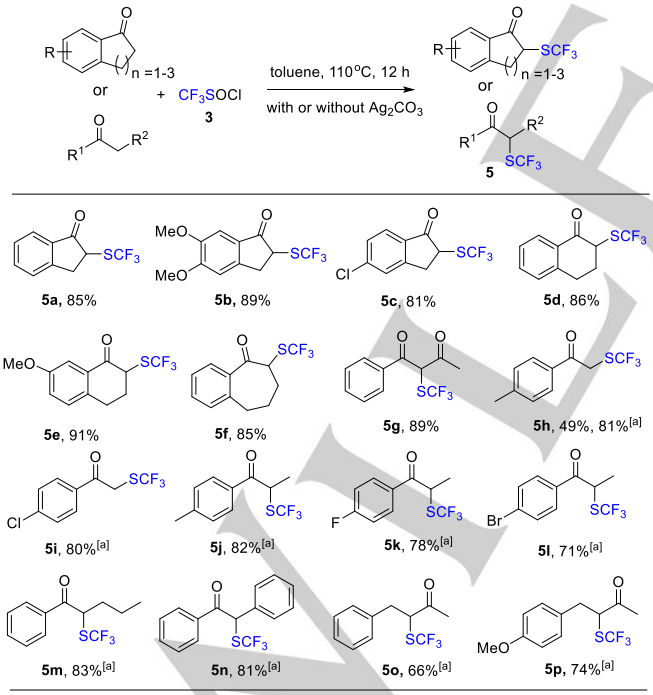
Conditions: benzothiophene (0.2 mmol), **3** (0.6 mmol), PhMe (1 mL), under N_2; [a] Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

Table 3. Trifluoromethylthiolation of other aromatic compounds



Reaction conditions: benzothiophene, benzofuran or indene (0.2 mmol), **3** (0.6 mmol), Ag_2CO_3 (0.04 mmol) in toluene (1 mL) under N_2 at 110 °C for 12 h; Isolated yields

Table 4. Trifluoromethylthiolation of ketones

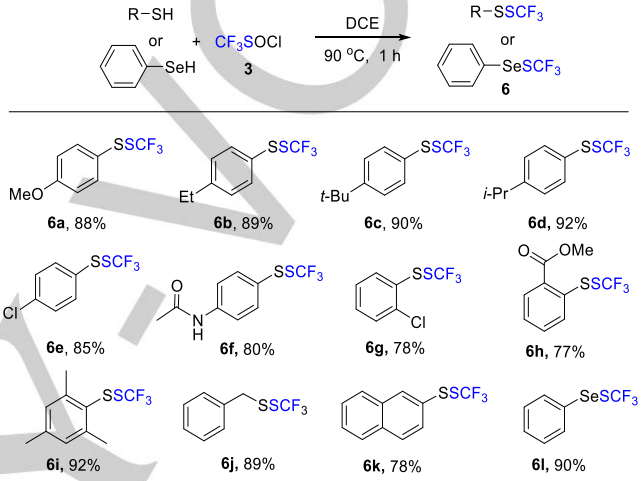


Reaction conditions: ketone (0.2 mmol), **3** (0.6 mmol), in toluene (1 mL) under N_2 at 110 °C for 12 h, isolated yields; [a] 0.2 equiv Ag_2CO_3 was used.

1-benzosuberone, and **5g** from 1-phenyl-1,3-butanedione all gave >80% yields, but only 49% yield for **5h** from acetophenone. However, addition of 0.2 equiv of Ag_2CO_3 increased the yield of **5h** to 81%. Thus, under the siliver-promoted conditions, reactions of seven acetophenone derivatives afforded products 5**h-n** in >70% yields. Reactions of benzylacetones also processed smoothly to afford products **5o-p**. Trifluoromethylthiolation of ketones with CF_3SOCl shown in Table 4 would not be achieved by previously reported reactions with CF_3SO_2Na or CF_3SO_2Cl.[19,21]

We have previously reported CF_3SO_2Cl-based reaction of thiols in the synthesis of trifluoromethylthiolated disulfides.[21b] CF_3SOCl was also able to react with thiols to generate disulfides in CH_2Cl_2 (Table 5). In addition to the reaction of substituted thiophenols for **6a-i,** benzyl thiol and naphthalene-1-thiol also gave products **6j** and **6k** in good yields. Under the same conditions, reaction of benzeneselenol afforded trifluoromethylthiolated product **6l** in 90% yield.

