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Facile synthesis of α-monofluoromethyl alcohols: Nucleophilic monofluoromethylation of aldehydes using $TMSCF(SO_2Ph)_2$[☆]

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ABSTRACT

α-Fluoromethyl phenyl sulfone derivatives have been extensively employed in various reactions as versatile fluoromethylating reagents. While nucleophilic monofluoromethylations of aldehydes have been achieved using fluoromethyl phenyl sulfone or fluorobis(sulfonyl)methanes, a facile protocol under mild reaction conditions remains an ardently sought goal. We now report a feasible synthetic approach toward β-monofluorinated alcohols using α-trimethylsilyl-α-fluorobis(phenylsulfonyl)methane [$TMSCF(SO_2Ph)_2$, TFBSM] as a novel monofluoromethylating reagent. Initiated by a catalytic amount of fluoride, the reagent can be readily added to a variety of aldehydes providing the desired products in high yields. Computational and kinetic studies have revealed the exceptional lability of the Si–C bond in TFBSM compared with other fluoromethylsilane counterparts.

1. Introduction

Selective incorporation of fluoromethyl moieties into organic molecules has received increasing attention because of the immense potential of fluoroorganics in life and materials sciences [1]. To address this synthetic demand, α-fluoromethyl phenyl sulfone derivatives were recently developed as viable fluoromethylating reagents [2]. Of particular interest, fluorobis(phenylsulfonyl)methane (FBSM) and its analogues have facilitated many transformations, which are otherwise difficult to achieve [3]. In spite of these successful documentations, the nucleophilic addition of FBSM to aldehydes was previously claimed to be unattainable because of its reversibility, thereby necessitating the utilization of 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide as the pronucleophile [4]. Hu et al., however, showed that FBSM anion can be added to aldehydes using LiHMDS as the base [5]. The obtained lithium carbinolates, stabilized through strong Li–O interactions, were then *in situ* quenched with Bronsted acids (for example, trifluoroacetic acid) to afford the corresponding alcohols (Scheme 1). We therefore surmised that FBSM anion-aldehyde adducts (carbinolates) can also be captured through a reaction with Lewis acids. Moreover, a one-pot addition reaction between the FBSM anion and aldehydes can be achieved under a *self*-quenching mechanism by utilizing α-trimethylsilyl-α-fluorobis(phenylsulfonyl)methane [$TMSCF(SO_2Ph)_2$, TFBSM], which serves as both a pronucleophile and a Lewis acid [6,7].

2. Results and discussion

To examine our proposal, we initially focused on the preparation of TFBSM using FBSM, which was readily obtained on large scale according to a method developed in our laboratory [8]. After an extensive reaction condition screening, the desired reagent was successfully prepared in 43% yield by treating FBSM sodium salt with TMSCl in THF (Scheme 2). The compound was found to be stable and can be stored in a glove box for several months. However, it underwent a swift decomposition (usually within a few days) to FBSM in the presence of moisture or in $CDCl_3$ solution, which contains some protic acid impurities. Surprisingly, unlike $TMSCF_3$ (the Ruppert-Prakash reagent) and [(phenylsulfonyl)difluoromethyl]trimethylsilane ($TMSCF_2SO_2Ph$), which are substantially inert toward aqueous HCl solution, instantly hydrolysis of TFBSM was observed in concentrated aq. HCl (12 M), indicating the exceptional lability of the Si–C_F bond.

With the desired reagent in hand, we initially performed the reaction between TFBSM and benzaldehyde using tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) as an initiator in THF. As expected, the desired β-fluoro silyl ether was obtained, however, in only 22% yield (Table 1, entry 1). In an effort to enhance the efficacy of the protocol, we further investigated various reaction parameters, such as initiators, solvents, temperatures, and proportions of substrates. We found that the proportions of the substrates can significantly impact outcomes of the reaction

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[☆] Dedicated to Professor Wei-Yuan Huang on the occasion of his Ninetieth Birthday.

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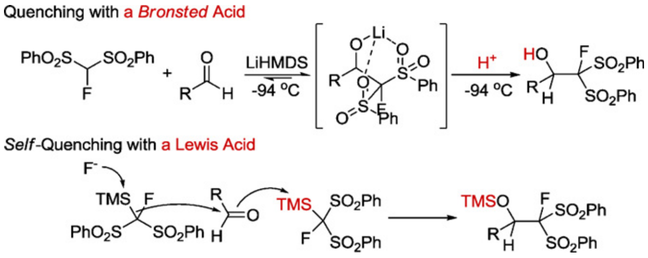
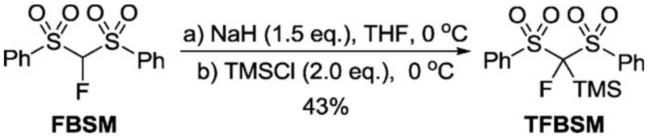


Scheme 1. Nucleophilic addition of FBSM and TFBSM to aldehydes.

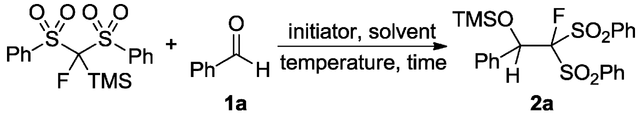


Scheme 2. Preparation of α-trimethylsilyl-α-fluorobis(phenylsulfonyl)methane (TFBSM).

