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Regio- and Stereocontrolled Nucleophilic Trifluoromethylthiolation of Morita–Baylis–Hillman Carbonates

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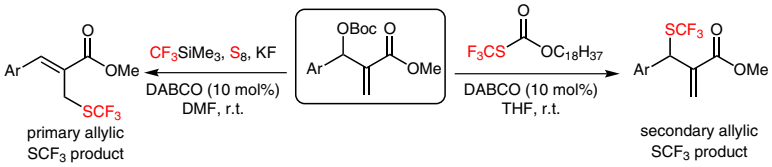

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Abstract Reactions of Morita–Baylis–Hillman carbonates with metal-free sources of trifluoromethylthio anion have been studied. The combination of $CF_3SiMe_3/S_8/KF/DMF$ gave the primary allylic SCF_3 products through apparent S_N2' reaction whereas the use of Zard's reagent, $CF_3SCO_2C_{18}H_{37}$, allowed us to intercept the fleeting secondary allylic SCF_3 product.

Key words fluorine, sulphur, Morita–Baylis–Hillman adduct, substitution, stereocontrol

Organofluorine chemistry has become, more than ever, an area of tremendous expansion. It is not only because fluorinated compounds play a key role in pharmaceutical, agrochemical, and material sciences, but also because fluorine is a fascinating atom revealing subtle effects.[1] Fluorine has sparked the imagination of chemists for the synthesis of a plethora of novel architectures featuring fluorine atom(s). Among the fluorinated motifs in vogue, the trifluoromethylthio group occupies a place of choice owing to its exceptional lipophilicity that it confers to molecules (Hansch hydrophobic parameter: $\pi = 1.44$ versus 0.88 for CF_3 and 1.04 for OCF_3)[2] and its high electron-withdrawing character (Hammett substituent constants: $\sigma_m = 0.40$, $\sigma_p = 0.50$ versus 0.43, 0.54, respectively for the CF_3 group).[3] Indeed, the SCF_3 group is very appealing for the conception of new drugs with enhanced capacity to pass cell membranes.[4] Several synthetic routes to SCF_3-bearing compounds have been elaborated including the direct introduction of the SCF_3 group, the trifluoromethylation of sulfur compounds, and various functional group interconversions.[5] Many of the direct approaches involved C(sp^2)–S bond-forming reactions because aryl– and heteroaryl–SCF_3 compounds are predominant in biologically active compounds bearing a SCF_3 group such as Toltrazuril,[6a] Tiflorex,[6b] and Vaniliprole[7] (Figure 1). Much less evaluated were the compounds featuring the C(sp^3)–SCF_3 sequence, as encountered in Cefazaflur[8] (Figure 1). The reason for this relative lack of C(sp^3)–SCF_3 compounds is due to the paucity of synthetic methods despite the growing interest for SCF_3 chemistry.

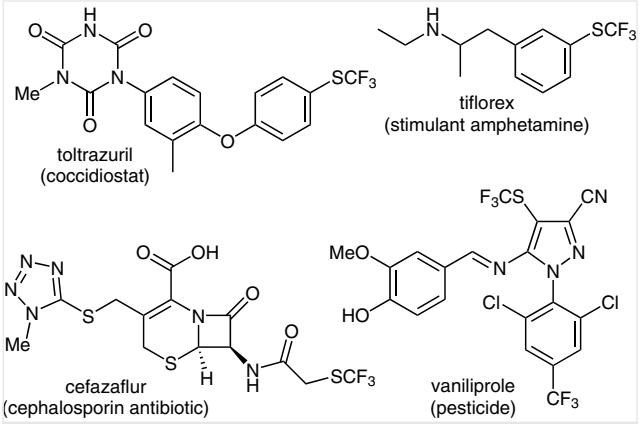
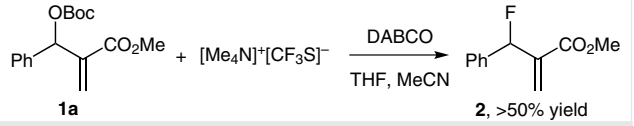


