Fluoromethylation

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2-Fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide: A Reagent for Nucleophilic Monofluoromethylation of Aldehydes**

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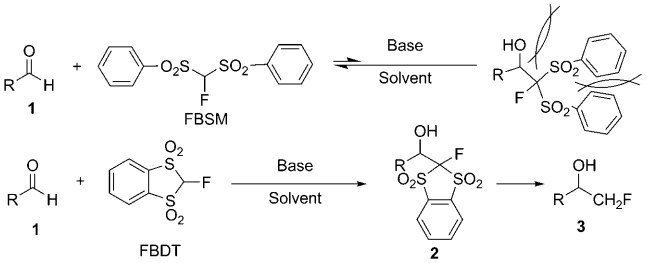
In recent years, fluorine-containing organic molecules have been identified as strong candidates for pharmaceuticals and advanced materials because of their unique properties,[1] despite their extremely rare natural occurrence.[2] Particularly, monofluorinated analogues of biologically active compounds are a peerless class of drug nominees, which are considered to be promising bioisosteres of the parent molecules.[3] In this respect, compounds with monofluoromethyl groups are particularly valuable because they can mimic the methyl or hydroxymethyl group, which are often encountered in biologically active materials.[4] The fluoromethyl group is best known as an effective functional group for the "Trojan horse" inhibition of vitamin B6 dependent enzymes.[4a] Monofluoromethylated amino acids such as D-fluoroalanine are well known to act as "suicide substrates" causing inactivation of the enzyme by alkylative capture of the aminoacrylate-pyridoxal-P species.[4j] Monofluoroacetic acid is responsible for "lethal synthesis" and it blocks the tricarboxylic acid cycle (Krebs cycle).[4f–h]

As a part of our efforts to develop efficient reaction systems for the synthesis of organofluorine compounds,[5] we developed 1-fluorobis(phenylsulfonyl)methane (FBSM) as a synthetic equivalent of a fluoromethide species.[6–8] FBSM reacts with a greater variety of electrophiles and has been widely applied in nucleophilic monofluoromethylation reactions based on Tsuji–Trost allylation, Mannich, Mitsunobu, Michael, and ring-opening reactions, as well as other reactions.[7,8] FBSM is much superior to (phenylsulfonyl)monofluoromethane[9] and is becoming popular in the nucleophilic monofluoromethylation reaction. However, FBSM failed to undergo nucleophilic addition to aldehydes regardless of the reaction conditions, leading instead to starting materials by a retro-type reaction (Scheme 1, top). 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. The use of sterically less demanding reagents should avoid this problem.



Scheme 1. Nucleophilic monofluoromethylation of aldehydes with FBSM or FBDT.

In an attempt to develop an alternative and efficient method, we now disclose a novel reagent, 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (FBDT), for the first nucleophilic monofluoromethylation of aldehydes (Scheme 1, bottom). The FBDT adducts of aldehydes are readily transformed in high yields into monofluoromethylated alcohols in a single step. Notable advantages of the present reagent include 1) the ability to perform 1,2-addition reactions of aldehydes, and 2) control of the 1,2- versus 1,4-regioselectivity of the reaction with α,β-unsaturated aldehydes by base. We also report the application of this strategy to the enantioselective syntheses of a fluorinated isostere of osmundalactone.

Previously unknown FBDT was prepared from readily available nonfluorinated precursor[10] by electrophilic fluorination.[11] The addition reaction was tested with benzaldehyde (**1a**) in the presence of base. No reaction of **1a** with FBSM proceeded at all, regardless of the base, presumably because of a facile retro-type reaction by two bulky bis(phenylsulfonyl)methane moieties (Table 1, entries 1–4). In contrast, the reaction with FBDT in the presence of *t*BuOK proceeded readily at room temperature to give monofluoromethylated product **2a** in 31% yield (Table 1, entry 5). Encouraged by this initial result, we pursued the reaction of **1a** with FBDT under various conditions. The reaction was next attempted using Et_3N or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base, but the results did not improve (Table 1, entries 6

