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First and second generation of trifluoromethanesulfenamide reagent: A trifluoromethylthiolating comparison☆

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ABSTRACT

Trifluoromethylthiolation of molecules is a more and more studied reaction. In particular, the direct electrophilic trifluoromethylthiolation plays an important role in this chemistry. Among the various developed reagents, trifluoromethanesulfenamides constitute an efficient family of reagents. However, no systematic comparison of these two generations has been realized. In this paper, the difference of reactivity of these reagents is studied towards various nucleophiles.

1. Introduction

With the fluorine discovery [1], Moissan has open the way to a fascinating chemistry which led to the design of new compounds with specific and particular properties for a large panel of various applications [2–5]. In particular, fluorinated molecules have found a crucial place in life sciences due to their original physico-chemical properties [6–12]. In this specific field of applications, the trifluoromethylthio group appeared to be very contributive. Indeed, this substituent is one of the most lipophilic fluoroalkyl groups, with a Hansch parameter $\pi_R = 1.44$ [13]. Such important physico-chemical property greatly contributes to enhancing molecules biodisponibility by favoring the transmembrane permeation [6,7,14–18].

This growing interest for the CF_3S group has largely contributed to the recent developments of new methodologies and new reagents to introduce this moiety onto organic molecules [19–21]. More specifically, a particular focus was recently laid on direct methods of trifluoromethylthiolation which are more elegant and practical in a synthetic point of view [19,20,22,23].

Such recent strategies have required the development of new shelf-stable reagents. More specifically, new electrophilic trifluoromethylthiolating reagents [24–30] were highly required to replace CF_3SCl, the only reagent available until recently, but very toxic [31].

2. Results and discussion

One of the first developed reagents was the 1st generation of trifluoromethanesulfenamide **1** [25,32–36]. Recently, the 2nd generation of trifluoromethanesulfenamide **2** has been introduced to realize more difficult reactions [29,37,38] (Fig. 1). A reactivity comparison between these reagents could be interesting to well rationalize the choice of the better trifluoromethanesulfenamide reagent.

The first reaction described was the electrophilic addition onto alkenes (Table 1) [32]. With Brønsted acids, the reagent **1a** gave the best results compared to **1b** (entries 1–2, 4–5). This is particularly clear with TFA since no addition product was observed (entries 4–5). This could be explained by the bigger counter ion of trifluoroacetate (N-Me anilinium) which strongly contribute to decrease its already weak nucleophilicity. With **2**, no reaction was

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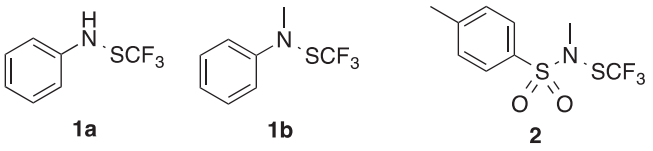


Fig. 1. 1st and 2nd generation of trifluoromethanesulfenamide.

observed with TsOH or TFA (entries 3, 6) because of the lower basicity of the nitrogen atom which could not be easily protonated by these too weak acids. This protonation step being crucial to activate the reagents, no reactions can occur in these conditions. With TfOH, all the reagents are reactive, even if the more basic reagents **1** stays more efficient (entries 7–9). It should be noticed that an increased temperature gave lower yields (entries 10–11), the degradation of activated reagents being more rapid than the electrophilic attack onto cyclohexene. With Lewis acid activation, same observations have been made. Strong Lewis acid such as $BF_3{\cdot}Et_2O$ succeeded to activate all the reagents (entries 12–14), but more efficiently **1**, whereas weak Lewis acid $ClSiMe_3$ seemed able to activate only **1b** (entries 15–16).

Friedel-Crafts reactions have been then studied (Table 2) [33,38]. With dimethoxybenzene (**5a**), reactions were observed with all the reagents with TsOH as activator, with a better yield obtained with **1a** (entries 1–3). The product formation by using **2** proves that TsOH, contrary to the previous observation with cyclohexene (Table 1, entry 3), could activate this one. Consequently, the reagent activation seems to be not the lone determining parameter, and the nucleophilicity of the nucleophile appears also to be important. Hence, the couple activator/nucleophilicity must be taken in consideration. Triflic acid could also promote this reaction, even at room temperature, with better results by using **2** (entries 4–7). Catalytic reaction was also possible with TfOH but only with the more reactive reagent **2**, subject to heat at 80 °C (entries 8–10). As with cyclohexene, $BF_3{\cdot}Et_2O$ was a better activator with **1b** than with **2** (entries 11–13).

