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Nucleophilic difluoro(phenylsulfonyl)methylation of carbonyls with $PhSO_2CF_2H$ reagent in the presence of *in situ* generated substoichiometric amount of base

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Aldehydes
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ABSTRACT

The reactions between carbonyl compounds and $PhSO_2CF_2H$ using substoichiometric amount of base in situ generated from $N(TMS)_3$ and catalytic amount of Me_4NF have been investigated. It is found that both enolizable and non-enolizable aldehydes are suitable substrates to undergo nucleophilic difluoro(phenylsulfonyl)methylation. Compared to the previously reported trifluoromethylation of carbonyls with CF_3H under the similar reaction conditions, the unique reactivity of $PhSO_2CF_2H$ is attributed to its higher acidity than CF_3H and the reversibility of its addition reaction with ketones under basic conditions.

1. Introduction

Nucleophilic fluoroalkylation is one of the most important transformations in organofluorine chemistry, which not only can transfer a fluoroalkyl group to carbon-electrophiles for the synthesis of fluoroalkylated molecules of interest in life and materials sciences [1], but also is a fundamental method for the synthesis of many other nucleophilic, radical, and electrophilic fluoroalkylation reagents such as Ruppert-Prakash reagent ($TMSCF_3$), $PhSO_2CF_2I$ reagent, and Togni reagents [2]. Although nucleophilic fluoroalkylation with (fluoroalkyl)silanes (R_3SiR_f) has become one of the widely used methods for the synthesis of fluorinated organic compounds [3], nucleophilic fluoroalkylation with hydrofluorocarbons and their derivatives (R_fH) is a more atom-economical way, in which the generation of the nucleophilic fluoroalkyl anion species R_f^- under the treatment of a proper base is involved.[1d,4] However, in cases of the thermally instable fluoroalkyl anions, their in situ generation from R_fH is usually required; therefore, the generality of nucleophilic fluoroalkylation with R_fH is largely influenced by the compatibility between the electrophiles and the bases [5–7].

As an important difluoromethylation reagent, the synthetic application of difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) has been intensively studied [8]. In 1972, Edwards and co-workers claimed in a patent that $PhSO_2CF_2^-$ anion (derived from $PhSO_2CF_2H$ and potassium *tert*-butoxide in diglyme/Et_2O at −78 °C) was able to undergo 1,4-addition to a cyclic α,β-unsaturated ketone, but the chemical yield was not reported [9a]. In 1989, Stahly reported the nucleophilic difluoro(phenylsulfonyl)methylation of carbonyls with $PhSO_2CF_2H$ using sodium hydroxide as a base, and only some aromatic aldehydes and sterically hindered aliphatic aldehydes (such as isobutyraldehyde) were demonstrated for the reaction [9b]. In 2005, a modified protocol was developed by Prakash and coworkers, in which sterically hindered base lithium hexamethyldisilazide (LiHMDS) was used, and various ketones and non-enolizable aldehydes were

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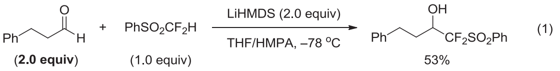
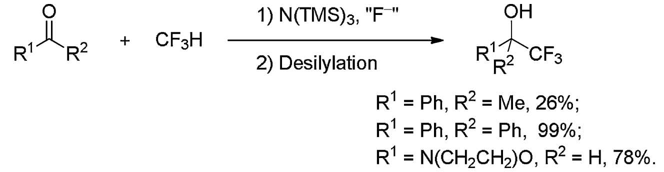
found to be suitable substrates for the reaction [6]. However, the difluoromethylation of eneolizable aldehydes with $PhSO_2CF_2H$ still remains a challenging task, which is mainly due to the facile enolization of these aldehydes caused by the presence of a stoichiometric amount of strong base (Eq. (1)) [6]. We envisioned that the enolization of aliphatic aldehydes might be diminished by significantly lowering the concentration of the base in the reaction system. Herein, we report an efficient nucleophilic difluoro(phenylsulfonyl)methylation of enolizable aldehydes with $PhSO_2CF_2H$ reagent in the presence of in situ generated substoichiometric amount of base.