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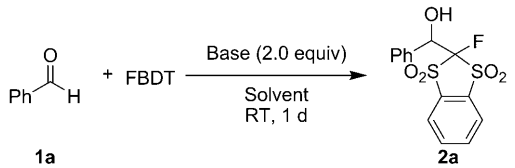
Table 1: Optimization of the reaction conditions.[a]



1a 2a

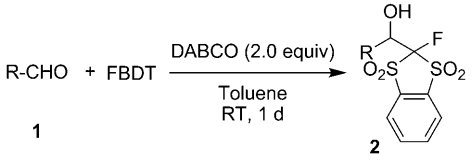
Entry	Base	Solvent	Yield [%][b]
1[c]	*t*BuOK	CH_2Cl_2	0
2[c]	Et_3N	CH_2Cl_2	0
3[c]	DBU	CH_2Cl_2	0
4[c]	DABCO	CH_2Cl_2	0
5	*t*BuOK	CH_2Cl_2	31
6	Et_3N	CH_2Cl_2	34
7	DBU	CH_2Cl_2	29
8	DABCO	CH_2Cl_2	62
9	DABCO	THF	64
10	DABCO	CH_3CN	78
11	DABCO	DMF	47
12	DABCO	MeOH	64
13	DABCO	toluene	81

[a] Reactions were carried out using FBDT (1.0 equiv), **1a** (1.2 equiv), and base (2.0 equiv) in solvent at room temperature for 1 day unless otherwise noted. Yields were calculated based on FBDT. [b] Yield of isolated product. [c] FBSM was used as a nucleophile instead of FBDT.

and 7). The yield improved to 62% when 1,4-diazabicyclo-[2.2.2]octane (DABCO) was used (Table 1, entry 8). An attempt to improve the yield of **2a** by varying the solvent was successful (Table 1, entries 9–12), and a high yield of **2a** was observed in toluene (Table 1, entry 13).

With the optimized conditions established, the scope of substrates in the FBDT-based 1,2-addition reaction was investigated (Table 2). By using DABCO, all substrates **1** afforded products **2** in good to excellent yields. A series of aldehydes with a variety of substituents, such as methyl, bromo, chloro, and nitro, on their aromatic rings **1b–g** were nicely converted into the corresponding monofluoromethylated products **2b–g** in good yields (Table 2, entries 1–6). Conjugated aldehyde **1h** was also compatible with the same reaction conditions and afforded 1,2-addition product **2h** selectively in 60% yield (Table 2, entry 7). The reaction of sterically demanding naphthyl aldehyde **1i** and heteroaryl aldehyde **1j** also proceeded in 73 and 77% yields, respectively (Table 2, entries 8 and 9). Good results were also observed with aliphatic aldehydes **1k** and **1l**, which have enolizable protons (Table 2, entries 10 and 11). The resulting 1,2-adducts **2** were readily transformed into the corresponding monofluoromethylated alcohols **3** by reductive desulfonylation using SmI_2 (Scheme 2). A slight excess of SmI_2 (4.0 equivalents is the stoichiometric amount) was used because of the instability of the reagent.

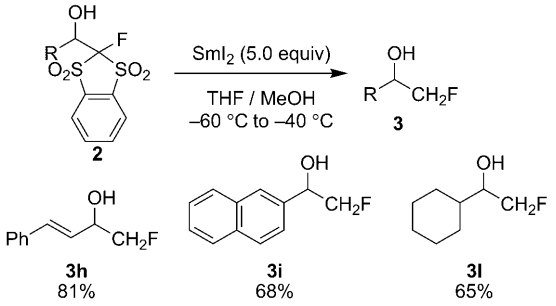
Table 2: Monofluoromethylation of aldehydes.[a]