Table 5. Trifluoromethylthiolation of thiols and benzeneselenol



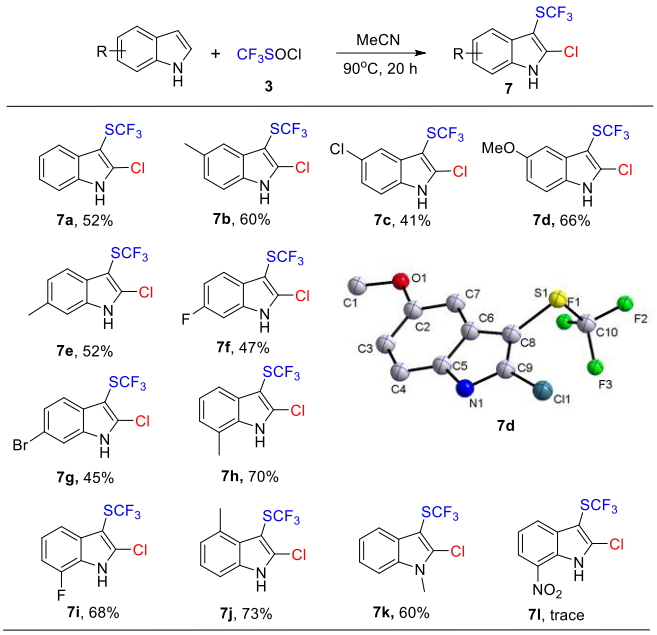
Reaction conditions: thiol or benzeneselenol (0.2 mmol), **3** (0.6 mmol), in DCE (1 mL) under N_2 at 90 °C for 1 h; isolated yields.

Bifunctionalization is an atom economic way to introduce functional groups to alkenes and alkynes.[26] Several CF_3SO_2Cl-initiated bifunctionalization reactions have been reported in the literature.[27] After successful trifluoromethylthiolation of heterocycles and thiols with CF_3SOCl, we explored CF_3S-based bifunctionalization with this reagent. To our surprise, by simply increasing the reaction time from 6 h to 20 h, 2-chloro-3-trifluoromethylthio-substituted indole **7a** was obtained in 52% yield. Reactions of various indoles under this condition afforded **7b-k** in good yields, except for **7l** which has a NO_2 group to deactivate the indole ring (Table 6). The structure of bifunctionalized product **7d** was confirmed by single crystal x-ray analysis. Very recently, the Liu group reported a similar transformation using $POCl_3$ as chlorination reagent.[28] We attempted to gain some insights into the reaction mechanism. ^{19}F NMR analysis of this reaction process showed that **4a** is an intermediate piror to the Chlorotrifluoromethylthiolated product **7a**, which means that **7a** was formed by chlorination of **4a**. To gain more insights, especially for the chlorination of **4a**, several control experiments conducted (Scheme 3). The results showed that both CF_3SO_2Cl and CF_3SOCl contributed to the chlorination, and their mixture were more efficient.

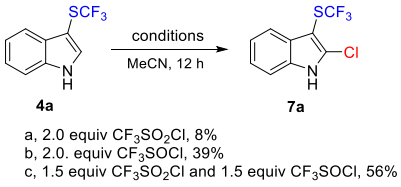
In addition to the bifunctionalization of indoles, we also explored bifunctionalization of alkenes and alkynes through 1,2-addition. We have noticed that Shen group's report on formoxy-, acetoxy-, or hydroxy-trifluoromethylthiolation of styrenes with *N*-trifluoromethylthiodibenzenesulfonimide **1d** in different reaction solvents.[13] It was determined that the solvent was crucial for the reaction, and DMF is favorable for the chlorotrifluoromethylthiolation reaction of styrene with CF_3SOCl. Thus, reaction of a series of styrene

10.1002/chem.201804027

Table 6. Bifuctional chlorotrifluoromethylthiolation of indoles



Reaction conditions: Indole (0.2 mmol), **3** (0.6 mmol), in MeCN (1 mL) under N_2 at 90 °C for 20 h; isolated yields.