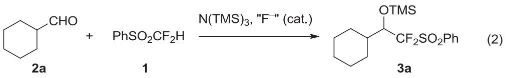
(1)

2. Results and discussion

In 2000, Langlois and coworkers developed a synthetically useful nucleophilic trifluoromethylation of carbonyl compounds in DMF using trifluoromethane (CF_3H) and tris(trimethylsilyl)amine [$N(TMS)_3$] in the presence of tetramethylamonium fluoride (TMAF) (Scheme 1) [10]. In their reaction, the $N(TMS)_3/F^-$ system generates bis(trimethylsilyl)amide slowly, and the base is always in low concentration, thus facilitating the trifluoromethylation of enolizable carbonyls (such as acetophenone) by diminishing their enolization. Inspired by this elegant work [10a] we decided to employ the same base system to solve the enolization problem in the (phenylsulfonyl)difluoromethylation of aliphatic aldehydes with $PhSO_2CF_2H$ (**1**). At the outset, we chose cyclohexanecarbaldehyde (**2a**) as a model substrate (Eq. (2)). The initial reaction of **1** (1.0 equiv.) with **2a** (1.5 equiv.) using a combination of $N(TMS)_3$ (1.5 equiv.) and Me_4NF (10 mol%) was carried out in DMF at −10 °C to room temperature (RT) over 20 h, and the silylated α-difluoro(phenylsulfonyl)methylcarbinol **3a** was obtained in 53% yield. A brief optimization of the reaction conditions revealed that an excellent yield (92%) of product **3a** was obtained when the reaction was performed at 45 °C using 2.0 equiv. of $N(TMS)_3$.



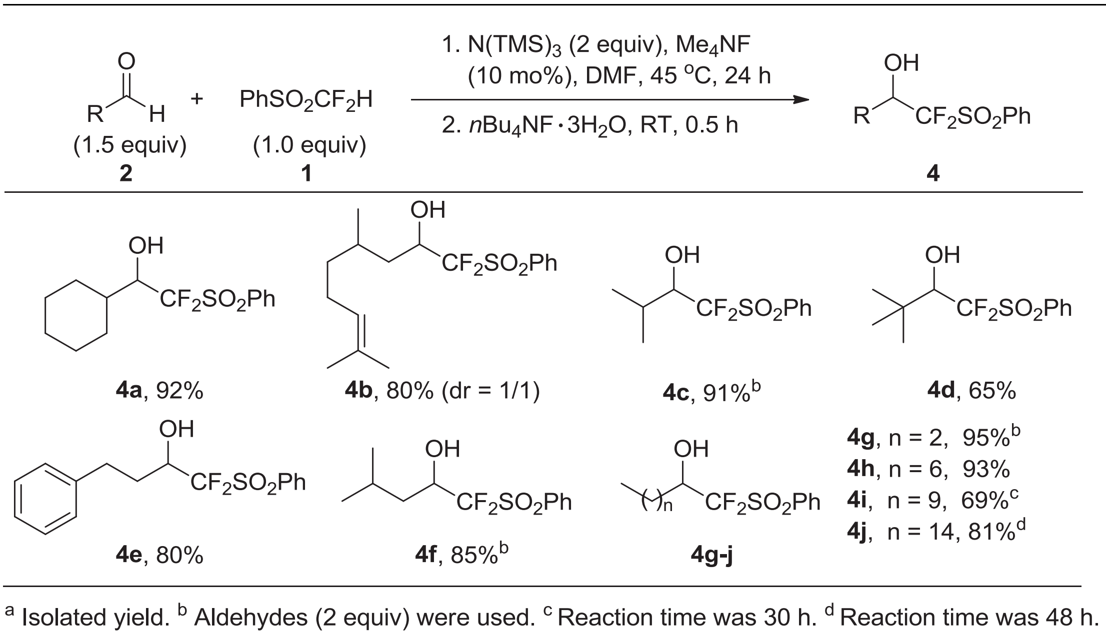
Scheme 1. Trifluoromethylation of carbonyls with CF_3H and in situ generated base [10].