1 2

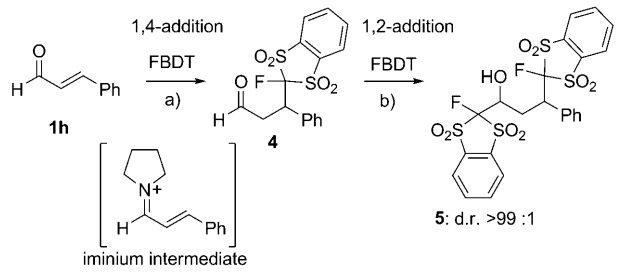
Entry	1	R	2	Yield [%][b]
1	**1b**	4-MeC_6H_4	**2b**	80
2	**1c**	4-ClC_6H_4	**2c**	88
3	**1d**	4-BrC_6H_4	**2d**	90
4	**1e**	4-$NO_2C_6H_4$	**2e**	94
5	**1f**	3-MeC_6H_4	**2f**	73
6	**1g**	3-ClC_6H_4	**2g**	95
7	**1h**	*trans*-PhCH=CH	**2h**	60
8	**1i**	2-naphthyl	**2i**	73
9	**1j**	2-thienyl	**2j**	77
10	**1k**	*n*-octyl	**2k**	74
11	**1l**	cyclohexyl	**2l**	86

[a] Reactions were carried out using FBDT (1.0 equiv), aldehyde (1.2 equiv), and DABCO (2.0 equiv) in toluene at room temperature for 1 day unless otherwise noted. Yields were calculated based on FBDT. [b] Yield of isolated product.



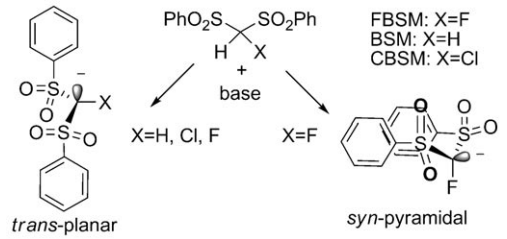
Scheme 2. Conversion of 1,2-adducts into monofluoromethylated compounds. Reactions were carried out using **2** (1.0 equiv) and SmI_2 (5.0 equiv) in THF and MeOH at −60 to −40°C for 3 h.

Attention was next turned to control of the selectivity of 1,2- versus 1,4-addition of FBDT to conjugated aldehyde **1h**. While 1,2-addition was predominantly observed in the presence of DABCO to afford **2h** as mentioned in the previous section (Table 1, entry 7), 1,4-adduct **4** was selectively obtained in the presence of pyrrolidine because of the formation of enamine as an intermediate (Scheme 3). It should be noted that excellent diastereoselectivity (>99%) was observed for the 1,2-addition of FBDT with FBDT-attached aldehyde **4** to give **5**, which has 1,3-stereocenters (Scheme 3).



Scheme 3. a) **1h** (1.5 equiv), pyrrolidine (20 mol%), FBDT (1.0 equiv), CH_2Cl_2, RT, 2 d, 51%; b) FBDT (1.0 equiv), DABCO (2.0 equiv), CH_2Cl_2, reflux, 5 h, 76%.

The structural investigation of α-fluorinated carbanions is a challenge.[12] It seems likely that the α-fluorine atom effectively stabilizes the carbanions through its strong electron-withdrawing effect; however, in practice, fluorine often destabilizes α-carbanions through Coulombic repulsion between the vicinal lone pairs of electrons of the carbanion and the neighboring fluorine atom.[12] Very recently, Prakash et al. reported studies on the α-fluorocarbanion of FBSM based on X-ray crystallographic analysis, NMR spectroscopy, and computations.[13] The X-ray crystallographic analysis of carbanion of FBSM revealed a *syn*-pyramidal conformation.[13] Both *syn*-pyramidal and *trans*-planar structures of FBSM were also found to be minima at the both B3LYP/6-31G(d) and B3LYP/6-311+G(2d,p) level of calculations, although the *trans*-planar structure was not observed experimentally (Scheme 4, X = F). In contrast, the carbanions of



Scheme 4. Conformations of carbanions derived from FBSM, BSM, and CBSM proposed by Prakash et al.[13] s*yn*-Pyramidal conformation occurs only with highly electronegative α-fluorine substituents.