Figure 1 Examples of SCF_3 bioactive compounds

Recently, several laboratories reported on electrophilic trifluoromethylthiolation at sp^3 carbons thanks to the availability of easy-to-handle reagents,[9] including asymmetric reactions.[10] Regarding the nucleophilic trifluoromethylthiolation, reactions of alkyl, benzyl, allyl, and propargyl halides with trifluoromethylthio metal compounds (Hg, Ag, Cu, Cs)[11,12a] or organic SCF_3 salts [NMe_4, $S(NMe_2)_3$, TDAE][12] were reported. In addition, the displacement of bromide in α-bromoketones was described.[13,14] Transformation of alcohols into trifluoromethyl sulfides through phosphitylation and reaction with bis(trifluoromethyl) disulfide was also reported.[15] Various α-diazo compounds reacted with $AgSCF_3$ in copper-mediated trifluoromethylthiolations to form C(sp^3)–SCF_3 bonds.[16] For a cheap and storable crystalline source of SCF_3 anion, Li and Zard reported the synthesis of *O*-octadecyl-*S*-trifluorothiolcarbonate, $CF_3SCO_2C_{18}H_{37}$, and reactions with gramines and α-bromoketones and -ester in the presence of KF and pyrrolidine.[14] Except these nucleophilic substitutions, there is no report of other types of substitution reactions. In order to complement the toolbox for the construction of new SCF_3 derivatives, we herein describe the regio- and stereocontrolled direct introduction of the nucleophilic SCF_3 group onto Morita–Baylis–Hillman (MBH) carbonates.

Among the sources of SCF_3 anion, we firstly selected the tetramethylammonium trifluoromethylthiolate $[NMe_4]^+[SCF_3]^-$, a metal-free reagent prepared from Me_4NF, S_8, and Ruppert–Prakash reagent (CF_3SiMe_3).[12a] Treatment of the MBH adduct **1a** with $[NMe_4]^+[SCF_3]^-$ in the presence of 10 mol% of DABCO in a mixture THF–MeCN (2:5) gave only a trace amount of a new SCF_3 compound as evidenced by its ^{19}F NMR spectrum (δ = –42.3 ppm). Instead, the monofluorinated secondary allylic fluoride **2** was formed as the major product (δ = –171.0 ppm) (Scheme 1).

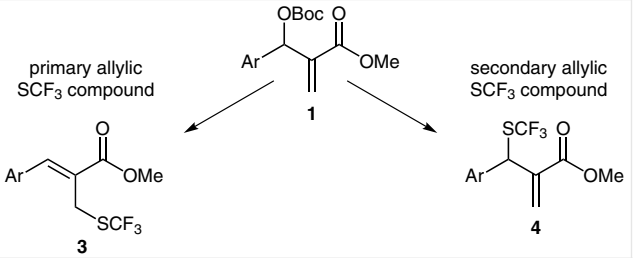


1a **2**, >50% yield

Scheme 1

Attempts to favor the SCF_3 compound were unsuccessful: these included the evaluation of MBH carbonate **1a** in various solvents, the use of additives such as CuI or KF, as well as the handling of silver trifluoromethylthiolate, $AgSCF_3$. Although monofluorinated compound **2** was not the expected target, it is nevertheless interesting because **2** is otherwise difficult to prepare. Indeed, MBH adducts reacted with DAST (diethylaminosulfur trifluoride) to give a mixture of primary and secondary allylic fluorides.[17] In our case, only the secondary allylic fluoride **2** was obtained; however, this method to install a single fluorine atom, which makes use of $[NMe_4]^+[SCF_3]^-$, is far from atom-economical. The decomposition of $[NMe_4]^+[SCF_3]^-$ into thiocarbonyl fluoride (F_2CS) and fluoride was a major obstacle in our quest for SCF_3 compounds.[18]

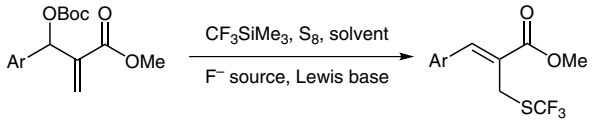
In order to solve this problem, we next investigated another metal-free approach to generate the SCF_3 anion by means of the combination of CF_3SiMe_3/S_8/KF/DMF by analogy to the oxidative trifluoromethylthiolation of terminal alkynes described by Qing and co-workers.[19] We anticipated the two possible SCF_3 products depicted in Scheme 2. The primary allylic SCF_3 product **3** having the alkene double bond conjugated with the aromatic ring is the result of an apparent S_N2' reaction whereas the secondary allylic SCF_3 product **4** retains the terminal alkene motif in an overall process that may be viewed as a simple S_N reaction.



Scheme 2

The addition of Me_3SiCF_3 to a DMF solution of sulfur and KF followed by the successive addition of the MBH carbonate and DABCO, gave after 22 hours the primary allylic SCF_3 product **3** as the main product without detection of **4**. It is worth noting that **3** (^{19}F NMR: δ = –42.3 ppm) was the product obtained in trace amounts in the reaction with $[NMe_4]^+[SCF_3]^-$. The order of addition of the reagents as well as the quantity of KF (10 equiv) were revealed to be important in reaching high yields of **3**. Further optimization of the reaction conditions was performed with MBH carbonate **1i** for easy monitoring by ^{19}F NMR. We were pleased to obtain the SCF_3 product **3i** in DMF at 20 °C in the presence of 10 mol% of DABCO in 84% isolated yield (Table 1, entry 1) and even in 94% yield in a more concentrated medium. The assignment of configuration was done by NOESY NMR experiment. Interestingly, **3i** was obtained as a single *Z*-isomer with a *trans* arrangement of the Ar function and the methyl ester. Other solvents were tested (Table 1, entries 3–6), leading either to no product formation in CH_2Cl_2, toluene, and acetonitrile or to a poor yield in THF. We also evaluated DBU, DMAP and PCy_3 as alternative Lewis bases, but lower yields were obtained compared to those obtained with the use of DABCO (Table 1, entries 1 and 7–9). Moreover, without Lewis base, **3i** was obtained in 69% yield (Table 1, entry 10), indicating that the active SCF_3 anion could directly add