(2)

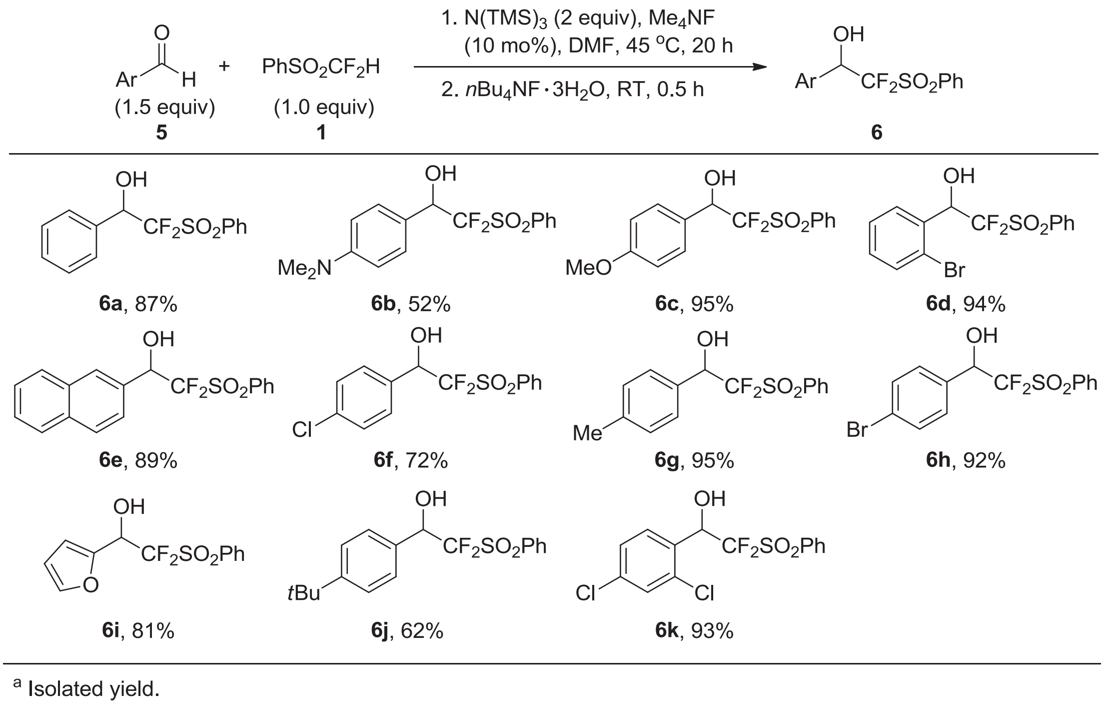
Encouraged by the aforementioned result, we further investigated the scope of this new protocol for difluoro(phenylsulfonyl)methylation. Firstly, we examined the nucleophilic difluoro(phenylsulfonyl)methylation of primary, secondary, and tertiary aldehydes **2** with $PhSO_2CF_2H$ (**1**) under the optimized reaction conditions (molar ratio, **1**/**2**/$N(TMS)_3$/TMAF = 1.0/1.5/2.0/10%; 45 °C; 20 h). The results are summarized in Table 1. In all cases, α-difluoro(phenylsulfonyl)methyl alcohols **4** were obtained in moderate to excellent isolated yields after subsequent desilylation with tetrabutylammonium fluoride trihydrate (TBAF·$3H_2O$). For the volatile aldehydes such as isobutyraldehyde (**3c**), 3-methylbutanal (**3f**), butyraldehyde (**3g**), the reaction using 2.0 equiv. of aldehydes can give much higher yields of the alcohols **4c**, **4f**, and **4g** than that under the standard conditions. In cases of the long-chain aldehydes such as undecanal (**3a**) and palmitaldehyde (**3b**), a prolonged reaction time is required due to their low solubility in DMF. In general, this protocol is highly effective for the difluoro(phenylsulfonyl)methylation of aliphatic aldehydes, even for the readily enolizable aldehydes.

Table 1
Nucleophilic difluoro(phenylsulfonyl)methylation of aliphatic aldehydes with reagent **1**.[a].



[a] Isolated yield.
[b] Aldehydes (2 equiv.) were used.
[c] Reaction time was 30 h.
[d] Reaction time was 48 h.

