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Introducing difluoromethylene sulfonamide group via nucleophilic addition of difluoromethylene anion with aromatic aldehydes

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Abstract—A new fluorine-containing synthon, $R^1COCF_2SO_2R^2$ (**2**, R^1, R^2=morpholino, piperidino, etc.), was developed for the introduction of difluoromethylene sulfonamide or difluoromethylene group. Under different conditions, **2** reacted readily with aromatic aldehydes to give the corresponding difluoromethylene-containing alcohols or diols in moderate to good yields in the presence of potassium *tert*-butoxide. Difluoromethylene sulfonamide group was introduced into organic compounds directly for the first time by this method.

1. Introduction

Recently, organofluorine compounds have drawn much attention due to their potential use in pharmaceutical, biological, and material science.[1] Among them, compounds containing difluoromethylene group (CF_2) are the focus of considerable research.[2] It is known that difluoromethylene is isosteric and isopolar to an ethereal oxygen atom and compounds containing it usually show interesting properties.[3] Therefore, the development of synthetic methodologies for this kind of organofluorine compounds has been the subject of current research in the field of both organofluorine chemistry and organic synthesis.

In the past decades, many reliable methods have been developed for the synthesis of compounds with difluoromethylene moiety.[2,4] Among the various methods reported, it is obvious that the most convenient and efficient way to make these compounds is the coupling of a difluoromethylene moiety with other molecules from the view of molecular construction. In 1997, Olah et al. reported a potential difluoromethylene dianion ($^-CF_2^-$) precursor, difluorobis(trimethylsilyl)methane ($TMSCF_2TMS$).[5] However, reaction of $TMSCF_2TMS$ was limited to one aldehyde. In 2003, the same group reported an effective difluoromethylene-containing synthon, difluoromethyl phenyl sulfone, which can couple with two electrophilic molecules.[4e] Although sulfonamide-containing compounds have been widely used and investigated,[6] to the best of our knowledge, no direct method to introduce difluoromethylene sulfonamide group into organic compounds has been reported. Here, we report a novel method to synthesize compounds containing the difluoromethylene or difluoromethylene sulfonamide group.

2. Results and discussion

Langlois et al. reported that the trifluoromethylation of nonenolizable carbonyl compounds could be achieved with trifluoroacetic acid derivatives,[7a,b] trifluoromethanesulfinic acid derivatives,[7c] or trifluoroacetophenone.[7d] Recently, trifluoroacetamides[7e] and trifluoromethyl phenyl sulfone or sulfoxide[7f] were also reported as trifluoromethylating reagents. The mechanism of these reactions is mostly based on the nucleophilic attack of alkoxide on the amide, sulfinate, sulfenamide, sulfone, or sulfoxide center to release a trifluoromethyl anion.

2,2-Difluoro-2-fluorosulfonylacetyl fluoride (**1**) is an important intermediate for the preparation of Nafion resin. Recently, it has found many applications in the synthesis of organofluorine compounds. For example, Chen et al. used it as a precursor of difluoromethylene carbene and thus developed an effective trifluoromethylation reagent, which has been widely used.[8,9] Starting from **1**, it is easy to make diamide **2**. As mentioned above, trifluoroacetamides and trifluoromethane sulfonamides can be attacked by strong nucleophiles such as alkoxide to afford trifluoromethyl anion. If a similar reaction takes place in the case of compound **2**, difluoromethylene sulfonamide anion (**a**) or

Keywords: Difluoromethylene; Difluoromethylene-containing alcohol; Aldehyde; Potassium *tert*-butoxide.
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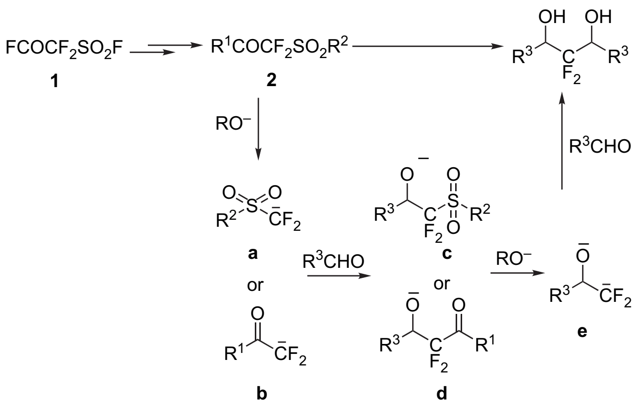
difluoromethylene amide anion (**b**) will be produced, which reacts with aldehydes to give amide **c** or **d**, respectively, as proposed in Scheme 1. Similar reaction may proceed further with **c** or **d** yielding difluoromethylene-containing diols through anion **e**.