bis(phenylsulfonyl)methane (BSM, $CH_2(SO_2Ph)_2$), and chlorobis(phenylsulfonyl)methane (CBSM, $CHCl(SO_2Ph)_2$) were both revealed to be *trans*-planar conformations (Scheme 4, X = H, Cl). On the basis of their work, we decided to investigate the conformations of FBDT and its carbanion. FBDT was characterized by single-crystal X-ray crystallography, which showed that the α-fluorinated carbon atom (C14) has an sp^3 structure, as evidenced by the angles S1-C14-F3 (110.9°), S2-C14-F3 (107.5°), H19-C14-F3 (110.7°), and S1-C14-S2 (105.9°). The C14–F3 bond length of 1.366 Å, which is typical for C_{sp^3}–F bonds in fluorocarbons and slightly shorter than that reported for FBSM (1.404 Å).[13,14] The most interesting point is that FBDT has a structure possessing an equatorial hydrogen atom and an axial fluorine atom, which is contrary to their steric factors (Figure 1 A). The preferred conformation has the hydrogen atom bisecting the two flanking SO_2 groups. Regarding the C–H bond as the more C lone-pair-like σ bond than the strongly polarized C–F bond, one would expect the C–H bond to bisect the two flanking SO_2 groups; furthermore, this arrangement exhibits potentially stabilizing electrostatic interactions between the positively polarized hydrogen atom and the four negatively polarized sulfonyl oxygen atoms, in contrast to the alternative arrangement, in which the hydrogen atom is axial and the negatively polarized fluorine ligand is juxtaposed to the four negatively polarized sulfonyl oxygen atoms.

Next, the conformation of carbanion of FBDT was investigated by computations based on the B3LYP/6-31+G-

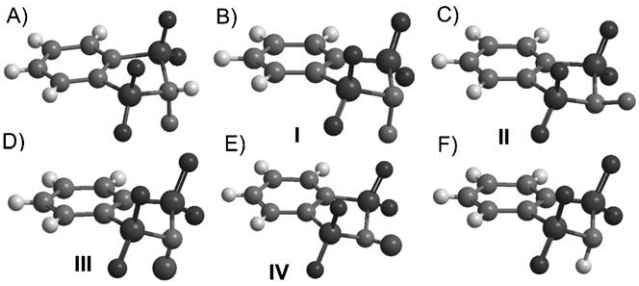
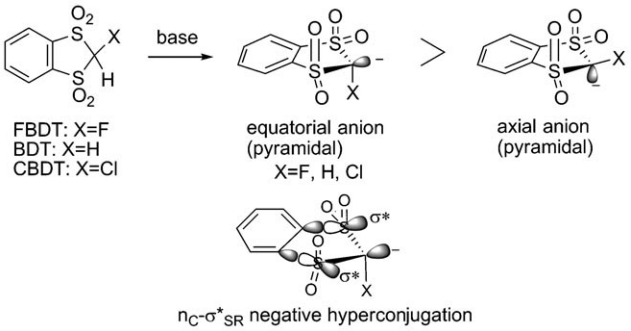


Figure 1. A) X-ray crystal structure of FBDT. B) Optimized structure of FBDT anion **I** (*eq*A-*ax*F conformation; 0 kcal mol^{-1}) calculated at the B3LYP/6-31+G(d,p) level. C) Optimized structure of FBDT anion **II** (*eq*F-*ax*A conformation; 3.49 kcal mol^{-1}) calculated at the B3LYP/6-31+G(d,p) level. D) Optimized structure of CBDT anion **III** (*eq*A-*ax*Cl conformation; 0 kcal mol^{-1}) calculated at the B3LYP/6-31+G(d,p) level. E) Optimized structure of CBDT anion **IV** (*eq*Cl-*ax*A conformation; 3.48 kcal mol^{-1}) calculated at the B3LYP/6-31+G(d,p) level. F) Optimized structure of BDT anion **I** (*eq*A-*ax*H conformation). The corresponding *eq*H-*ax*A conformation does not have a local minimum.