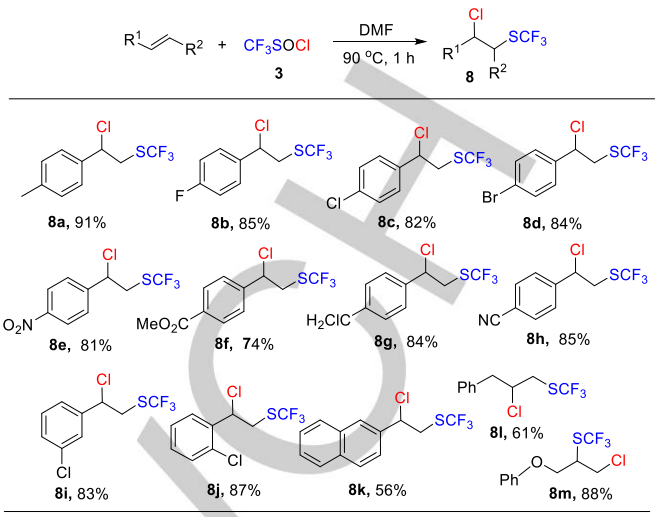
Scheme 3. Chlorination of **4a** under different conditions

derivatives with CF_3SOCl in DMF at 90 °C for 1 h afforded **8a-k** in good yields (Table 7). Reaction of two nonstyrene-type alkenes afforded **8l** and **8m** in >80% yields. The regiochemistry of the bifunctionalized products was confirmed by ^1H NMR analysis,[21e] **8a-8l** were Markovnikov products while **8m** was produced in high anti-Markovnikov selectivity. The regiochemistry was similar to our previous CF_3SO_2Cl/PPh_3/DMF system,[21e] which made us believe that the process of bifunctionalization of alkenes is also an electrophilic addition by the decomposition product CF_3SCl.

The extension of the scope of bifunctionalization for alkynes was also achieved using DMF as a solvent. Reactions of a series of phenylacetylenes and other alkynes with CF_3SOCl under catalyst-free conditions at 90 °C for 6 h afforded products **9a-o** in 52-92% yields (Table 8). It seems that the CF_3SOCl system was more efficient than our previously reported CF_3SO_2Cl/PPh_3 system and higher yields were obtained. Similar to alkenes, **9a-9l** were found to be Markovnikov products while **9m** and **9n** were anti-Markovnikov products by ^1H NMR analysis.[21e] Different from our previous report, internal alkyens, for example, 1,2-diphenylethyne, was also applicable to give the product 9o in 70% yield (**9o**).

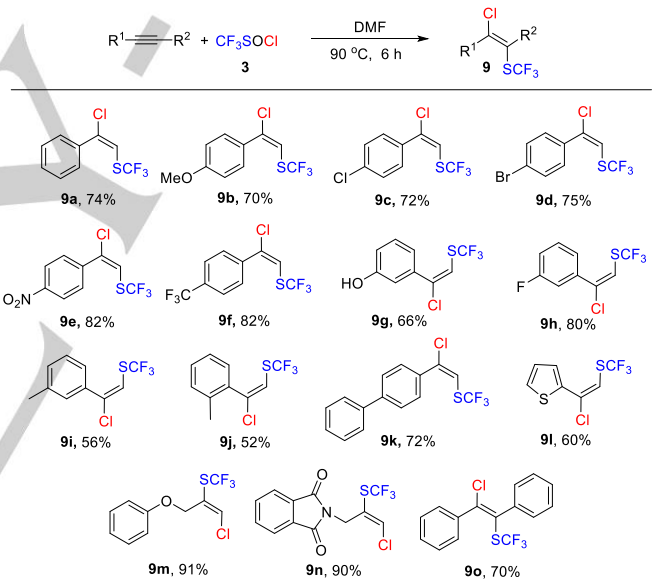
The SCF_2H-containing molecules have also shown to be uniquely effective in bioactive compounds.[29] To our delight, CF_2HSOCl was successfully synthesized by using CF_2HSO_2Na (see Experimental Section for details). Next, we sought to extended the reaction scope for difluoromethylthiolation (Table 9). Reactions of a series of indole

Table 7. Chlorotrifluoromethylthiolation of alkenes



Reaction conditions: styrene derivative (0.2 mmol), **3** (0.6 mmol), in DMF (1 mL) under N_2 at 90 °C for 1 h; isolated yields.

Table 8. Chlorotrifluoromethylthiolation of alkynes



Reaction conditions: alkyne (0.2 mmol), **3** (0.6 mmol), in DMF (1 mL) under N_2 at 90 °C for 6 h, isolated yields.