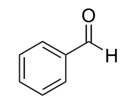
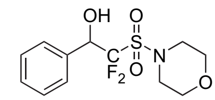
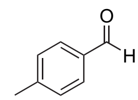
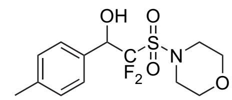
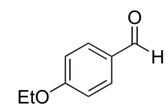
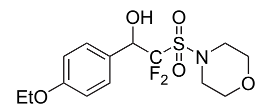
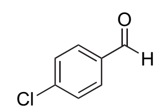
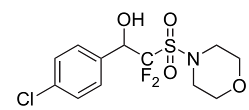
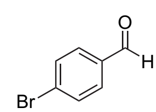
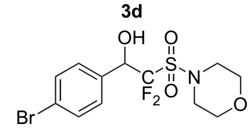
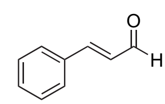
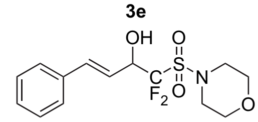


Scheme 1.

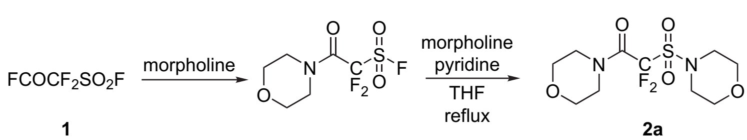
With the above consideration in mind, amide **2a** was prepared from **1** as shown in Scheme 2 and its reaction with aldehydes was investigated.

Benzaldehyde was first chosen as the electrophile. In the presence of 4 equiv of potassium *tert*-butoxide, **2a** reacted readily with benzaldehyde in DMF at −50 °C. The reaction was completed in 1 h and then quenched with ice water. 2,2-Difluoro-2-morpholinosulfonyl-1-phenylethanol (**3a**) was obtained in 85% yield after workup (Scheme 3).

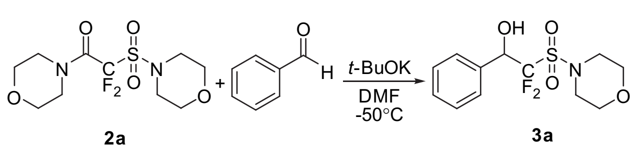
Table 1. The reaction of **2a** and aldehydes at −50 °C[a]

Entry	Substrate	Product	Yield[b] (%)
1		 **3a**	85
2		 **3b**	86
3		 **3c**	88
4		 **3d**	91
5		 **3e**	88
6		 **3f**	70

[a] ^{t}BuOK (4 equiv) was used in all reactions.
[b] Isolated yield based on **2a**.



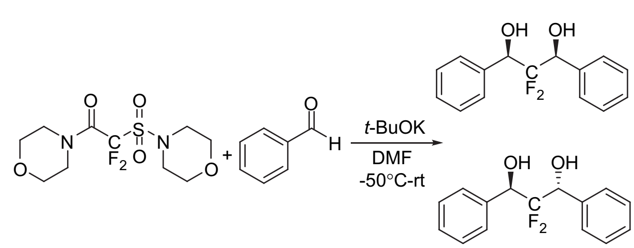
Scheme 2. The preparation of **2a**.



Scheme 3. The reaction of PhCHO and **2a** at −50 °C.

Under similar conditions, other aromatic aldehydes could also react with **2a** to give the corresponding products **3a**–**3e** in moderate to excellent yields. The results are summarized in Table 1. The substituent in the aromatic ring had little influence on the reaction. Aldehydes with both electron-donating and withdrawing groups reacted with **2a** readily with satisfactory yields. The reaction of *trans*-cinnamaldehyde and **2a** gave compound **3f** in moderate yield (Table 1, entry 6). In all these reactions, neither diol nor 2,2-difluoro-2-morpholinocarbonyl-1-arylethanol (the product formed through anion **b** in Scheme 1) was obtained, indicating that the amide group was more reactive than the sulfonamide under the reaction conditions. In the case of aliphatic aldehydes containing an α-hydrogen, the reaction was very complicated and no desired product was obtained.

Under different reaction conditions, different results were obtained. When the reaction of **2a** and benzaldehyde was first carried out at −50 °C for 1 h and then the reaction mixture was allowed to warm to room temperature prior to quenching with ice water, diol **4a** was obtained in 11% yield along with **3a** (Scheme 4).