(d,p) level. Two optimized conformations **I** (equatorial anion and axial fluorine conformation; *eq*A-*ax*F) and **II** (*eq*F-*ax*A) were generated, both of which show the pyramidal nature of α-fluorocarbanion (Figure 1 B,C, Scheme 5). The fluorine



Scheme 5. Calculated conformations of carbanions derived from FDT, BDT, and CBDT. Equatorial anion conformations are always more stable than their counterparts independent of the substituents (X = F, H, Cl) because of n_C–σ^*_{SAr} negative hyperconjugation.

atom occupies the axial position in conformation **I**, whereas conformation **II** has an equatorial fluorine atom. Calculations led to the prediction that the axial fluorine conformation **I** should be slightly more stable by 3.49 kcal mol^{-1}. We next examined the conformations of carbanions of 2-chloro-1,3-benzodithiole-1,1,3,3-tetraoxide (CBDT) and 1,3-benzodithiole-1,1,3,3-tetraoxide (BDT) under the same computation method. The results are quite surprising. Similar to the case of FBDT, the equatorial carbanion conformations are more stable than axial ones, independent of the substituents (Figure 1 D–F and Scheme 5). Thus, the axial chlorine conformation **III** is more stable by 3.48 kcal mol^{-1} than the equatorial chlorine conformation **IV** (Figure 1 D,E), and the axial hydrogen conformation was found to be a minimum in the BDT carbanion (Figure 1 F). These results are distinct from those of FBSM and its analogues shown in Scheme 4.

The constraints of the five-membered ring have a profound effect upon the stereochemistry of the anion. While Prakash et al. have shown that the α-fluoroanion adopts a conformation that is distinct from all other derivatives, the five-membered ring yields isostructural anions for all α-substituents. The conformational stability of FBDT as well as its carbanion and analogues is governed essentially by the stabilization effects originating from n_C–σ^*_{SAr} negative hyperconjugation,[15] which was estimated to be 10.42 kcal mol^{-1} (5.21 kcal mol^{-1} × 2) each by natural bond order (NBO) analysis (B3LYP/6-31 + G**),[16] but not by the effects of the substituents such as fluorine, chlorine, or hydrogen. Since in the more stable equatorial carbanion configurations the anion lone pair orbital lies in the plane that contains the two σ* orbitals of S−Ar, whereas there is hardly any interaction between anion lone pair orbital and two σ* orbitals of S−Ar in the less stable axial isomers, the stabilization occurs depends on the degree to which the empty σ* orbital of the S−Ar bond participates (Scheme 5).

With facile access to this range of α-monofluoromethylated alcohols **3**, we finally considered synthetic applications. Osmundalactone **6** (R = H) is an aglycon of osmundalin isolated from *Osmunda japonica* by Hollenbeak and Kuehne in 1974.[17] Fluorinated isostere **7** was selected as our synthetic target from a pharmaceutical point of view.[1] The interest in fluoro-substituted osmundalactone **7** stems from the fact that osumundalactone is not only a biologically active natural product but also a useful reactive intermediate in organic synthesis, since it readily undergoes Michael addition, Baylis–Hillman reaction, 1,3-dipolar cycloaddition, and other olefin-related reactions.[18] In addition, hydroxylated analogues **8** (R′ = H) are widely useful synthetic intermediates for the preparation of various types of biologically attractive compounds (Figure 2).[18] Consequently, compound **7** should

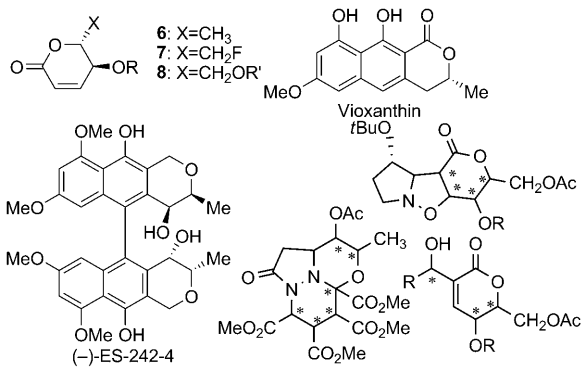
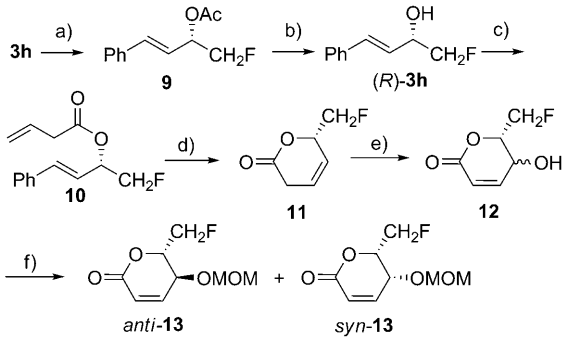