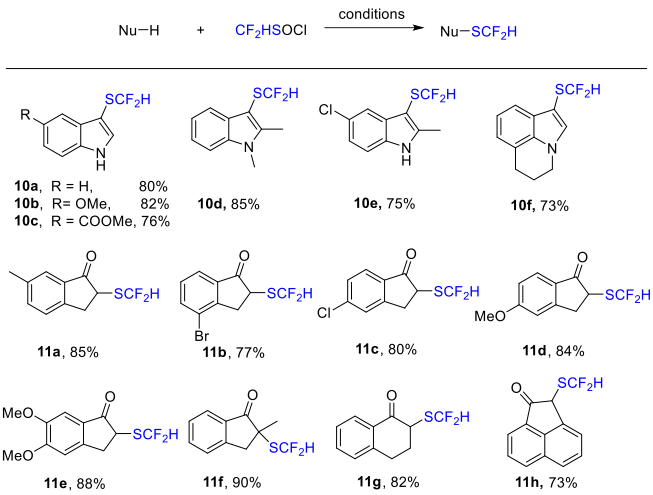
derivatives with CF_2HSO_2Cl afforded **10a-10f** in good yields. Ketones were also tested under similar conditions. Research on direct difluoromethylthiolation of kentones are very limited up to now. Reactions of a series of indanone derivatives with CF_2HSO_2Cl gave difluoromethylthiolated **11a-10f** in 73-90% yields. Other ketones like 1-tetralone and 1-acenaphthenone also afforded corresponding products **11g** and **11h** in 82% and 73% yields, respectively.

Conclusions

In summary, CF_3SOCl is introduced as a new reagent for electrophilic trifluoromethylthiolation and bifunctionalization. The new reaction process is different from previously reported methods using CF_3SO_2-based reagents such as CF_3SO_2Na and CF_3SO_2Cl. The $SOCF_3$ intermediate was first generated and then reduced by CF_3SOCl to form

10.1002/chem.201804027

Table 9. Difluoromethylthiolation using CF_2HSOCl



Reaction conditions: indole or ketone (0.2 mmol), CF_2HSOCl (0.6 mmol), in MeCN (1 mL) under N_2 at 90 ^{0}C for 6 h (for indole) or in toluene (1 mL) under N_2 at 110 ^{0}C for 12 h (for ketone), isolated yields; isolated yields.

SCF_3 product. Meanwhile, CF_3SOCl also generates reactive CF_3S^+ through self-disproportionation. Under catalyst-free conditions, CF_3SOCl is able to trifluoromethylthiolate indoles, ketones, thiols and benzeneselenols effectively without an additiona reductant. In the present of Ag_2CO_3 catalyst, CF_3SOCl reacts with benzothiophenes, benzofurans and indenes. In addition, by simply increasing the reaction time or changing the reaction solvent, 1,2-bifunctional chlorotrifluoromethylthiolation could be achieved for indoles, alkenes and alkyens. CF_2HSOCl was also successfully synthesized and used for difluoromethylthiolation under the catalyst-free conditions.

Experimental Section

General Procedure for Reaction of Indoles for 4a-o

A 10 mL oven-dried reaction vessel was charged with an indole (0.2 mmol) and trifluoromethansulfinyl chloride (**3**, 0.6 mmol). Acetonitrile (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 90 ^{0}C for 6 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolation substituted products.

General Procedure for Reaction of Thiophenes for 4p, 4q

A 10 mL oven-dried reaction vessel was charged with a thiophene (0.2 mmol) and trifluoromethansulfinyl chloride (**3**, 0.6 mmol). Dichloroethane (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 90 0C for 6 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolation substituted products.

General Procedure for the synthesis of 4r-v

A 10 mL oven-dried reaction vessel was charged with a benzothiophene, benzofuran or indene (0.2 mmol), trifluoromethansulfinyl chloride (3, 0.6 mmol) and silver carbonate (Ag_2CO_3, 0.04 mmol). Toluene (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 110 ^{0}C for 12 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolated product.

General procedure for Trifluoromethylthiolation of Kentones (5a-5p).

A 10 mL oven-dried reaction vessel was charged with a ketone (0.2 mmol), trifluoromethansulfinyl chloride (3, 0.6 mmol) (for 5i-5p, silver carbonate (Ag_2CO , 0.04 mmol) was also added). Toluene (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 110 ^{0}C for 12 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolated product.

General Procedure for Reaction of Thiols and Benzeneselenol for 6a-l

A 10 mL oven-dried reaction vessel was charged with a thiol or benzeneselenol (0.2 mmol) and trifluoromethansulfinyl chloride (3, 0.6 mmol). Dichloroethane (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 90 ^{0}C for 1 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding trifluoromethylthiolated product.