4a

Scheme 4. The reaction of **2a** and PhCHO at −50 °C to rt.

From Scheme 1, it is evident that **4a** was formed from **3a**. When the reaction was carried out at higher temperature, the initial product **3a** reacted further with excess potassium *tert*-butoxide to give dianion **e** through addition–fragmentation, which reacted with another aldehyde to give the final product **4a**. Similar result was obtained by Prakash with an analog of **3a**.[4e]

To improve the yield of diols, the reaction of **2a** and benzaldehyde under various conditions was investigated. As shown in Table 2, the reaction was greatly influenced by the amount of potassium *tert*-butoxide. The yield of **4a** increased when more potassium *tert*-butoxide was used in the reaction and the best result was obtained with 8 equiv of potassium *tert*-butoxide (Table 2, entry 5). Further increasing the amount of potassium *tert*-butoxide decreased the yield of **4a**. From the results, it is obvious that higher temperature is necessary for the reaction of sulfonamide group and potassium *tert*-butoxide. No desired product was formed when the reaction was carried out at −50 to 0 °C (Table 2, entry 8). However, high temperature is unfavorable for the first step of this reaction. The reaction became complicated when it was carried out at room temperature directly: neither **3a** nor **4a** was obtained (Table 2, entry 3). Obviously, the intermediate formed (anion **a** in Scheme 1) from the reaction of **2a** and potassium *tert*-butoxide was not stable at room temperature and decomposed before reacting with benzaldehyde.

To explore the scope of this reaction and find a more effective reagent, a series of diamides were prepared from **1** for screening. The results of their reaction with benzaldehyde under the optimized conditions are summarized in Table 3. In general, when R^1 and R^2 were both cyclic amines, the reaction gave moderate yields with 82–86% diastereoselectivity and the best result was obtained with diamide **2f**. In the case of linear amino, the yield of **4a** was very poor (Table 3, entry 5). As demonstrated in the literature, the diastereoselectivity of this reaction can be explained by the charge–charge repulsion effect of the dianion intermediate formed in the reaction.[4e]

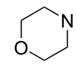
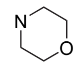
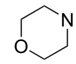
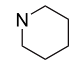
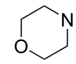
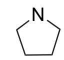
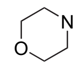
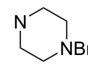
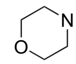
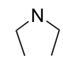
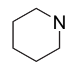
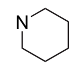
Using the optimized conditions, the reaction of **2f** and other aromatic aldehydes was investigated. As shown in Table 4, the reaction was influenced by the substituents in the aromatic ring of aldehydes. Aldehydes containing an electron-withdrawing group such as Cl and Br gave better diastereoselectivities, but resulted in lower yields compared with benzaldehyde. In the case of aldehydes with electron-donating group such as CH_3O and CH_3, only trace products were detected.

Table 2. The reaction of **2a** and benzaldehyde under different conditions

Entry	^{t}BuOK (equiv)	Temperature	Solvent	Yield[a] (%)
1	4	−50 °C to rt	DMF	11
2	5	−50 °C to rt	DMF	27
3	5	rt	DMF	—[b]
4	7	−50 °C to rt	DMF	49
5	8	−50 °C to rt	DMF	66
6	9	−50 °C to rt	DMF	54
7	10	−50 °C to rt	DMF	54
8	8	−50 to 0 °C	DMF	—[b]
9	8	−50 °C to rt	THF	24

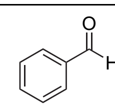
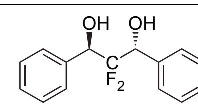
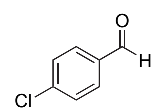
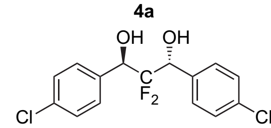
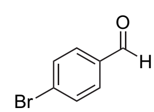
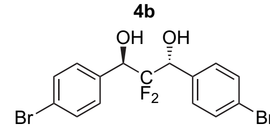
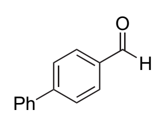
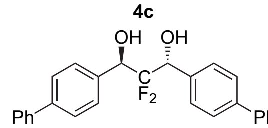
[a] Determined by ^{19}F NMR using $PhOCF_3$ as an internal standard.
[b] No desired product was detected by ^{19}F NMR.

