Fluoromethylation

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Nucleophilic Fluoromethylation of Aldehydes with Fluorobis(phenylsulfonyl)methane: The Importance of Strong Li–O Coordination and Fluorine Substitution for C–C Bond Formation**

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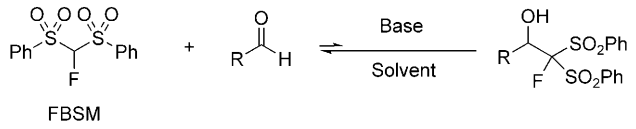
Recently, the selective introduction of fluorinated moieties into organic molecules with α-fluorinated carbanions has attracted substantial interest in organic synthesis, owing to the increasingly important applications of selectively fluorinated organics in life and materials sciences.[1–5] In particular, α-fluoro(phenylsulfonyl)methane (FSM) derivatives, such as difluoromethyl phenyl sulfone ($PhSO_2CF_2H$), fluoromethyl phenyl sulfone ($PhSO_2CH_2F$), and fluorobis(phenylsulfonyl)-methane (FBSM), have been extensively studied as excellent precursors of α-fluorinated carbanions for nucleophilic di- and monofluoromethylations.[2] In this context, FBSM, a reagent independently reported by Shibata et al. and our group in 2006,[3a,4] has been widely recognized as a robust nucleophilic monofluoromethylating agent for many applications, including catalytic enantioselective monofluoromethylation reactions.[3a,b,4–6] However, although FBSM reacts with a great variety of electrophiles,[3–5] its nucleophilic addition reaction with aldehydes still remains a challenge.

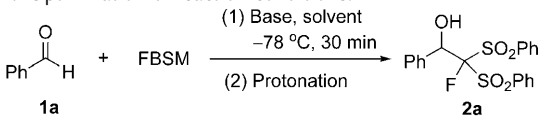
Very recently, Shibata et al. reported that "FBSM failed to undergo nucleophilic addition to aldehydes regardless of the reaction conditions, leading instead to starting materials by a retro-type reaction", and they also reasoned that "this behavior presumably results from the instability of the resulting β-hydroxy-α-fluorobis(phenylsulfonyl)methanes caused by the steric hindrance of the two phenylsulfonyl groups" (Scheme 1).[7] Prompted by their report, herein we wish to disclose our remarkable success in the efficient nucleophilic addition of FBSM to aldehydes. Our study shows that both the strong Li–O coordination at low temperatures and fluorine substitution play very important roles in the successful nucleophilic addition of FBSM to aldehydes, which provides new intriguing insights into the nucleophilic fluoroalkylation reactions with α-fluorinated carbanions.[8]



Scheme 1. Unsuccessful monofluoromethylation of aldehydes with FBSM.[7]

The nucleophilic addition reaction of FBSM to aldehydes was tested by using benzaldehyde (**1a**) as a model substrate (Table 1). When lithium hexamethyldisilazide (LiHMDS) was added to a CH_2Cl_2 solution of **1a** and FBSM at −78 °C (and the solution was stirred for 30 min), followed by quenching with hydrochloric acid (10 M) at −30 °C, no addition product **2a** was observed (Table 1, entry 1). Interestingly, when the reaction was quenched by hydrochloric acid (10 M) at lower temperature (−78 °C), product **2a** was formed in 27 % yield (Table 1, entry 2). Increasing the solvent polarity by adding hexamethylphosphoramide (HMPA) resulted in the failure of the addition reaction (Table 1, entry 3). When the addition reaction was quenched by trifluoroacetic acid, the yield of **2a** increased to 45 % (Table 1, entry 4). After further scanning of the reaction solvents, temperatures, reactant ratios, and bases (Table 1,

Table 1: Optimization of reaction conditions.[a]