Table 1 Screening of Reaction Parameters[a]



1i Ar = 4-FC_6H_4 **3i**

Entry	Solvent	Fluoride source	Lewis base	Temp (°C)	Yield (%)
1	DMF	KF	DABCO	20	84 (94)[b]
2	DMF	KF[c]	DABCO	20	58
3	CH_2Cl_2	KF	DABCO	20	0
4	toluene	KF	DABCO	20	0
5	THF	KF	DABCO	20	5
6	MeCN	KF	DABCO	20	0
7	DMF	KF	DBU	20	46
8	DMF	KF	DMAP	20	36
9	DMF	KF	PCy_3	20	75
10	DMF	KF	–	20	69
11	DMF	KF	DABCO	50	75
12	DMF	Me_4NF	DABCO	20	0

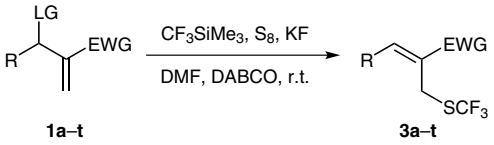
[a] The reactions were performed with 10 mol% of Lewis base, 10 equiv of fluoride source and with a combination of CF_3SiMe_3/S_8/KF = 5:6:10 in solvent (4 mL) for 22 h under dry air.
[b] The reaction was run in DMF (2 mL).
[c] The amount of KF used was 2 equiv.

to the MBH carbonate through a S_N2' addition–elimination mechanism. Running the reaction at higher temperature (50 °C) did not contribute to enhance the yield of the reaction (Table 1, entry 11). The use of Me_4NF as fluoride source instead of KF was detrimental to the reaction (Table 1, entry 12).

Encouraged by these promising results, we examined the substrate scope for the regio- and stereoselective allylic trifluoromethylthiolation of other MBH carbonates and acetates, aryl and alkyl derivatives, conjugated esters, ketone, and nitrile (Table 2). First, the reaction with MBH acetate **1a′** was realized but **3a** was isolated only in 34% yield as compared to the 93% of the corresponding carbonate **1a**; this might be due to the difficulty of elimination of the acetoxy group (Table 2, entries 1 and 2). Hence, the carbonates were chosen as starting material for screening the impact of both R and EWG groups. For aryl esters, either electron-withdrawing (Cl, Br, F) or electron-donating (Me, MeO) substituents on the aromatic ring provided good to excellent yields of **3** after 22 hours (Table 2, entries 3–13). The metal-free approach is particularly suitable to avoid undesired reactions with halogen substituents on the aromatic ring that sometimes occur when transition metals are used. Sterically more demanding naphthyl groups and the 2-thienyl heteroaromatic also led to high yields (Table 2, entries 14–16). The trifluoromethylthiolation worked as well with the alkyl MBH carbonate **1p** but in a much lower yield probably caused by the absence of conjugation with the phenyl ring (Table 2, entry 17). The impact of the steric hindrance of the ester moiety was examined and it was found that increasing the size of the alkyl group tended to reduce the yield of the reaction (Table 2, entries 18 and 19). MBH carbonates derived from the methylvinylketone **1s** and acrylonitrile **1t** were well tolerated in the trifluoromethylthiolation reaction giving the corresponding SCF_3 products **3s** and **3t**, respectively, in good yields (Table 2, entries 20 and 21). In contrast to ester and ketone products, which were obtained as single *Z*-isomers, nitrile **3t** was produced with a *E*/*Z* ratio of 82:18.[20]

Although we have found appropriate conditions to prepare the primary allylic SCF_3 products **3** through a regio- and stereoselective allylic trifluoromethylthiolation, the access to secondary allylic SCF_3 products **4**, which contain a stereogenic carbon, would be of high interest as well.