Table 3. The reaction of diamides and benzaldehyde at −50 °C to rt

Entry	2	R[1]	R[2]	Yield[a] (%)	*anti*/*syn*[b]	de (%)
1	**2a**			48	93:7	86
2	**2b**			58	91:9	82
3	**2c**			54	94:6	88
4	**2d**			49	91:9	82
5	**2e**			Trace		
6	**2f**			64	92:8	84

[a] Isolated yield based on **2**.
[b] *anti*/*syn* ratios were determined by ^{19}F NMR.

Table 4. The reaction of **2f** and aldehydes at −50 °C to rt

Entry	Substrate	Product	Yield[a] (%)	*anti*/*syn*[b]
1		 **4a**	64	92:8
2		 **4b**	41	>99:1
3		 **4c**	38	>99:1
4		 **4d**	18	>99:1

[a] Isolated yield based on **2f**.
[b] *anti*/*syn* ratios were determined by ^{19}F NMR.

3. Conclusion

In summary, a novel fluorine-containing synthon, R^1-$COCF_2SO_2R^2$ (R^1, R^2=morpholino, piperidino, etc.), has been developed from 2,2-difluoro-2-fluorosulfonylacetyl fluoride. Nucleophilic addition of difluoromethylene anions formed from the reaction of **2** and potassium *tert*-butoxide to aromatic aldehydes gave the corresponding difluoromethylene-containing alcohols or diols, providing a convenient method for the introduction of difluoromethylene sulfonamide or difluoromethylene group into organic compounds.

4. Experimental section

4.1. General

Melting points were uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. ^{19}F NMR spectra were taken on a 282 MHz spectrometer using $CFCl_3$ as external standard. Mass spectra were obtained on an MS instrument operated at 70 eV in the electron impact mode. Column chromatography was performed on silica gel H, particle size 10–40 μm.

4.2. Typical procedure for the synthesis of 2

A three-necked flask equipped with a dropping funnel and a condenser was charged with CH_2Cl_2 (70 mL) and compound **1** (12.69 g, 70 mmol). The resulting mixture was cooled to 0 °C and a solution of morpholine (5.5 mL, 63 mmol) in 40 mL CH_2Cl_2 was added through the dropping funnel. After addition, the reaction mixture was allowed to warm to room temperature under stirring. Then the mixture was quenched with ice water and extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was washed with saturated NaCl solution and water. After drying over $MgSO_4$, the solvent was removed under vacuum to give 11.74 g crude product, which was used directly in the next step.

A mixture of the crude product (2.47 g), morpholine (3.15 mL), pyridine (2.5 mL), and THF (35 mL) was stirred under reflux. After the reaction was complete (monitored by TLC), the reaction mixture was cooled to room temperature. Water was added and the mixture was extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was washed with aqueous HCl solution, saturated NaCl solution, and water. After drying over $MgSO_4$, the solvent was removed under vacuum. The crude product was purified by recrystallization from CCl_4/petroleum ether to give 2.38 g (75% yield) of *2,2-difluoro-1-morpholino-2-(morpholinosulfonyl)ethanone* (**2a**) as a white solid. Mp: 102–103 °C; IR (KBr): 2861, 1671, 1457, 1369, 1181, 1116 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.86–3.70 (m, 12H), 3.68–3.52 (m, 4H); ^{19}F NMR ($CDCl_3$): δ −99.53 (s, 2F); MS (EI) *m*/*z* (%): 314 (M^+, 0.17), 228 (2.03), 164 (5.45), 150 (11.37), 114 (52.26), 86 (100). Anal. Calcd for $C_{10}H_{16}F_2N_2O_5S$: C, 38.21; H, 5.13; F, 12.09; N, 8.91. Found: C, 38.22; H, 5.11; F, 12.32; N, 8.84.

4.2.1. 2,2-Difluoro-1-morpholino-2-(piperidin-1-ylsulfonyl)ethanone (2b). White solid, 71% yield. Mp: 62–63 °C; IR (KBr): 2957, 1680, 1442, 1369, 1183, 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.80–3.78 (m, 2H), 3.76–3.70 (m, 6H), 3.59–3.40 (m, 4H), 1.66–1.60 (m, 6H); ^{19}F NMR ($CDCl_3$): δ −100.25 (s, 2F); MS (EI) *m*/*z* (%): 313 (M^++1, 0.64), 228 (0.20), 165 (19.70), 148 (2.49), 114 (21.22), 86 (4.88), 84 (100). Anal. Calcd for $C_{11}H_{18}F_2N_2O_4S$: C, 42.30; H, 5.81; F, 12.17; N, 8.97. Found: C, 42.22; H, 5.76; F, 12.30; N, 8.84.