Entry	Base	Solvent	Protonation conditions	Yield [%][b]
1	LiHMDS	THF	HCl (aq), −30 °C	0
2	LiHMDS	THF	HCl (aq), −78 °C	27
3	LiHMDS	THF/HMPA[c]	HCl (aq), −78 °C	0
4	LiHMDS	THF	CF_3COOH, −78 °C	45
5	LiHMDS	Et_2O	CF_3COOH, −78 °C	52
6	LiHMDS	CH_2Cl_2	CF_3COOH, −78 °C	85
7	LiHMDS	$PhCH_3$	CF_3COOH, −78 °C	86
8	LiHMDS	CH_2Cl_2	CF_3COOH, −94 °C	92
9	LiHMDS[d]	CH_2Cl_2	CF_3COOH, −94 °C	92
10	NaHMDS[d]	CH_2Cl_2	CF_3COOH, −94 °C	71
11	KHMDS[d]	CH_2Cl_2	CF_3COOH, −94 °C	27
12	LiHMDS[e]	CH_2Cl_2	CF_3COOH, −94 °C	83

[a] Reactions were carried out using FBSM (1 equiv), **1a** (2.0 equiv), and base (1.2 equiv) in solvent at −78 °C unless otherwise noted. [b] Determined by ^{19}F NMR spectroscopy. [c] THF/HMPA = 10:1 (v/v). [d] **1a** (1.5 equiv) was used. [e] **1a** (1.2 equiv) was used.

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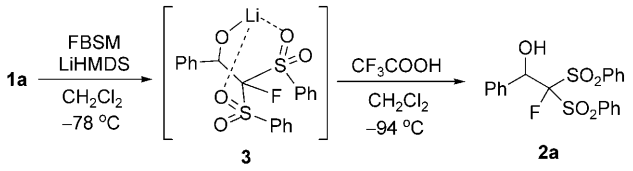
entries 5–12), we found that an optimal yield of **2a** (92%) could be obtained when the reaction was carried out in CH_2Cl_2 at −78°C (with a reactant ratio FBSM/**1a**/LiHMDS = 1:1.5:1.2) and quenched by trifluoroacetic acid at −94°C (Table 1, entry 9).

It should be mentioned that, among the lithium, sodium, and potassium hexamethyldisilazides, LiHMDS serves as the best base for this addition reaction, which indicates that the strong Li–O coordination in the carbinolate intermediate **3** plays a very important role in the success of the reaction (Scheme 2). This assumption is supported by the experimental observations that the use of weak-coordinating solvent (such as CH_2Cl_2) and low reaction/quenching temperatures facilitates the addition of FBSM to benzaldehyde **1a** (Table 1). Furthermore, the existence of strong coordination between Li and three neighboring oxygen atoms in lithium carbinolate **3** was confirmed by our computationally optimized structure (the Li–O distances are 1.761, 1.985, and 1.986 Å, respectively; see Figure 3A).[9]



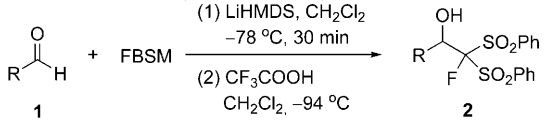
Scheme 2. Formation of carbinol **2a** through lithium carbinolate **3**.

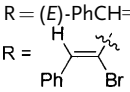
With the optimized conditions in hand, we then examined the substrate scope of this nucleophilic monofluoromethylation reaction between FBSM and aldehydes **1**. As shown in Table 2, the reaction turned out to be general and a variety of structurally diverse aldehydes were successfully monofluoromethylated by FBSM to give the corresponding carbinols **2** in high yields (82–95%). The reaction tolerates many substituents such as methoxy, bromo, and chloro groups (Table 2, entries 3–8). Heteroaryl aldehyde **1i** can also react with FBSM, affording carbinol product **2i** in 85% yield (Table 2, entry 9). α,β-Unsaturated aldehydes **1j** and **1k** are also compatible with the reaction, and only 1,2-addition products **2j** and **2k** were formed in 93 and 87% yield, respectively (Table 2, entries 10 and 11). It is remarkable that the current nucleophilic monofluoromethylation reaction is also amenable to aliphatic aldehydes **1l**–**1n**, giving the products **2l**–**2n** in 82–94% yield (Table 2, entries 12–14). All the products **2a**–**2n** were purified and isolated by silica gel chromatography, and the structure of **2h** was confirmed by X-ray crystal structure analysis (Figure 1).[10]