In the case of indole (**5b**), same results than with **5a** were observed when TsOH was used as the catalyst (entries 14–16). Nevertheless, because of the nitrogen atom of **5b**, no reaction was observed with TfOH (entry 17). By using $ClSiMe_3$, in acetonitrile, good yields were observed with **2** (entry 19), contrary to the case of cyclohexene (Table 1, entry 16). This confirms the necessity to consider both activator and nucleophilicity to analyze results. Catalytic amount of $ClSiMe_3$ could be used both with **1b** and **2** to trifluoromethylthiolate indole (**5b**) (entries 20–21), which is more nucleophile than **5a**.

When less electron-rich aromatic compounds were considered, no reactions where observed with **1b** or **1a**, only **2** with TfOH (or $ClSiMe_3$ if the aromatic compound contents a nitrogen atom) was able to perform aromatic trifluoromethylthiolation [38].

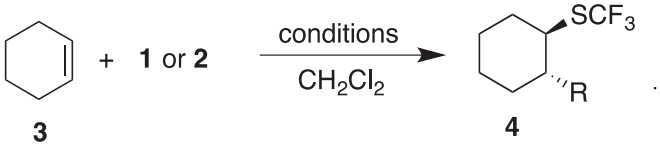
Trifluoromethylthiolation of Grignard reagent constitutes also a convenient way to obtain various trifluoromethylthioethers (Table 3) [34].

With Grignard compounds, **2** was systematically the better trifluoromethylthiolating reagent. More particularly, in the case of benzyl Grignard (**7b**), a degradation of the resulting product **8b** was observed in the reacting medium by using **1b** whereas **8b** seemed stable when obtained from **2**. This lets suggest that the released amide during the reaction contribute to the degradation of **8b** (because of the acidic benzylic hydrogens in α position of SCF_3). Therefore, if the *N*-methylanilide arising from **1b** is basic enough, the sulfonamide coming from **2** is a too weak base to contribute to this degradation.

In the same strategy, terminal alkynes have been also trifluoromethylthiolated in presence of lithium base (Table 4).

When the alkynes were previously deprotonated with 1 eq. of BuLi, similar results than for Grignard reagents were obtained (entries 1–4). With non base-sensitive trifluoromethylthiolated alkyne (**10a**), both reagents gave similar yields (entries 1–2) whereas with more sensitive product (**10b**), in situ degradation was observed with **1b** and not with **2** (entries 3–4). However, this trifluoromethylthiolation could also work with catalytic amount of BuLi but only by using **1b**. With **2** the generated sulfonamide anion is not basic enough to deprotonate the terminal alkynes and, thus, to catalyze the reaction.

Table 1
Electrophilic addition onto alkenes



Entry	Reagent	Conditions	*T* (°C)	**4** (%)[a]
1	**1a**	TsOH (2.5 eq.)	50	**4a**: X = OTs (80)
2	**1b**	TsOH (2.5 eq.)	50	**4a**: X = OTs (70)
3	**2**	TsOH (2.5 eq.)	50	**4a**: X = OTs (0)
4	**1a**	TFA (2.5 eq.)	50	**4b**: X = O_2CCF_3 (75)
5	**1b**	TFA (2.5 eq.)	50	**4b**: X = O_2CCF_3 (0)
6	**2**	TFA (2.5 eq.)	50	**4b**: X = O_2CCF_3 (0)
7	**1a**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	RT	**4c**: X = O_2CPh (69)
8	**1b**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	RT	**4c**: X = O_2CPh (71)
9	**2**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	RT	**4c**: X = O_2CPh (54)
10	**1b**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	50	**4c**: X = O_2CPh (50)
11	**2**	TfOH (2.0 eq.)/$PhCO_2H$ (1.5 eq.)	50	**4c**: X = O_2CPh (35)
12	**1a**	$BF_3{\cdot}Et_2O$ (5.0 eq.)/TsONa (1.5 eq.)	50	**4a**: X = OTs (85)
13	**1b**	$BF_3{\cdot}Et_2O$ (5.0 eq.)/TsONa (1.5 eq.)	RT	**4a**: X = OTs (90)
14	**2**	$BF_3{\cdot}Et_2O$ (5.0 eq.)/TsONa (1.5 eq.)	RT	**4a**: X = OTs (0)
15	**1b**	$ClSiMe_3$ (5.0 eq.)	RT	**4d**: X = Cl (84)
16	**2**	$ClSiMe_3$ (5.0 eq.)	RT	**4d**: X = Cl (0)

[a] Crude yield determine by ^{19}F NMR using $PhOCF_3$ as an internal standard. All the compounds were isolated with yields in accordance with titration.