Table 2 Substrate Scope

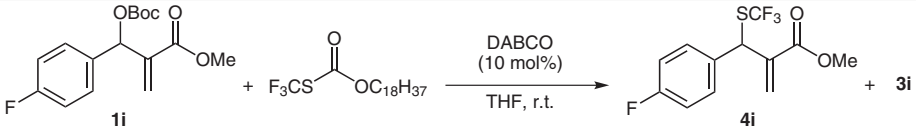


1a–t **3a–t**

Entry	Substrate	R	LG	EWG	Product	Yield (%)[a]
1	**1a**	Ph	OBoc	CO_2Me	**3a**	93
2	**1a′**	Ph	OAc	CO_2Me	**3a**	34
3	**1b**	2-ClC_6H_4	OBoc	CO_2Me	**3b**	79
4	**1c**	3-ClC_6H_4	OBoc	CO_2Me	**3c**	80
5	**1d**	4-ClC_6H_4	OBoc	CO_2Me	**3d**	86
6	**1e**	2,4-$Cl_2C_6H_3$	OBoc	CO_2Me	**3e**	93
7	**1f**	2-BrC_6H_4	OBoc	CO_2Me	**3f**	86
8	**1g**	3-BrC_6H_4	OBoc	CO_2Me	**3g**	69
9	**1h**	4-BrC_6H_4	OBoc	CO_2Me	**3h**	99
10	**1i**	4-FC_6H_4	OBoc	CO_2Me	**3i**	94
11	**1j**	2-$OMeC_6H_4$	OBoc	CO_2Me	**3j**	64
12	**1k**	4-$OMeC_6H_4$	OBoc	CO_2Me	**3k**	88
13	**1l**	4-MeC_6H_4	OBoc	CO_2Me	**3l**	93
14	**1m**	1-naphthyl	OBoc	CO_2Me	**3m**	95
15	**1n**	2-naphthyl	OBoc	CO_2Me	**3n**	94
16	**1o**	2-thienyl	OBoc	CO_2Me	**3o**	88
17	**1p**	$PhCH_2CH_2$	OBoc	CO_2Me	**3p**	20
18	**1q**	Ph	OBoc	CO_2Et	**3q**	84
19	**1r**	Ph	OBoc	CO_2t-Bu	**3r**	28
20	**1s**	Ph	OBoc	COMe	**3s**	65
21	**1t**	Ph	OBoc	CN	**3t**	79[b]

[a] Yield of the isolated pure product as single *Z*-isomer.
[b] *E*/*Z* ratio = 82:18.

As mentioned earlier in the text, Zard demonstrated that *O*-octadecyl-*S*-trifluorothiolcarbonate, $CF_3SCO_2C_{18}H_{37}$, could be used as an efficient SCF_3 anion donor by activation with the aid of an amine.[14] We surmised that DABCO could play a dual role in activating both the nucleophilic reagent and the MBH carbonate. The trifluoromethylthiolation was examined with Zard's reagent and DABCO at room tem-



Reaction time (min)	Conversion	Kinetic / thermodynamic product **4i/3i**
5	100	88:12
10	100	30:70
30	100	4:96

Scheme 3

perature in THF (Scheme 3). The reaction was very fast and full conversion was reached within five minutes. ^{19}F NMR monitoring of the reaction revealed the kinetic formation of the secondary allylic SCF_3 product **4i** that rapidly isomerized to the primary allylic SCF_3 product **3i** (thermodynamic product) when the reaction time was extended. Compared to the combination of $CF_3SiMe_3/S_8/KF/DMF$, Zard's reagent allowed to catch the fleeting secondary allylic SCF_3 (kinetic product) during its brief existence. Indeed, by quenching the reaction mixture after five minutes and purification on silica gel, we were pleased to isolate the kinetic product **4i** in 78% yield although with some contamination by the long chain alcohol side product. Interestingly, the reaction only required a catalytic amount of DABCO to activate Zard's reagent.

In summary, we have found the appropriate conditions for the regio- and stereocontrolled trifluoromethylthiolation of MBH carbonates: the thermodynamically more stable primary allylic SCF_3 derivatives were synthesized by means of the metal-free combination of $CF_3SiMe_3/S_8/KF/DMF$ whereas the kinetic secondary allylic SCF_3 derivatives were obtained by using Zard's reagent.[21] Further studies that include mechanistic investigation, asymmetric variant, and chemical transformations of these novel SCF_3 products are underway in our laboratory.[22]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379162.

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(21) **General Procedure for the Preparation of Compounds 3**: Caution! This reaction should be conducted with a gas pressure regulator and in a well-ventilated hood to avoid exposure to

toxic bis(trifluoromethyl)sulfide and higher analogues. In an oven-dried tube, sulfur (19.2 mg, 0.6 mmol) and KF (58.1 mg, 1 mmol) in anhydrous DMF (2 mL) were stirred at r.t. under dry air for 30 min. Me_3SiCF_3 (71 mg, 0.5 mmol) was then added to the mixture followed by addition of the MBH carbonate (0.1 mmol) and DABCO (1.12 mg, 0.01 mmol). After 22 h, the reaction went to completion (monitored by ^{19}F NMR analysis). The reaction was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether–EtOAc, 40:1) to give the corresponding primary allylic SCF_3 compound.

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