4.2.2. 2,2-Difluoro-1-morpholino-2-(pyrrolidin-1-ylsulfonyl)ethanone (2c). White solid, 82% yield. Mp: 72–73 °C; IR (KBr): 2990, 1674, 1462, 1361, 1155, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.79–3.74 (m, 8H), 3.56 (t, *J*=6.6 Hz, 4H), 2.02 (t, *J*=6.6 Hz, 4H); ^{19}F NMR ($CDCl_3$): δ −99.27 (s, 2F); MS (EI) *m*/*z* (%): 164 (1.93), 134 (12.06), 114 (21.75), 86 (5.18), 70 (100). Anal. Calcd for $C_{10}H_{16}F_2N_2O_4S$: C, 40.26; H, 5.41; F, 12.74; N, 9.39. Found: C, 40.29; H, 5.30; F, 13.12; N, 9.34.

4.2.3. 2-(4-Benzylpiperidin-1-ylsulfonyl)-2,2-difluoro-1-morpholinoethanone (2d). White solid, 70% yield. Mp: 102–103 °C; IR (KBr): 2962, 1671, 1457, 1369, 1159, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.34–7.31 (m, 5H), 3.77–3.74 (m, 8H), 3.62–3.50 (m, 6H), 2.65–2.50 (m, 4H); ^{19}F NMR ($CDCl_3$): δ −99.90 (s, 2F); MS (EI) *m*/*z* (%): 403 (M^+, 0.76), 239 (2.82), 228 (2.44), 175 (54.30), 164 (1.12), 114 (3.68), 91 (100), 86 (1.78). Anal. Calcd for $C_{17}H_{23}F_2N_3O_4S$: C, 50.61; H, 5.75; F, 9.42; N, 10.42. Found: C, 50.90; H, 5.70; F, 9.58; N, 10.38.

4.2.4. *N*,*N*-Diethyl-1,1-difluoro-2-morpholino-2-oxoethane sulfonamide (2e). Oil, 54% yield. IR (neat): 2981, 1678, 1444, 1368, 1151, 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.76–3.72 (m, 8H), 3.45–3.43 (m, 4H), 1.24 (t, *J*=7.2 Hz, 6H); ^{19}F NMR ($CDCl_3$): δ −100.21 (s, 2F); MS (EI) *m*/*z* (%): 301 (M^++1, 1.18), 228 (1.68), 164 (10.67), 136 (21.99), 114 (64.01), 86 (8.35), 72 (100). Anal. Calcd for $C_{10}H_{18}F_2N_2O_4S$: C, 39.99; H, 6.04; F, 12.65; N, 9.33. Found: C, 40.18; H, 5.98; F, 12.76; N, 9.20.

4.2.5. 2,2-Difluoro-1-(piperidin-1-yl)-2-(piperidin-1-ylsulfonyl)ethanone (2f). White solid, 71% yield. Mp: 66–67 °C; IR (KBr): 2945, 1674, 1446, 1375, 1184, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.66–3.64 (m, 4H), 3.51–3.41 (m, 4H), 1.66–1.59 (m, 12H); ^{19}F NMR ($CDCl_3$): δ −98.82 (s, 2F); MS (EI) *m*/*z* (%): 311 (M^++1, 0.24), 226 (0.21), 162 (5.80), 148 (2.49), 148 (5.06), 112 (46.54), 84 (100). Anal. Calcd for $C_{12}H_{20}F_2N_2O_3S$: C, 46.44; H, 6.50; F, 12.24; N, 9.03. Found: C, 46.56; H, 6.47; F, 12.70; N, 9.06.

4.3. Typical procedure for the synthesis of 3

The reaction was carried out in a Schlenk flask under nitrogen atmosphere. Into 3 mL DMF solution of **2a** (320 mg, 1 mmol) and benzaldehyde (0.3 mL, 3 mmol) was added 3 mL DMF solution of ^{t}BuOK (457 mg, 4 mmol) at −50 °C. The mixture was stirred at −50 °C for 1 h. Then the reaction was quenched with 10 mL ice water and the resulting mixture was extracted with ether (25 mL×3). The combined ethereal solution was washed with saturated NH_4Cl solution and water. After drying over $MgSO_4$, the solvent was removed under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=4/1) to give 267 mg of *2,2-difluoro-2-(morpholinosulfonyl)-1-phenylethanol* (**3a**) as a yellow solid in 85% yield. Mp: 85–86 °C; IR (KBr): 3524, 2858, 1458, 1355, 1170, 1118, 959 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.46–7.45 (m, 2H), 7.40–7.38 (m, 3H), 5.29 (d, *J*=22.4 Hz, 1H), 3.72–3.60 (m, 5H), 3.46 (t, *J*=4.4 Hz, 4H); ^{19}F NMR ($CDCl_3$): δ −104.71 (d, *J*=241.7 Hz, 1F), −118.17 (dd, *J*=241.7, 22.4 Hz, 1F); MS (EI) *m*/*z* (%): 307 (M^+, 3.47), 157 (0.28), 150 (0.27), 107 (100), 86 (7.04), 77 (12.29). Anal. Calcd for $C_{12}H_{15}F_2NO_4S$: C, 46.90; H, 4.92; F, 12.36; N, 4.56. Found: C, 47.16; H, 5.05; F, 12.45; N, 4.50.