Figure 2. Osmundalactone (**6**), its fluorinated isostere **7**, and various biologically active target compounds.

become a sought-after building block in the synthesis of fluorinated isosteres of biologically relevant compounds derived form **6** or **8** because of the isosteric relationships between fluorine and hydrogen or the hydroxy group. The approach to fluorinated isosteres of osmundalactone is shown in Scheme 6. Although the synthesis of osmundalactone from nonfluorinated (*E*)-4-phenylbut-3-en-2-ol has been reported,[18h] the method was found not to be applicable for the synthesis of the fluorinated analogue, and several modifications were eventually required for conversion of **3h** into fluorinated isosteres of osmundalactone. Hence, the enzyme-catalyzed reaction for dynamic kinetic resolution of **3h** using lipase-PS in the presence of vinyl acetate proceeded smoothly to give enantiomerically pure **9** with greater than 99% *ee*.[19] Removal of acetyl group followed by esterification with 3-butenoic acid under 1,3-dicyclohexylcarbodiimide (DCC) coupling conditions furnished **10** via (*R*)-**3h** in high yield. Vinyl ester **10** was subjected to ring-closing metathesis by the use of 2nd generation Grubbs catalyst[20] to form β,γ-unsaturated lactone **11** in 84% yield. Finally, in situ catalytic epoxidation of **11** using methyl(trifluoromethyl)dioxirane[21] with subsequent ring-opening reaction gave the target fluorinated osmundalactone **12** as a mixture of diastereoisomers. Treatment of crude **12** with dimethoxymethane in the presence of P_2O_5 in $CHCl_3$ afforded *anti*-**13** (46%) and *syn*-**13** (26%), both of which should be attractive as building blocks for the synthesis of nonnatural fluorinated sugars and biologically active compounds.[18]



Scheme 6. a) Lipase-PS, vinyl acetate, *i*Pr$_2$O, 37 °C, 6 h; b) 1 N aq. NaOH, MeOH, RT, 30 min, 33%, over two steps; c) 3-butenoic acid (1.2 equiv), DCC (1.1 equiv), 4-dimethylaminopyridine (10 mol%), CH_2Cl_2, RT, 1 h; d) 2nd generation Grubbs catalyst (1.3 mol%), CH_2Cl_2, reflux, 4 h, 84%; e) CF_3COCH_3 (14.0 equiv), $KHSO_5$ (4.0 equiv), $NaHCO_3$ (6.2 equiv), EDTA buffer, CH_3CN, RT, 4 h; f) $(MeO)_2CH_2$, $CHCl_3$, RT, 30 min, 72% (*anti*: 46%, *syn*: 26%) over two steps.

In summary, we have developed a novel nucleophilic monofluoromethylating reagent, FBDT, which was shown to be suitable for the first nucleophilic monofluoromethylation of aldehydes based on the generation of an α-fluorocarbanion. Control of the selectivity of 1,2- versus 1,4-addition of FBDT to conjugated aldehydes was achieved by the choice of organic base. Monofluoromethylated alcohols can be accessed from aldehydes by this method in only two steps in good to high yields. The α-fluorocarbanion of FBDT was structurally characterized by X-ray crystallographic analysis and theoretical calculations. Both FBDT and its carbanion have structures possessing an axial fluorine atom, which is contrary to its steric factors, as a result of n_C–σ^*_{SAr} negative hyperconjugation. We close with a brief discussion of the functionally equivalent McCarthy reagent, $(EtO)_2P(=O)CHFSO_2Ph$,[22] of which FBDT is essentially a sulfonyl analogue. The McCarthy reagent has been effectively used for

fluoromethylenation of aldehydes to give fluoromethylene compounds. Hydrogenation of the resulting fluoromethylene group might give the fluoromethyl group being installed herein. Although McCarthy chemistry has been shown to be quite robust, strong inorganic bases such as lithium diisopropylamide and lithium hexamethyldisilazanide are required for deprotonation. The advantage of FBDT will be much clearer, provided the organocatalyzed enantioselective monofluoromethylation of aldehydes is achieved, and we are now working in this direction.

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