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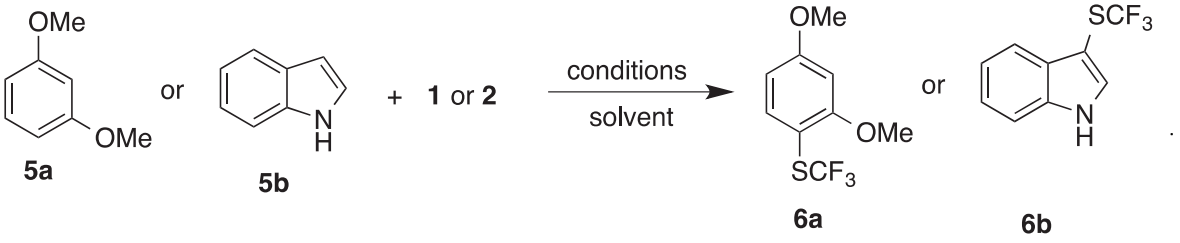
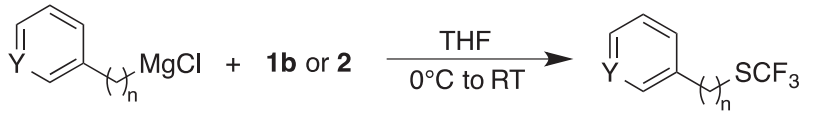
Table 2
Aromatic electrophilic substitution



Entry	Reagent	Aromatic	Conditions	Solvent	T(°C)	**6** (%)[a]
1	**1a**	**5a**	TsOH (2.5 eq.)	CH_2Cl_2	50	**6a** (94)
2	**1b**	**5a**	TsOH (2.5 eq.)	CH_2Cl_2	50	**6a** (45)
3	**2**	**5a**	TsOH (2.5 eq.)	CH_2Cl_2	50	**6a** (36)
4	**1b**	**5a**	TfOH (1 eq.)	CH_2Cl_2	50	**6a** (65)
5	**2**	**5a**	TfOH (1 eq.)	CH_2Cl_2	50	**6a** (92)
6	**1b**	**5a**	TfOH (1 eq.)	CH_2Cl_2	RT	**6a** (66)
7	**2**	**5a**	TfOH (1 eq.)	CH_2Cl_2	RT	**6a** (88)
8	**2**	**5a**	TfOH (0.2 eq.)	CH_2Cl_2	50	**6a** (40)
9	**2**	**5a**	TfOH (0.2 eq.)	$ClCH_2CH_2Cl$	80	**6a** (90)
10	**1b**	**5a**	TfOH (0.2 eq.)	$ClCH_2CH_2Cl$	80	**6a** (<5)
11	**1b**	**5a**	$BF_3{\cdot}Et_2O$ (5 eq.)	CH_2Cl_2	RT	**6a** (69)
12	**2**	**5a**	$BF_3{\cdot}Et_2O$ (5 eq.)	CH_2Cl_2	RT	**6a** (0)
13	**2**	**5a**	$BF_3{\cdot}Et_2O$ (5 eq.)	CH_2Cl_2	50	**6a** (16)
14	**1a**	**5b**	TsOH (2.5 eq.)	CH_2Cl_2	50	**6b** (100)
15	**1b**	**5b**	TsOH (2.5 eq.)	CH_2Cl_2	50	**6b** (80)
16	**2**	**5b**	TsOH (2.5 eq.)	CH_2Cl_2	50	**6b** (0)
17	**2**	**5b**	TfOH (1 eq.)	CH_2Cl_2	50	**6b** (0)
18	**2**	**5b**	$ClSiMe_3$ (1 eq.)	CH_2Cl_2	50	**6b** (0)
19	**2**	**5b**	$ClSiMe_3$ (1 eq.)	CH_3CN	80	**6b** (95)
20	**2**	**5b**	$ClSiMe_3$ (0.2 eq.)	CH_3CN	80	**6b** (95)
21	**1b**	**5b**	$ClSiMe_3$ (0.2 eq.)	CH_3CN	80	**6b** (95)

[a] Crude yield determine by ^{19}F NMR using $PhOCF_3$ as an internal standard. All the compounds were isolated with yields in accordance with titration.