4.3.1. 2,2-Difluoro-2-(morpholinosulfonyl)-1-*p*-tolylethanol (3b). Yellow solid, 86% yield. Mp: 83–84 °C; IR (KBr): 3556, 2978, 1699, 1454, 1355, 1261, 1166, 1114, 952 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.37 (d, *J*=7.6 Hz, 2H), 7.22 (d, *J*=7.6 Hz, 2H), 5.29 (d, *J*=20.4 Hz, 1H), 3.73 (t, *J*=3.9 Hz, 4H), 3.51 (t, *J*=3.9 Hz, 4H), 3.11 (s, 1H), 2.37 (s, 3H); ^{19}F NMR ($CDCl_3$): δ −105.31 (d, *J*=239.7 Hz, 1F), −119.06 (dd, *J*=239.7, 20.4 Hz, 1F); MS (EI) *m*/*z* (%): 321 (M^+, 4.06), 171 (0.18), 150 (0.35), 121 (100), 91 (9.48), 86 (2.78). Anal. Calcd for $C_{13}H_{17}F_2NO_4S$: C, 48.59; H, 5.33; N, 4.36. Found: C, 48.63; H, 5.20; N, 4.17.

4.3.2. 1-(4-Ethoxyphenyl)-2,2-difluoro-2-(morpholinosulfonyl)ethanol (3c). Yellow solid, 88% yield. Mp: 107–108 °C; IR (KBr): 3347, 2889, 1613, 1515, 1376, 1171, 947 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.39 (d, *J*=8.6 Hz, 2H), 6.92 (d, *J*=8.6 Hz, 2H), 5.26 (d, *J*=22.5 Hz, 1H), 4.05 (q, *J*=7.0 Hz, 2H), 3.73 (t, *J*=4.5 Hz, 4H), 3.51 (t, *J*=4.5 Hz, 4H), 3.11 (s, 1H), 1.42 (t, *J*=7.0 Hz, 3H); ^{19}F NMR ($CDCl_3$): δ −104.96 (d, *J*=239.0 Hz, 1F), −118.84 (dd, *J*=239.0, 22.5 Hz, 1F); MS (EI) *m*/*z* (%): 351 (M^+, 3.77), 200 (0.89), 151 (100), 121 (3.90), 86 (2.87), 45 (3.67). Anal. Calcd for $C_{14}H_{19}F_2NO_5S$: C, 47.86; H, 5.45; F, 10.81; N, 3.99. Found: C, 48.02; H, 5.50; F, 10.97; N, 3.94.

4.3.3. 1-(4-Chlorophenyl)-2,2-difluoro-2-(morpholinosulfonyl)ethanol (3d). White solid, 91% yield. Mp: 115–116 °C; IR (KBr): 3357, 2999, 1596, 1494, 1365, 1168, 1105, 943 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.44–7.37 (m, 4H), 5.32 (d, *J*=21.2 Hz, 1H), 3.74 (t, *J*=4.5 Hz, 4H), 3.52 (t, *J*=4.5 Hz, 4H), 3.29 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −105.27 (d, *J*=240.7 Hz, 1F), −118.97 (dd, *J*=240.7, 21.2 Hz, 1F); MS (EI) *m*/*z* (%): 341 (M^+, 2.50), 200 (2.74), 141 (100), 111 (9.91), 86 (10.56). Anal. Calcd for $C_{12}H_{14}ClF_2NO_4S$: C, 42.17; H, 4.13; F, 11.12; N, 4.10. Found: C, 41.98; H, 4.13; F, 10.98; N, 3.96.