To gain more insight into the efficient nucleophilic addition of FBSM to aldehydes, we carefully monitored the progress of the reaction of FBSM, benzaldehyde (**1a**), and LiHMDS in CD_2Cl_2 by variable-temperature (VT) ^{19}F NMR spectroscopy (Figure 2).[11] First of all, under a N_2 atmosphere, a mixture of **1a** (0.15 mmol) and FBSM (0.10 mmol) in CD_2Cl_2 (1 mL) was placed in an NMR tube, and a peak (δ = −170 ppm) of FBSM was observed at −76°C (Figure 2A). Thereafter, LiHMDS (0.12 mmol) was added to the NMR tube and the temperature was kept at −79°C. The peak of FBSM diminished quickly, and new peaks ranging from δ = −121 to −128 ppm appeared with a major peak at δ = −126 ppm, which represents the lithium alcoholate **3** (Figure 2B). When the temperature of the NMR tube was slowly raised from −79 to 25°C, the major peak at δ = −126 ppm diminished slowly (Figure 2B–F), and finally several broad peaks ranging from δ = −121 to −128 ppm were left (Figure 2F).[11] This indicates that at higher temperatures (such as above −19°C) a quick equilibrium may exist between lithium alcoholate **3** and the retro-addition products [that is, aldehyde **1a** and $(PhSO_2)_2CF^-Li^+$ (**8**), as shown in Eq. (1)].

$$(PhSO_2)_2CF^-Li^+\ (\mathbf{8}) + \mathbf{1a} \rightleftharpoons \mathbf{3} \qquad (1)$$

Table 2: Monofluoromethylation of aldehydes with FBSM.[a]



Entry	Aldehyde **1**		Product **2**	Yield [%][b]
1	**1a**	R = Ph	**2a**	92
2	**1b**	R = *p*-Me-C_6H_4	**2b**	88
3	**1c**	R = *p*-MeO-C_6H_4	**2c**	87
4	**1d**	R = 2,5-MeO-C_6H_4	**2d**	89
5	**1e**	R = *o*-Cl-C_6H_4	**2e**	92
6	**1f**	R = *p*-Cl-C_6H_4	**2f**	91
7	**1g**	R = 2,4-Cl-C_6H_4	**2g**	95
8	**1h**	R = *p*-Br-C_6H_4	**2h**	90
9	**1i**	R = 2-furyl	**2i**	85
10	**1j**	R = (*E*)-PhCH=CH	**2j**	93
11	**1k**	R = 	**2k**	87
12[c]	**1l**	R = $PhCH_2CH_2$	**2l**	93
13[c]	**1m**	R = $(CH_3)_2CH$	**2m**	94
14[c]	**1n**	R = cyclohexyl	**2n**	82

[a] Reactions were carried out using FBSM (1.0 equiv), aldehyde (1.5 equiv), and LiHMDS (1.2 equiv) in CH_2Cl_2 at −78°C for 30 min unless otherwise noted. [b] Yield of isolated product. [c] FBSM was stirred with LiHMDS first in CH_2Cl_2 at −78°C for 30 min, and then the aldehyde was added and the mixture was stirred for an additional 30 min.

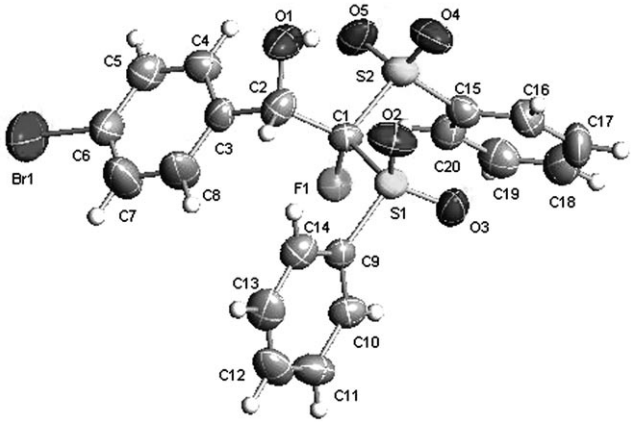


Figure 1. X-ray crystal structure of product **2h**.[10]