Table 3
Trifluoromethylthiolation of Grignard reagents



7a: Y = CH, n=0
7b: Y = CH, n=1
7c: Y = N, n=0

Entry	Reagent	Grignard **7**	**8** (%)[a]
1	**1b**	**7a**	**8a** (86)
2	**2**	**7a**	**8a** (94)
3	**1b**	**7b**	**8b** (10)
4	**2**	**7b**	**8b** (63)
5	**1b**	**7c**	**8c** (67)
6	**2**	**7c**	**8c** (72)

[a] Crude yield determine by ^{19}F NMR using $PhOCF_3$ as an internal standard. All the compounds were isolated with yields in accordance with titration.

Ketones could be also trifluoromethylthiolated with trifluoromethanesulfenamide (Table 5) [29].

In basic conditions, only reagent **2** was able to react with ketones, no reaction being observed with **1b**. Nevertheless, by using **2** in these conditions, only bis-trifluoromethylthiolation (**12b**) was observed (entries 1–2). By analogy with halogenation of ketones, acidic conditions have been also tested [39]. Again, only **2** was enough reactive to give the expected mono-trifluoromethylthiolated product (**12a**) with good yields. These results suggest that a very reactive reagent should be used to quickly trap enol or enolate forms before side reactions, such as auto-aldol reactions, can occur.

Finally, trans-amination reactions to access to other trifluoromethanesulfenamides (**14**) have been envisaged (Scheme 1) [36].

Both reagents gave same results (**14a**), but with more hindered amine, the highest reactivity of **2** allowed to achieve better yield (**14b**). With very weak nucleophilic amine, **1b** appeared to be not enough electrophilic to react whereas **2** succeeded to perform *N*-trifluoromethylthiolation with a good yield (**14c**).

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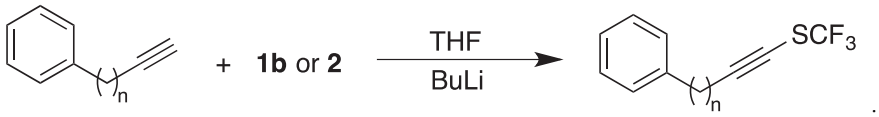
Table 4
Trifluoromethylthiolation of terminal alkynes



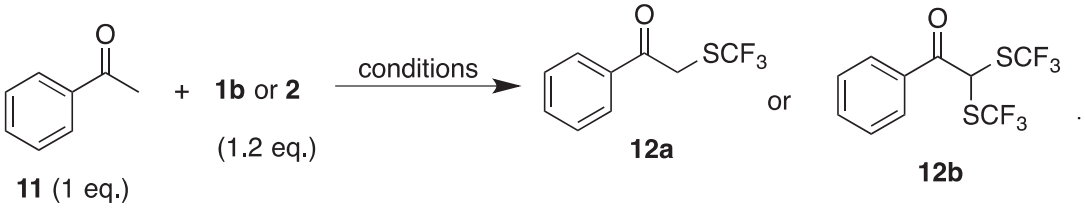
9a: n=0
9b: n=2

10

Entry	Reagent	9	BuLi (eq.)	T (°C)	10 (%)[a]
1	**1b**	**9a**	1	−78	**10a** (73)
2	**2**	**9a**	1	−78	**10a** (72)
3	**1b**	**9b**	1	−78	**10b** (19)
4	**2**	**9b**	1	−78	**10b** (90)
5	**1b**	**9a**	0.1	0	**10a** (88)
6	**2**	**9a**	0.1	0	**10a** (0)

[a] Crude yield determine by ^{19}F NMR using $PhOCF_3$ as an internal standard. All the compounds were isolated with yields in accordance with titration.

Table 5
Trifluoromethylthiolation of ketones



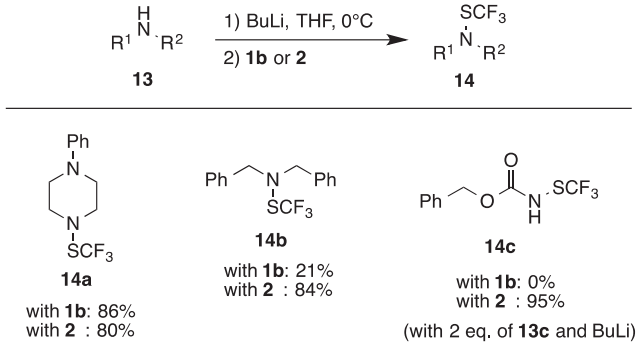
11 (1 eq.)