4.3.4. 1-(4-Bromophenyl)-2,2-difluoro-2-(morpholinosulfonyl)ethanol (3e). Yellow solid, 88% yield. Mp: 114–115 °C; IR (KBr): 3365, 2934, 1593, 1490, 1365, 1168, 1104, 943 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.53 (d, *J*=8.4 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 5.27 (d, *J*=20.7 Hz, 1H), 3.71 (t, *J*=4.4 Hz, 4H), 3.66 (s, 1H), 3.49 (t, *J*=4.4 Hz, 4H); ^{19}F NMR ($CDCl_3$): δ −104.99 (d, *J*=240.6 Hz, 1F), −118.48 (dd, *J*=240.6, 20.7 Hz, 1F); MS (EI) *m*/*z* (%): 385 (M^++1, 4.28), 185 (94.08), 155 (2.94), 150 (1.03), 86 (12.40). Anal. Calcd for $C_{12}H_{14}BrF_2NO_4S$: C, 37.32; H, 3.65; F, 9.84; N, 3.63. Found: C, 37.29; H, 3.58; F, 10.14; N, 3.56.

4.3.5. (*E*)-1,1-Difluoro-1-(morpholinosulfonyl)-4-phenylbut-3-en-2-ol (3f). Yellow liquid, 70% yield. IR (neat): 3387, 2928, 1733, 1451, 1370, 1263, 1173, 1114, 956 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.44 (d, *J*=6.9 Hz, 2H), 7.44–7.30 (m, 3H), 6.87 (d, *J*=15.8 Hz, 1H), 6.26 (dd, *J*=15.8, 6.6 Hz, 1H), 5.04–4.91 (m, 1H), 3.76 (t, *J*=4.8 Hz, 4H), 3.54 (t, *J*=4.8 Hz, 4H), 2.94 (d, *J*=5.1 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −107.59 (dd, *J*=239.4, 7.0 Hz, 1F), −115.59 (dd, *J*=239.4, 16.3 Hz, 1F); MS (EI) *m*/*z* (%): 333 (M^+, 4.46), 256 (0.12), 183 (0.42), 150 (0.25), 133 (100), 103 (3.37), 86 (2.14), 77 (4.27). Anal. Calcd for $C_{14}H_{17}F_2NO_4S$: C, 50.44; H, 5.14; N, 4.20. Found: C, 50.54; H, 5.40; N, 4.02.

4.4. Typical procedure for the preparation of diols

The reaction was carried out in a Schlenk flask under nitrogen atmosphere. Into 5 mL DMF solution of **2f** (312 mg, 1 mmol) and benzaldehyde (0.3 mL, 3 mmol) was added 9 mL DMF solution of ^{t}BuOK (913 mg, 8 mmol) at −50 °C. The mixture was stirred at −50 °C for 1 h and then allowed to warm to room temperature slowly under stirring and quenched with 10 mL ice water. The resulting mixture was extracted with ether (30 mL×3). The combined ethereal solution was washed with saturated NH_4Cl solution and water. After drying over $MgSO_4$, the solvent was removed under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate=9/1 to 4/1) to give 171 mg of *2,2-difluoro-1,3-diphenylpropane-1,3-diol* (**4a**)[4e] as a white solid in 64% yield. ^{1}H NMR (D_3CCOCD_3): δ 7.50 (d, *J*=7.2 Hz, 4H), 7.30–7.38 (m, 6H), 5.35–5.25 (m, 4H); ^{19}F NMR (D_3CCOCD_3) for *anti*-isomer: δ −122.26 (t, *J*=16.1 Hz, 2F).

4.4.1. 1,3-Bis(4-chlorophenyl)-2,2-difluoropropane-1,3-diol (4b).[4e] Yellow solid, 41% yield. IR (KBr): 3593, 1492, 1090, 1074, 1015 cm^{-1}; ^{1}H NMR (D_3CCOCD_3): δ 7.50 (d, *J*=8.6 Hz, 4H), 7.38 (d, *J*=8.6 Hz, 4H), 5.48 (d, *J*=5.4 Hz, 2H), 5.33 (dt, *J*=5.4, 11.5 Hz, 2H); ^{19}F NMR (D_3CCOCD_3) for *anti*-isomer: δ −122.42 (t, *J*=11.5 Hz, 2F); MS (EI) *m*/*z* (%): 332 (M^+−1, 0.77), 141 (78.11), 111 (7.07).