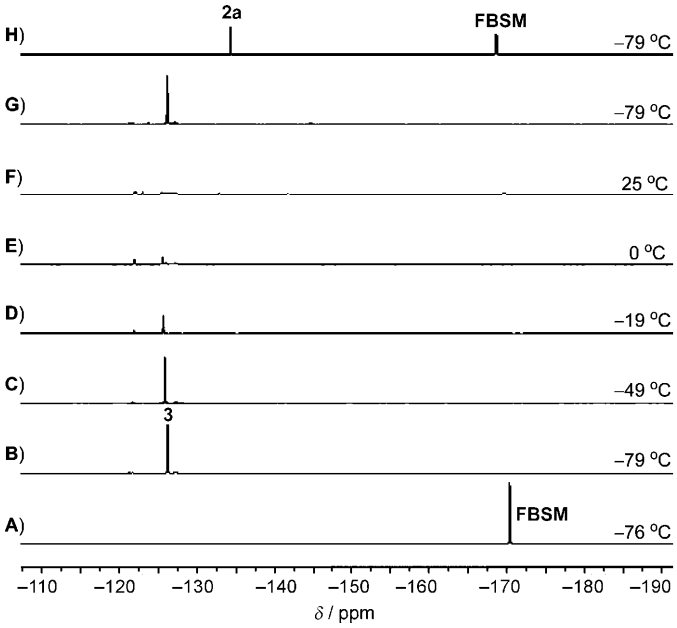
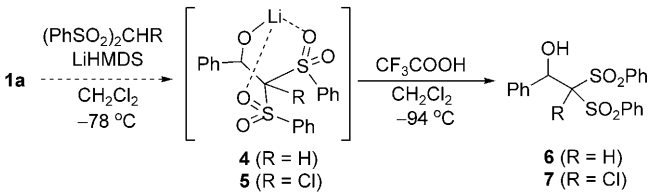


Figure 2. Monitoring of the reaction of FBSM, PhCHO (**1a**), and LiHMDS by VT ^{19}F NMR spectroscopy. A) An NMR sample containing **1a** (0.15 mmol), FBSM (0.10 mmol), and CD_2Cl_2 (1 mL) at −76 °C. B) LiHMDS (0.12 mmol) was added to the above sample at −79 °C. C–F) The temperature of the sample was raised to −49, −19, 0, and 25 °C, respectively. G) The sample was cooled to −79 °C again. H) CF_3COOH (0.5 mL) was added to the sample at −79 °C.

Furthermore, when we cooled the NMR tube to low temperature (−79 °C) again, a peak corresponding to **3** ($\delta = -126$ ppm) reappeared (Figure 2G), which suggested that low temperature is beneficial to push the equilibrium [Eq. (1)] to the right-hand side, thus facilitating the formation of **3**. Finally, after the NMR sample was quenched with CF_3COOH at −79 °C, the peaks of carbinol product **2a** ($\delta = -134$ ppm) and of FBSM ($\delta = -169$ ppm) appeared (Figure 2H).[12] These results clearly demonstrate that not only does the strong Li–O coordination play an important role for the generation of **3** (as shown in Table 1), but also the control of the reaction at low temperature is crucial to stabilize the carbinolate **3**. This probably also explains why when Shibata and co-workers performed the same addition reaction of FBSM to benzaldehyde **1a** by using other bases (such as *t*BuOK, Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene, and 1,4-diazabicyclo[2.2.2]octane) at room temperature, no addition product **2a** could be obtained.[7]

Encouraged by these results, we further tested the nucleophilic additions of bis(phenylsulfonyl)methane (BSM) and chlorobis(phenylsulfonyl)methane (CBSM) to benzaldehyde **1a**. The reaction conditions were exactly the same as those for the reaction with FBSM (as described in Table 1, entry 9). Much to our surprise, neither of these two reactions produced the desired addition product **6** or **7** (Scheme 3), and the BSM or CBSM starting material was recovered almost quantitatively. It should be mentioned that compound **6**, which could be prepared by a different method,[13] was found to be stable even at room temperature. Therefore, the failure of the addition reactions with BSM and



Scheme 3. Unsuccessful nucleophilic additions to PhCHO (**1a**) with $(PhSO_2)_2CH_2$ (BSM) and $(PhSO_2)_2CHCl$ (CBSM).