12a

12b

Entry	Reagent	Conditions	T (°C)	12 (%)[a]
1	**1b**	LDA (1.2 eq.) in THF	−78	0
2	**2**	LDA (1.2 eq.) in THF	−78	**12b** (56)
3	**1b**	TMSCl (0.3 eq.) in CH_3CN	90	0
4	**2**	TMSCl (0.3 eq.) in CH_3CN	90	**12a** (92)

[a] Crude yield determine by ^{19}F NMR using $PhOCF_3$ as an internal standard. All the compounds were isolated with yields in accordance with titration.



Scheme 1. Trans-amination reaction with amines. (Crude yield determine by ^{19}F NMR using $PhOCF_3$ as an internal standard. All the compounds were isolated with yields in accordance with titration).

3. Conclusion

In this paper, the comparison of reactivity between both generations of trifluoromethanesulfenamide reagents has been realized. These results confirmed clearly that the 2nd generation (**2**) is more electrophilic than the 1st one (**1**). Nevertheless, it is noteworthy that to determine which reagent used, the reaction conditions could also play a crucial role in this selection. To resume, the electrophilicity of the reagent, the nature of the released amide, the choice of the used activator and the nucleophilicity of the substrate must be carefully analyzed to select the better trifluoromethylthiolating reagent.

To conclude, these two generations of trifluoromethanesulfenamide are fully complementary and, even if the 2nd generation seems more reactive, for certain reactions the 1st generation conserves some specificities and cannot be advantageously substituted by the 2nd generation.

4. Experimental

4.1. General information

Dry solvents were purchased from Sigma Aldrich. Commercial reagents were used as supplied. NMR spectra were recorded on a Bruker AV 400 spectrometer at 400 MHz (^1H NMR), 100 MHz (^{13}C NMR), 376 MHz (^{19}F NMR). All coupling constants were reported in Hz.

4.2. Electrophilic addition onto alkenes (Brønsted acid)

To a solution of **1** or **2** (0.30 mmol, 1.0 equiv.) in dry DCM (1 mL) were added cyclohexene (**3**) (0.30 mmol, 1.0 equiv.) and the Bronsted acid (0.75 mmol, 2.5 equiv.). The reaction mixture was stirred at the indicated temperature for 18 h. The organic phase

was washed with water, dried over Na_2SO_4 and filtered. After removing solvent in vacuo, the crude was purified by flash chromatography to afford the desired product.

4.3. Electrophilic addition onto alkenes (mixture of Brønsted acids)

To a solution of **1** or **2** (0.30 mmol, 1.0 equiv.) in dry DCM (1 mL) were added cyclohexene (**3**) (0.30 mmol, 1.0 equiv.), benzoic acid (0.45 mmol, 1.5 equiv.) and TfOH (0.60 mmol, 2.0 equiv.). The reaction mixture was stirred at the indicated temperature for 18 h. The organic phase was washed with water, dried over Na_2SO_4 and filtered. After removing solvent in vacuo, the crude was purified by flash chromatography to afford the desired product.

4.4. Electrophilic addition onto alkenes (Lewis acid)

To a solution of **1** or **2** (0.30 mmol, 1.0 equiv.) in dry DCM (1 mL) were added cyclohexene (**3**) (0.30 mmol, 1.0 equiv.) and sodium tosylate (0.45 mmol, 1.5 equiv.). The resulting suspension was vigorously stirred at room temperature. After stirring for 5 min, the Lewis acid (1.5 mmol, 5.0 equiv.) was added dropwise. The resulting mixture was stirred at the defined temperature for 4 h. The reaction mixture was then partitioned between Et_2O and H_2O, the organic phase was washed with aqueous HCl (2 M), dried over Na_2SO_4 and filtered. After removing solvent in vacuo, the crude was purified by flash chromatography to afford the desired product

4.5. (1R*,2R*)-2-[(trifluoromethyl)sulfanyl]cyclohexyl 4-methylbenzene-1-sulfonate (**4a**)

Eluent for the flash chromatography: pentane/acetone: 70/1.
^{1}H NMR: δ = 7.80 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 4.49 (td, J = 6.6 Hz, 3.6 Hz, 1H), 3.29 (td, J = 6.9 Hz, 4.2 Hz, 1H), 2.44 (s, 3H), 2.22 (m, 1H), 2.03 (m, 1H), 1.69–1.65 (m, 3H), 1.48–1.44 (m, 3H).
^{19}F NMR: δ = −40.06 (s, 3F).
In accordance with literature [32].