General Procedure for Chlorotrifluoromethylthiolation of Indoles for 7a-k

A 10 mL oven-dried reaction vessel was charged with an indole (0.2 mmol) and trifluoromethansulfinyl chloride (**3**, 0.6 mmol). Acetonitrile (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 90 0C for 20 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding chlorotrifluoromethylthiolated product.

General Procedure for Chlorotrifluoromethylthiolation of Alkenes for 8a-m

A 10 mL oven-dried reaction vessel was charged with an alkene (0.2 mmol) and trifluoromethansulfinyl chloride (**3**, 0.6 mmol). DMF (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 90 ^{0}C for 1 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding chlorotrifluoromethylthiolated product.

General Procedure for Chlorotrifluoromethylthiolation of Alkynes for 9a-o

A 10 mL oven-dried reaction vessel was charged with an alkyne (0.2 mmol) and trifluoromethansulfinyl chloride (**3**, 0.6 mmol). DMF (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 90 ^{0}C for 6 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding chlorotrifluoromethylthiolated product.

Synthesis of CF_2HSOCl

A 10 mL oven-dried reaction vessel was charged with CF_2HSO_2Na (10g, 72.5 mmol) and benzyltriethylammonium chloride (0.5g, 2.2 mmol). Toluene (30 mL) was added to the sealed reaction vessel by syringe. Thionyl chloride ($SOCl_2$) was added dropwise under vigorous stirring at room temperature, and the mixture was kept for 18 h. The ^{19}F NMR showed that the conversion ratio was about 70%.

For the isolation of CF_2HSOCl, the crude mixture was filtered by Silica gel, and the residue was washed by toluene (20 ml). The collected liquid contains CF_2HSOCl and toluene, which cannot be separated by small-scale distillation. The sample of CF_2HSOCl containing traces of toluene was obtained by fractional distillation through a 15-cm column with glass filling.

General Procedure for Difluoromethylthiolation of Indoles for 10a-f

A 10 mL oven-dried reaction vessel was charged with an indole (0.2 mmol) and difluoromethansulfinyl chloride (0.6 mmol). Acetonitrile (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 90 ^{0}C for 6 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding difluoromethylthiolation substituted products.

General Procedure for Difluoromethylthiolation of Kentones for 11a-h

A 10 mL oven-dried reaction vessel was charged with a ketone (0.2 mmol), difluoromethansulfinyl chloride (0.6 mmol). Toluene (1 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred under N_2 at 110 ^{0}C for 12 h. After cooling to room temperature the volatiles were removed under vacuum and the residue was purified by column chromatography to give the corresponding difluoromethylthiolated product.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21776138, 21476116), Fundamental Research Funds for the Central Universities (30916011102, 30918011314), Natural Science Foundation of Jiangsu Province (BK20180476), Qing Lan and Six Talent Peaks in Jiangsu Province, Priority Academic Program Development of Jiangsu Higher Education Institutions, and the Centre for Green Chemistry at the University of Massachusetts Boston and the Center for Advanced Materials and Technology in Nanjing University of Science and Technology for financial support. We also acknowledge the Bruker DRX 500 at Analysis and Test Center Nanjing University of Science and Technology for the help in obtaining NMR data.

Author Contributions

‡ L. Jiang and Q. Yan contributed equally

Keywords: Trifluoromethanesulfinyl Chloride • Reductant-free • Trifluoromethythiolation• Bifunctional Chlorotrifluoromethythiolation

[1] a) C. Hansch, Leo, A. R.W. Taft, *Chem. Rev.* **1991**, *91*, 165; b) T. Hiyama, Organofluorine Compounds: Chemistry and Properties; Springer: Berlin, 2000; c) K. Uneyama, Organofluorine Chemistry; Blackwell: Oxford, U.K., **2006**; (d) D. O'Hagan, *Chem. Soc. Rev.* **2008**, 37, 308.