4.4.2. 1,3-Bis(4-bromophenyl)-2,2-difluoropropane-1,3-diol (4c).[4e] Yellow solid, 38% yield. IR (KBr): 3591, 1488, 1076, 1011 cm^{-1}; ^{1}H NMR (D_3CCOCD_3): δ 7.53 (d, *J*=8.6 Hz, 4H), 7.44 (d, *J*=8.6 Hz, 4H), 5.48 (s, 2H), 5.31 (t, *J*=13.5 Hz, 2H); ^{19}F NMR (D_3CCOCD_3) for *anti*-isomer: δ −122.43 (t, *J*=13.5 Hz, 2F); MS (EI) *m*/*z* (%): 422 (M^+, 1.25), 186 (7.32), 156 (1.73).

4.4.3. 1,3-Di(biphenyl-4-yl)-2,2-difluoropropane-1,3-diol (4d).[4e] Yellow solid, 18% yield. ^{1}H NMR (D_3CCOCD_3): δ 7.77–7.58 (m, 12H), 7.48–7.43 (m, 4H), 7.35 (t, *J*=7.2 Hz, 2H), 5.44–5.34 (m, 4H); ^{19}F NMR (D_3CCOCD_3) for *anti*-isomer: δ −122.06 (t, *J*=12.1 Hz, 2F).

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References and notes

1. (a) Welch, J. T.; Eswarakrishman, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, NY, 1991; (b) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biochemical Applications*; Elsevier: Amsterdam, 1993; (c) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, NY, 1994; (d) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; American Chemical Society: Washington, DC, 1990; (e) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996.
2. (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619–8683; (b) Burton, D. J.; Yang, Z. Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641–1715; (c) Plantier-Royon, R.; Portella, C. *Carbohydr. Res.* **2000**, *327*, 119–146.

3. (a) Berkowitz, D. B.; Bhuniya, D.; Peris, G. *Tetrahedron Lett.* **1999**, *40*, 1869–1872; (b) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16.
4. (a) Wang, Z. G.; Hammond, G. B. *Chem. Commun.* **1999**, 2545–2546; (b) Itoh, T.; Kudo, K.; Tanaka, N.; Sakabe, K.; Takagi, Y.; Kihara, H. *Tetrahedron Lett.* **2000**, *41*, 4591–4595; (c) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276–8279; (d) Cox, L. R.; DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M. *Org. Lett.* **2003**, *5*, 337–339; (e) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216–5219.
5. Yudin, A. K.; Prakash, G. K. S.; Deffieux, D.; Bradley, M.; Bau, R.; Olah, G. A. *J. Am. Chem. Soc.* **1997**, *119*, 1572–1581.
6. (a) Moree, W. J.; van der Marel, G. A.; Liskamp, R. M. J. *Tetrahedron Lett.* **1991**, *32*, 409–412; (b) Zecchini, G. P.; Paradisi, M. P.; Torrini, I.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G. *Tetrahedron Lett.* **1991**, *32*, 6779–6782; (c) Moree, W. J.; van der Marel, G. A.; Liskamp, R. J. *J. Org. Chem.* **1995**, *60*, 5157–5169; (d) Gennari, C.; Nestler, H. P.; Salom, B.; Still, W. C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1765–1768.
7. (a) Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185–193; (b) Jablonski, L.; Joubert, J.; Billard, T.; Langlois, B. R. *Synlett* **2003**, 230–232; (c) Inschauspe, D.; Sortais, J.-P.; Billard, T.; Langlois, B. R. *Synlett* **2003**, 233–235; (d) Jablonski, L.; Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **2003**, *44*, 1055–1057; (e) Joubert, J.; Roussel, S.; Christophe, C.; Billard, T.; Langlois, B. R.; Vidal, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3133–3136; (f) Prakash, G. K. S.; Hu, J.; Olah, G. A. *Org. Lett.* **2003**, *5*, 3253–3256.
8. (a) Chen, Q.; Wu, S. *J. Chem. Soc., Chem. Commun.* **1989**, 705–706; (b) Chen, Q.; Duan, J. *J. Chem. Soc., Chem. Commun.* **1993**, 918–919; (c) Duan, J.; Dolbier, W. R.; Chen, Q. *J. Org. Chem.* **1998**, *63*, 9486–9489; (d) Xu, W.; Chen, Q. *J. Org. Chem.* **2002**, *67*, 9421–9427; (e) Tian, F.; Kruger, V.; Bautista, O.; Duan, J.; Li, A.; Dolbier, W. R.; Chen, Q. *Org. Lett.* **2000**, *2*, 563–564.
9. (a) Roche, A. J.; Dolbier, W. R. *J. Org. Chem.* **2000**, *65*, 5282–5290; (b) Veliz, E. A.; Stephens, O. M.; Beal, P. A. *Org. Lett.* **2001**, *3*, 2969–2972; (c) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701–2704.