4.6. (1R*,2R*)-2-[(trifluoromethyl)sulfanyl]cyclohexyl 2,2,2-trifluoroacetate (**4b**)

Eluent for the flash chromatography: pentane/acetone: 70/1.
^{1}H NMR: δ = 4.94 (td, J = 9.3 Hz, 4.2 Hz, 1H), 3.28 (m, 1H), 2.30 (m, 1H), 2.15 (m, 1H), 1.87–1.35 (m, 6H).
^{19}F NMR: δ = −39.82 (s, 3F), −75.68 (s, 3F).
In accordance with literature [32].

4.7. (1R*,2R*)-2-[(trifluoromethyl)sulfanyl]cyclohexyl benzoate (**4c**)

Colorless oil.
Eluent for the flash chromatography: pentane/acetone: 200/1.
^{1}H NMR: δ = 8.06 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 5.01 (td, J = 9.0 Hz, 4.1 Hz, 1H), 3.40 (td, J = 9.6 Hz, 4.1 Hz, 1H), 2.34 (m, 1H), 2.20 (m, 1H), 1.84–1.42 (massif, 6H).
^{13}C NMR: δ = 166.0, 133.5, 133.3 (q, J = 307 Hz), 130.4, 130.1, 128.8, 74.1, 47.5 (q, J = 2 Hz), 33.2, 31.5, 25.2, 23.5.
^{19}F NMR: δ = −39.60 (s, 3F).

4.8. (1R*,2R*)-1-chloro-2-[(trifluoromethyl)sulfanyl]cyclohexane (**4d**)

Eluent for the flash chromatography: pentane/acetone: 200/1.
^{1}H NMR: δ = 4.10 (m, 1H), 3.45 (m, 1H), 2.39 (m, 1H), 2.22 (m, 1H), 1.86–1.67 (m, 3H), 1.62–1.38 (m, 3H).
^{19}F NMR: δ = −39.95 (s, 3F).
In accordance with literature [32].

4.9. Aromatic electrophilic substitution

A 10 mL sealed tube equipped with a magnetic stirrer was charged with **5** (0.50 mmol, 1.0 equiv.) and **1** or **2** (1.2 equiv.) in dry solvent. The reaction was stirred at room temperature for 1 min. and acid was slowly added. The reaction mixture was stirred at the indicated temperature for the indicated time. Conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. After completion, the reaction was cooled to room temperature, DCM was added and the organic phase was washed three times with distilled water and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by flash chromatography (100% pentane to 95/5 pentane/Et_2O) to afford the desired product.

4.10. Synthesis of 2,4-dimethoxy-1-[(trifluoromethyl)sulfanyl]benzene (**6a**)

^{1}H NMR: δ = 7.53 (m, 1H), 6.54–6.50 (massif, 2H), 3.88 (s, 3H), 3.83 (s, 3H).
^{19}F NMR: δ = −44.13 (s, 3F).
In accordance with literature [33].

4.11. Synthesis of 3-[(trifluoromethyl)sulfanyl]-1H-indole (**6b**)

^{1}H NMR: δ = 8.56 (br, 1H), 7.80 (m, 1H), 7.53 (d, J = 2.6 Hz, 1H), 7.42 (m, 1H), 7.32–7.24 (massif, 2H).
^{19}F NMR: δ = −45.36 (s, 3F).
In accordance with literature [33].

4.12. Trifluoromethylthiolation of Grignard reagents

A dry and nitrogen-flushed 10 mL flask equipped with a magnetic stirrer and a septum was charged with **1** or **2** (1.2 equiv.). The flask was cooled to 0 °C, and Grignard reagent solution (**7**) (in THF, 1.0 equiv.) was added dropwise. After 10 min of stirring, the reaction temperature was increased to 20 °C. The reaction was stirred for further 3 h (conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard) and was then quenched with aqueous HCl (0.5 M). Pentane was added and the organic phase was washed with aqueous HCl (12 M) and water, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (pentane) to afford the desired product.