[2] a) P. Laczay, G. Voros, G. Semjen, *Int. J. Parasitol.* **1995**, *25*, 753; b) P. Pommier, A. Keïta, S. W. Robert, B. Dellac, H. C. Mundt, *Rev. Med. Vet.* **2003**, *154*, 416; c) J. N. Andre, L. G. Dring, G. Gillet, Mas-Chamberlin, C. Br. *J. Pharmacol.* **1979**, *66*, 506P; d) T. Silverstone, J. Fincham, J. Br. Plumley, *J. Clin. Pharmacol.* **1979**, *7*, 353; e) G. W. Counts, D. Gregory, D. Zeleznik, M. Turck, *Antimicrob. Agents Chemother.* **1977**, *11*, 708; f) N. Aswapokee, H. C. Neu, *Antimicrob. Agents Chemother.* **1979**, *15*, 444; g) C. Hansch, A. Leo, Substituent constants for correlation analysis in chemistry and biology; Wiley: New York, **1979**; p339; h) J. Wang, M. S. Rosello, J. Acena, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.

[3] A. Aajoud, M. Raveton, D. Azrou-Isghi, M. Tissut, P. J. Ravanel, *Agric. Food Chem.* **2008**, *56*, 3732.

[4] T. Silverstone, J. Fincham, J. Plumley, Br. *J. Clin. Pharmacol.* **1979**, *7*, 353.

[5] L. M. Yagupolskii, I. I. Maletina, K. I. Petko, D. V. Fedyuk, R. Handrock, S. S. Shavaran, B. M. Klebanov, S. Herzig, *J. Fluorine Chem.* **2001**, *109*, 87.

[6] R. B. Strelkov, L. F. Semenov, *Radiobiologiya* **1964**, *4*, 756.

[7] a) V. N. Boiko, Beilstein *J. Org. Chem.* **2010**, *6*, 880; b) A. Tlili, T. Billard, *Angew. Chem. Int. Ed.* **2013**, *52*, 6818; c) X. H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731; d) X. Shao, C. Xu, L. Lu, Q. Shen, *Acc. Chem. Res.* **2015**, *48*, 1227; e) K. Zhang, X. H. Xu, F. L. Qing, Chin. *J. Org. Chem.* **2015**, *35*, 556; f) J. H. Lin, Y. L. Ji, J. C. Xiao, *Curr. Org. Chem.* **2015**, *19*, 1541.

[8] a) W. A. Sheppard, *J. Org. Chem.* **1964**, *29*, 895; b) T. S. Croft, J. J. McBrady, *J. Heterocycl. Chem.* **1975**, *12*, 845; c) A. Haas, M. Lieb, Y. Zhang, *J. Fluorine Chem.* **1985**, *29*, 311.

[9] T. R. Sharpe, S. C. Cherkofsky, W. E. Hewes, D. H. Smith, W. A. Gregory, S. B. Haber, M. R. Leadbetter, J. G. Whitney, *J. Med. Chem.* **1985**, *28*, 1188.

[10] T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 12856.

[11] C. Xu, B. Ma, Q. Shen, *Angew. Chem. Int. Ed.* **2014**, *53*, 9316.

[12] S. Alazet, L. Zimmer, T. Billard, *Chem. Eur. J.* **2014**, *20*, 8589.

[13] P. Zhang, M. Li, X. S. Xue, C. Xu, Q. Zhao, Y. Liu, H. Y. Wang, Y. Guo, L. Lu, Q. Shen, *J. Org. Chem.* **2016**, *81*, 7486.

[14] a) X. Shao, X. Q. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem. Int. Ed.* **2013**, *52*, 3457; b) E. V. Vinogradova, P. Muller, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2014**, *53*, 3125

[15] F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382.

[16] A. Ferry, T. Billard, B. R. Langlois, E. Bacqu, *Angew. Chem. Int. Ed.* **2009**, *48*, 8551.

[17] a) Y. D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782; b) Z. Huang, Y. D. Yang, E. Tokunaga, N. Shibata, *Org. Lett.* **2015**, *17*, 1094; c) S. Arimori, M. Takada, N. Shibata, *Org. Lett.* **2015**, *17*, 1063.

[18] Z. Huang, K. Okuyama, C. Wang, E. Tokunaga, X. Li, N. Shibata, *ChemistryOpen* **2016**, DOI: 10.1002/open.201500225.

[19] a) L. Jiang, J. Qian, W. Yi, G. Lu, C. Cai, W. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14965; b) Q. Yan, L. Jiang, W. Yi, W. Zhang, Q. Liu, *Adv. Synth. Catal.* **2017**, *359*, 2471; c) M. Bu, G. Lu, C. Cai, *Org. Chem. Front.*, **2017**, *4*, 266; d) D.-W. Sun, X. Jiang, M. Jiang, Y. Lin, J.-T. Liu, *Eur. J. Org. Chem.* **2017**, 3505; e) X. Zhao, A. Wei, B. Yang, T. Li, Q. Li, D. Qiu, K. Lu, *J. Org. Chem.* **2017**, 82, 9175.