CBSM could be attributed to the instability of lithium carbinolates **4** and **5** when compared to the fluorine-substituted analogue **3** (Scheme 2).

However, the fact that fluorine-substituted lithium carbinolate **3** possesses higher stability than nonsubstituted and chlorine-substituted analogues **4** and **5** is anti-intuitive, especially when one considers that: a) the steric strain of **3** is not likely to be significantly smaller than that of **4** and **5**, b) the Li–O coordination is similarly strong in **3**–**5** (Figure 3), and c) the electronegative fluorine atom may

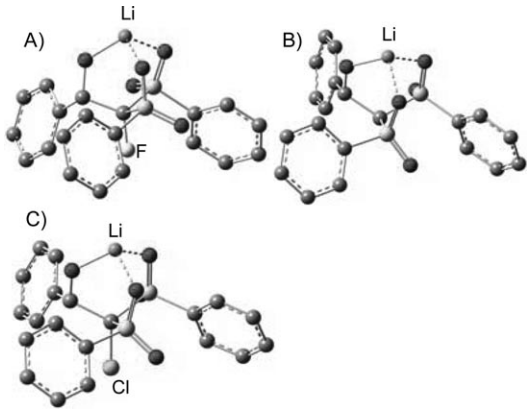


Figure 3. A) Optimized structure of fluorine-substituted lithium carbinolate (**3**). The length of the FC–COLi bond is 1.570 Å, and the lengths of the three O–Li coordination bonds are 1.761, 1.985, and 1.986 Å, respectively. B) Optimized structure of lithium carbinolate (**4**). The length of the HC–COLi bond is 1.605 Å, and the lengths of the three O–Li coordination bonds are 1.769, 1.942, and 2.01 Å, respectively. C) Optimized structure of chlorine-substituted lithium carbinolate (**5**). The length of the ClC–COLi bond is 1.622 Å, and the lengths of the three O–Li coordination bonds are 1.761, 1.933, and 1.967 Å, respectively. All three optimized structures were calculated at the B3LYP/6-31+G(d,p) level, and all the hydrogen atoms in these structures have been omitted for clarity.

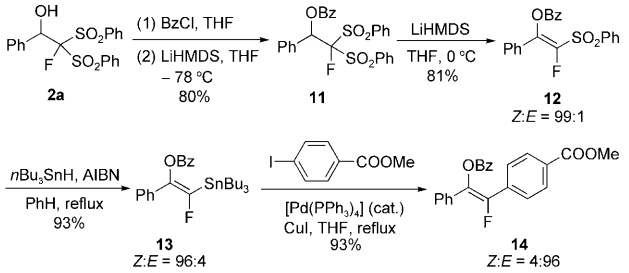
make the fluorobis(phenylsulfonyl)methyl group a better leaving group than the (phenylsulfonyl)methyl group itself. To understand the "unusual" stability of **3**, we first investigated the optimized gas-phase structures of **3**–**5** by DFT calculation based on the B3LYP/6-31+G(d,p) level of theory (Figure 3).[9] It was found that the length of the newly formed C–C bond (from the addition reaction between FBSM and **1a**) in **3** is 1.570 Å, which is shorter than those in **4** and **5** (1.605 and 1.622 Å, respectively). The different C–C bond lengths of carbinolates **3**–**5** suggest that species **3** possesses the

least tendency to undergo decomposition through retro-addition reaction.