4.13. Synthesis of [(trifluoromethyl)sulfanyl]benzene (**8a**)

^{1}H NMR: δ = 7.67 (d, J = 7.2 Hz, 2H), 7.45 (m, 3H).
^{19}F NMR: δ = −43.26 (s, 3F).
In accordance with literature [34].

4.14. Synthesis of {[(trifluoromethyl)sulfanyl]methyl}benzene (**8b**)

^{1}H NMR: δ = 7.35 (m, 5H), 4.15 (s, 2H).
^{19}F NMR: δ = −42.15 (s, 3F).
In accordance with literature [40].

4.15. Synthesis of 3-[(trifluoromethyl)sulfanyl]pyridine (8c)

A dry and nitrogen-flushed 10 mL flask equipped with a magnetic stirrer and a septum was charged with *i*PrMgCl·LiCl solution (1.3 M in THF, 1.1 equiv.). The reaction mixture was cooled to −15 °C, and a solution of 3-bromopyridine (1.0 equiv.) in THF (0.5 mL) was added dropwise. After 1 h of stirring, the reaction temperature was increased to 0 °C and a solution of **1** or **2** (1.2 equiv.) in dry THF (1 M) was added dropwise. After 10 min of stirring, the reaction temperature was increased to 25 °C. The

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reaction was stirred for further 3 h (conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard) and was then quenched with saturated aqueous NH_4Cl solution (2 mL). Pentane was added and the organic phase was washed with saturated aqueous NH_4Cl solution and water, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (pentane) to afford the desired product.

^1H NMR: δ = 8.84 (m, 1*H*), 8.72 (m, 1*H*), 7.98 (m, 1*H*), 7.38 (m, 1*H*).

^{19}F NMR: δ = −42.85 (s, 3F).

In accordance with literature [34].

4.16. Trifluoromethylthiolation of terminal alkynes

Procedure A: A dry and nitrogen-flushed 10 mL flask equipped with a magnetic stirrer and a septum was charged with alkyne (**9**) (1.0 equiv.) and dry THF (0.5 M). The reaction mixture was cooled to −78 °C, and *n*BuLi solution (1.6 M in THF, 1.1 equiv.) was added dropwise. After 1 h of stirring, a solution of **1** or **2** (1.2 equiv.) in dry THF (0.5 M) was added dropwise. The reaction was stirred for further 3 h (conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard) and was then quenched with aqueous HCl. Pentane was added and the organic phase was washed with aqueous HCl and water, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (pentane) to afford the desired product.

Procedure B: A dry and nitrogen-flushed 10 mL Schlenk tube equipped with a magnetic stirrer and a septum was charged with **1** or **2** (1.2 equiv.) and alkyne (**9**) (1.0 equiv.) and was evacuated and refilled with nitrogen three times. Dry THF (2 M) was added and the reaction flask was again evacuated and refilled with nitrogen three times. The reaction mixture was cooled to 0 °C, and *n*BuLi solution (1.6 M in THF, 10–20 mol%) was added at 0 °C. After 1 min of stirring (conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard), the reaction mixture was quenched with aqueous HCl. Pentane was added and the organic phase was washed with aqueous HCl and water, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (pentane) to afford the desired product.

4.17. Synthesis of {2-[(trifluoromethyl)sulfanyl]ethynyl}benzene (*10a*)

^1H NMR: δ = 7.51 (m, 2*H*), 7.48 (m, 3*H*).

^{19}F NMR: δ = −44.10 (s, 3F).

In accordance with literature [34].

4.18. Synthesis of {4-[(trifluoromethyl)sulfanyl]but-3-yn-1-yl}benzene (*10b*)

^1H NMR: δ = 7.26 (m, 5*H*), 2.87 (d, *J* = 7.3 Hz, 2*H*), 2.68 (d, *J* = 7.3, 2*H*).

^{19}F NMR: δ = −44.70 (s, 3F).

In accordance with literature [35].

4.19. Synthesis of 1-phenyl-2-[(trifluoromethyl)sulfanyl]ethan-1-one (*12a*)

A 10 mL sealed tube equipped with a magnetic stirrer was charged with acetophenone (**11**) (0.50 mmol, 1.0 equiv.) in dry ACN followed by **1** or **2** (0.60 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 1 min., TMSCl was added and the reaction was stirred at 90 °C for 18 h. The conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. After completion, the reaction mixture was cooled to room temperature, the solvent was removed under vacuum and the residue was purified by flash chromatography to afford the desired product.