[20] Y. Yang, L. Xu, S. Yu, X. Liu, Y. Zhang, D. A. Vicic, *Chem. Eur. J.* **2016**, *22*, 858.

[21] a) H. Chachignon, M. Maeno, H. Kondo, N. Shibata, D. Cahard, *Org. Lett.* **2016**, *18*, 2467; b) L. Jiang, W. Yi, Q. Liu, *Adv. Synth. Catal.* **2016**, *358*, 3700; c) K. Lu, Z. Deng, M. Li, T. Li, X. Zhao, *Org. Biomol Chem.* **2017**, *15*, 1254; d) X. Zhao, T. Li, B. Yang, D. Qiu, K. Lu, *Tetrahedron* **2017**, 73, 3112; e) L. Jiang, T. Ding, W. Yi, X. Zeng, W. Zhang, *Org. Lett.* **2018**, *20*, 2236.

[22] H. Han, Z. Zhou, J. Nie, X. Cheng, S. Gong; Patent CN102916096, 2012.

[23] a) O.D. Gupta, W. A. Kamil, *J. M.* Shreeve, *Inorg. Chem.* **1985**, *24*, 2127; b) V. D. Romanenko, C. Thoumazet, V. Lavallo, F. S. Tham, G. Bertrand, *Chem. Commun.* **2003**, 1680; c) L. J. Liu, L. J. Chen, P. Li, X. B. Li, J. T. Liu, *J. Org. Chem.* **2011**, *76*, 4675.

[24] C. T. Ratcliffe, J. M. Shreeve, *J. Am. Chem. Soc.* **1968**, *90*, 5403.

[25] a) Q. Lefebvre, E. Fava, P. Nikolaienko, M. Rueping, *Chem. Commun.* **2014**, *50*, 6617; b) M. Y. Hu, J. Rong, W. J. Miao, C. F. Ni, Y. X. Han, J. B. Hu, *Org. Lett.* **2014**, *16*, 2030; c) S. Alazet, E. Ismalaj, Q. Glenadel, D. Le Bars, T. Billard, *Eur. J. Org. Chem.* **2015**, *4607*; d) W. Wu, X. Zhang, F. Liang, S. Cao, *Org. Biomol. Chem.* **2015**, *13*, 6992.

[26] a) F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269; b) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981. c) J. P. Wolfe, *Angew. Chem. Int. Ed.* **2012**, *51*, 10224.

[27] a) X.-J. Tang, W. R. Dolbier, Jr., *Angew. Chem. Int. Ed.* **2015**, *54*, 4246; b) H. S. Han, Y. J. Lee, Y.-S. Jung, S. B. Han, *Org. Lett.* **2017**, *19*, 1962.

[28] D.-W. Sun, X. Jiang, M. Jiang, Y. Lin, J.-T. Liu, *Eur. J. Org. Chem.* **2018**, *18*, 2078.

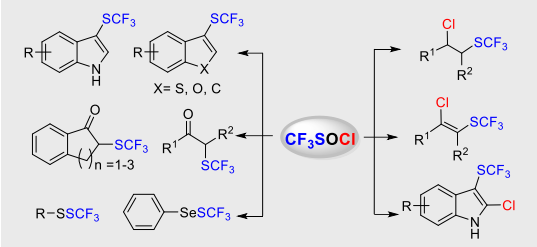
[29] J. Hu, *J. Fluorine Chem.* **2009**, *130*, 1130.

10.1002/chem.201804027

WILEY-VCH

Entry for the Table of Contents

FULL PAPER



Trifluoromethanesulfinyl chloride (CF_3SOCl) is introduced as a new reagent for C-H trifluoromethylthiolation of indoles, thiophenes, ketones, thiols and benzeneselenols, as well as 1,2-chlorotrifluoromethylthiolation of indoles, styrenes, and alkyens.

Lvqi Jiang, Qiang Yan, Rongkang Wang, Tianqi Ding, Wenbin Yi and Wei Zhang**

Page No. – Page No.

Trifluoromethanesulfinyl Chloride for Electrophilic Trifluoromethythiolation and Bifunctional Chlorotrifluoromethythiolation