Secondly, based on DFT calculations, Prakash et al. reported that the gas-phase proton affinities of the anions are: $(PhSO_2)_2CF^-$, 335.1 kcal mol^{-1}; $(PhSO_2)_2CH^-$, 332.7 kcal mol^{-1}; and $(PhSO_2)_2CCl^-$, 330.1 kcal mol^{-1}.[6] These proton affinity data indicate that among these three anions, $(PhSO_2)_2CF^-$ possesses the highest basicity and the lowest leaving-group ability, which is in good agreement with our experimental result that **3** is the most stable lithium carbinolate species among **3**–**5**.[14]

Thirdly, we investigated the gas-phase Gibbs free energies of three addition reactions between carbanions **8**–**10** (**9** = $(PhSO_2)_2CH^-Li^+$; **10** = $(PhSO_2)_2CCl^-Li^+$) and benzaldehyde **1a** by DFT calculation based on the B3LYP/6-311 + G(2d,p)//B3LYP/6-31 + G(d,p) level of theory.[9] It was found that the Gibbs free energies (ΔG) of these addition reactions at −78 °C (1 atm) are −2.3, +6.5, and +5.5 kcal mol^{-1} for the formation of **3**–**5**, respectively. These ΔG values suggest that among these three reactions, only the formation of **3** can spontaneously proceed at −78 °C, but adducts **4** and **5** prefer decomposing into **9** (or **10**) and **1a** at the same temperature, which is also in good agreement with our experimental observations (see Schemes 2 and 3).

To demonstrate the synthetic application of the addition products **2**, we converted carbinol **2a** into benzoate **11** (Scheme 4). Upon treatment of LiHMDS in THF at 0 °C,



Scheme 4. Synthetic application of product **2a**. Bz = benzoyl, AIBN = azobisisobutyronitrile.

compound **11** was converted into monofluorinated alkene **12** with excellent stereoselectivity (Z/E = 99:1). The phenylsulfonyl group in **12** was efficiently transformed into a tributylstannyl group in **13** by using nBu$_3$SnH/AIBN, possibly through a radical addition–elimination process.[15] Finally, a stereospecific Stille coupling reaction efficiently converted **13** into fluorinated *E*-stilbene derivatives **14**.

In conclusion, the nucleophilic addition reaction between FBSM and an aldehyde, a reaction that was previously believed to be unattainable,[7] has been successfully accomplished. Our experimental results showed that both the strong Li–O coordination at low temperature and fluorine substitution play very important roles in the successful nucleophilic addition of FBSM to aldehydes, which was further supported by our VT NMR study and DFT calculations. Not only does our study provide new mechanistic insights into understanding the nucleophilic addition of substituted methides to aldehydes, but also it opens up new synthetic possibilities such as the design of enantioselective fluoromethylations of carbonyl compounds. Further investigations in this direction are currently under way in our laboratory.

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[9] For details of the DFT calculations, see the Supporting Information.

[10] CCDC 798880 (**2h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] For more detailed VT ^{19}F NMR spectra, see the Supporting Information.

[12] Since it is difficult to stir the solution in the NMR tube during the quenching process, a local exothermic reaction may lead to the generation of $(PhSO_2)_2CF^-Li^+$ (**8**) from **3**. This partially explains why the yield of **2a** in the NMR experiments was lower than those in flask reactions (Table 1).

[13] Compound **6** was prepared by nucleophilic addition of bis(phenylthio)methane to benzaldehyde, followed by oxidation with *meta*-perbenzoic acid (see the Supporting Information). It should be noted that when we added LiHMDS to the CH_2Cl_2 solution of **6** at −78 °C, then quenched with CF_3COOH at −94 °C, compound **6** decomposed to give PhCHO and BSM.

[14] For discussions on basicity and leaving-group ability, see: E. Buncel, J. M. Dust, *Carbanion Chemistry: Structures and Mechanisms*, Oxford University Press, New York, **2003**.

[15] J. R. McCarthy, D. P. Matthews, D. M. Stemerick, E. W. Huber, P. Bey, B. J. Lippert, R. D. Snyder, P. S. Sunkara, *J. Am. Chem. Soc.* **1990**, *113*, 7439 – 7440.