Eluent for flash chromatography: 100% pentane to pentane/Et_2O: 97/3.

^1H NMR: δ = 7.96 (dd, *J* = 8.3 Hz, 1.3 Hz, 2*H*), 7.66 (t, *J* = 8.4 Hz, 1*H*), 7.53 (t, *J* = 7.6 Hz, 2*H*), 4.51 (s, 2*H*).

^{19}F NMR: δ = −41.91 (s, 3F).

In accordance with literature [41].

4.20. Synthesis of 1-phenyl-2,2-bis[(trifluoromethyl)sulfanyl]ethan-1-one (*12b*)

A dry and nitrogen-flushed 10 mL tube equipped with a magnetic stirrer and a septum was charged with acetophenone (**11**) (0.50 mmol, 1.0 equiv.) and was evacuated and refilled with nitrogen three times. Dry THF (0.5 mL) was added and the reaction flask was again evacuated and refilled with nitrogen three times. Under nitrogen atmosphere, the reaction mixture was cooled to −78 °C, and LDA solution (1.6 M in THF, 0.375 mL, 0.60 mmol, 1.2 equiv.) was added dropwise via a syringe. After 1 h of stirring at −78 °C, a solution of **1** or **2** (2.2 equiv.) in dry THF (1 mL) was added dropwise. Conversion was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. After completion, the reaction was quenched with distilled water. The reaction mixture was warmed to room temperature and Et_2O was added. The organic phase was washed with aqueous HCl 0.5 M, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated to dryness under a moderate vacuum of 400 mbar at 20 °C. The crude residue was purified by flash chromatography to afford the desired product.

Eluent for flash chromatography: 100% pentane to pentane/DCM: 9/1.

^1H NMR: δ = 7.97 (dq, *J* = 8.3 Hz, 1.2 Hz, 2*H*), 7.70 (tt, *J* = 7.5 Hz, 1.2 Hz, 1*H*), 7.56 (tt, *J* = 8.2 Hz, 1.4 Hz, 2*H*), 6.11 (s, 1*H*).

^{19}F NMR: δ = −40.17 (s, 6F).

In accordance with literature [29].

4.21. Trans-amination reaction with amines

A dry and nitrogen-flushed 10 mL round bottom flask equipped with a magnetic stirrer and a septum was charged with amine (**13**) (0.50 mmol, 1.0 equiv.) and was evacuated and refilled with nitrogen three times. Dry THF (0.5 mL) was added and the reaction flask was again evacuated and refilled with nitrogen three times. The reaction mixture was cooled to 0 °C, and *n*BuLi solution (1.6 M in THF, 0.55 mmol, 1.1 equiv.) was added. After 5 min of stirring, **1** or **2** (0.55 mmol, 1.1 equiv.) was added at 0 °C and the reaction was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. Reaction was quenched with saturated aqueous $NaHCO_3$ and EtOAc was added. The organic phase was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography to afford the desired product.

4.22. 1-Phenyl-4-[(trifluoromethyl)sulfanyl]piperazine (*14a*)

Eluent for flash chromatography: cyclohexane/EtOAc: 95/5.

^1H NMR: δ = 7.24 (m, 2*H*), 6.84 (m, 3*H*), 3.38 (m, 4*H*), 3.19 (m, 4*H*).

^{19}F NMR: δ = −46.53 (s, 3F).

In accordance with literature [36].

4.23. Dibenzyl[(trifluoromethyl)sulfanyl]amine (*14b*)

Eluent for flash chromatography: cyclohexane/EtOAc: 99/1.

^1H NMR: δ = 7.49–7.37 (m, 10*H*), 4.35 (s, 4*H*).

^{19}F NMR: δ = −47.72 (s, 3F).

In accordance with literature [36].

*4.24. Benzyl N-[(trifluoromethyl)sulfanyl]carbamate (**14c**)*

Eluent for flash chromatography: cyclohexane/EtOAc: 80/20.
^{1}H NMR: δ = 7.43–7.39 (massif, 5*H*), 6.15 (NH), 5.42 (s, 2*H*).
^{19}F NMR: δ = −53.31 (s, 3F).
In accordance with literature [42].

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