(Table 1, entries 1–5 and 6–9). Low yields observed in entries 1–5 can be rationalized as the competitive protonation of FBSM anion due to the presence of moisture in the reaction system. Employing an excess amount of TFBSM can, therefore, compensate the consumption of the pronucleophile. In addition, CsF was found to be a superior initiator over several other Lewis bases (Table 1, entries 1–9). Solvent effects were also pronounced (Table 1, entries 9, 11–13), which showed THF as the optimal reaction medium. While addition sequences of reagents were critical (Table 1, entries 8 and 10), yields did not decrease, when the reaction time was shortened to 4 h (Table 1, entry 14). In particular, performing the reaction at room temperature resulted in a decrease in yield to 75%.

With optimized reaction conditions established, we explored the scope of this protocol (Table 2). The reaction was found to be applicable to aromatic aldehydes bearing both electron-withdrawing and electron-donating groups, and furnished products in high yields (entries 1–5, Table 2). While the 2,4,6-trimethoxybenzaldehyde **1d** underwent the reaction smoothly (entry 4, Table 2), the

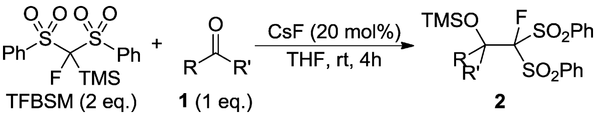
Table 1
Optimization of the addition reaction of TFBSM with benzaldehyde.

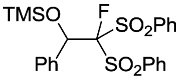
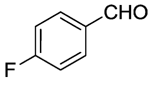
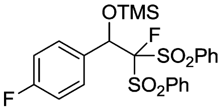
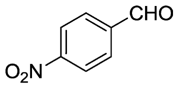
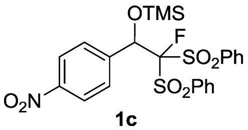
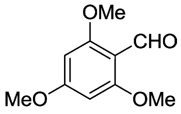
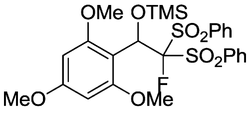
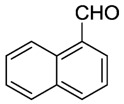
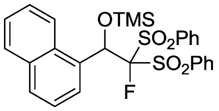
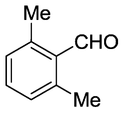
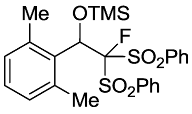
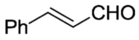
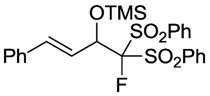
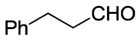
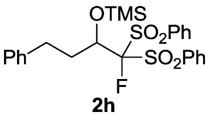
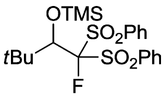
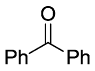
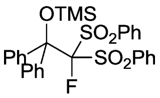


Entry	Initiator	Solvent	TFBSM/**1a**/Initiator	Temp. (°C)	Time (h)	Yield (%)[c]
1[a]	TBAT	THF	1/2/0.05	0–rt	12	22
2[a]	TBAF[d]	THF	1/2/0.05	0–rt	12	0
3[a]	$Me_3N^+{-}O^-$	THF	1/2/0.20	0–rt	12	34
4[a]	KF	THF	1/2/0.20	0–rt	12	38
5[a]	CsF	THF	1/2/0.20	0–rt	12	31
6[a]	TBAT	THF	2/1/0.05	0–rt	12	66
7[a]	$Me_3N^+{-}O^-$	THF	2/1/0.20	0–rt	12	71
8[a]	KF	THF	2/1/0.20	0–rt	12	78
9[a]	CsF	THF	2/1/0.20	0–rt	12	99
10[b]	KF	THF	2/1/0.20	0–rt	12	0
11[a]	CsF	Et_2O	2/1/0.20	0–rt	12	25
12[a]	CsF	DMF	2/1/0.20	0–rt	12	0
13[a]	CsF	Toluene	2/1/0.20	0–rt	12	54
14[a]	CsF	THF	2/1/0.30	0	4	99
15[a]	CsF	THF	2/1/0.20	rt	4	75

[a] Fluoride source in THF was added to a mixture of TFBSM and **1a** in THF.
[b] TFBSM in THF was added to a mixture of KF and **1a** in THF.
[c] ^{19}FNMR yields.
[d] A TBAF solution in THF (1M) containing 5 wt% H_2O was used.

Table 2
Monofluoromethylation of aldehydes with TFBSM.



Entry	Carbonyl compounds	Product	Yield (%)[a]
1	PhCHO **1a**	 **2a**	99/81
2	 **1b**	 **2b**	93/90
3	 **1c**	 **1c**	99/86
4	 **1d**	 **2d**	97/87
5	 **1e**	 **1e**	96/83
6	 **1f**	 **2f**	0/0
7	 **1g**	 **2g**	88/80
8	 **1h**	 **2h**	64/54
9	*t*Bu−CHO **1i**	 **2i**	0/0
10	 **1j**	 **2j**	0/0

[a] ^{19}F NMR yields/isolated yields.