Table 2
Nucleophilic difluoro(phenylsulfonyl)methylation of aromatic aldehydes with reagent **1**.[a].

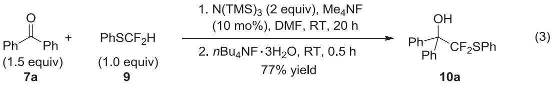


[a] Isolated yield.

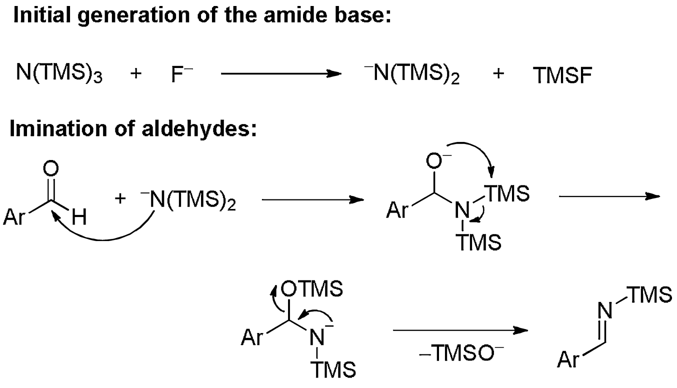
It is worthwhile to note that this reaction represents the first example of $(TMS)_3N/F^-$ mediated nucleophilic reaction between an enolizable aldehyde and a pronucleophile R_fH. In the reported reaction between carbonyls and CF_3H, this $(TMS)_3N/F^-$ system only works for the trifluoromethylation of ketones and formylamides (Scheme 1) [10]. In a recent report using this base system for the deprotonative functionalization of heteroaromatic C(sp^2)–H and activated C(sp^3)–H bonds with carbonyls, only the reaction of ketones and non-enolizable aldehydes was demonstrated [11]. We believe that both the low concentration of the in situ generated base and the high acidity of $PhSO_2CF_2H$ play important roles in this deprotonative difluoromethylation of enolizable aldehydes.

Subsequently, we extended this protocol to aromatic aldehydes, and the results are summarized in Table 2. The reaction proved to be general and amenable to a range of aromatic aldehydes **5**, and the desired products **6a**–**k** were produced in moderate to excellent yields. The reactivity of aromatic aldehydes in this reaction is different from that of CF_3H in the trifluoromethylations. In the trifluoromethylation with CF_3H, the amide anion $(TMS)_2N^-$ was reported to undergo imination with the benzaldehyde to give *N*-trimethylsilyl imine (Scheme 2) [10a,12]; however, in the present difluoro(phenylsulfonyl)methylation, due to the higher acidity of $PhSO_2CF_2H$ (than CF_3H), the amide anion $(TMS)_2N^-$ can readily remove the proton of $PhSO_2CF_2H$ to promote the difluoro(phenylsulfonyl)methylation of aldehydes.

Finally, encouraged by the unique reactivity of $PhSO_2CF_2H$ toward various aldehydes, we investigated its reaction with ketones by using the aforementioned base system. To our surprise, among all the ketones that were tested, the reactions were found to be very sluggish, and $PhSO_2CF_2SPh$ was detected as the major product in all cases (Table 3). These results are in distinct contrast to the trifluoromethylation of ketones with CF_3H (Scheme 1) [10] and our previously reported difluoro(phenylsulfonyl)methylation of ketones with $TMSCF_2SO_2Ph$ [13]. We attributed these differences to the reversibility of the addition of $PhSO_2CF_2^-$ to ketones [14] and the slower silylation of the alcoholate intermediate by $N(TMS)_3$ than by $TMSCF_2SO_2Ph$. Consequently, the decomposition of $PhSO_2CF_2^-$ would lead to the formation of PhSSPh, which further reacted with $PhSO_2CF_2^-$ to afford the byproduct $PhSO_2CF_2SPh$ (Scheme 3) [9b]. Based on this rationalization, we also tried the reaction between ketones and $PhSCF_2H$ (**9**), assuming that the relatively lower nucleofuge of $PhSCF_2^-$ (than $PhSO_2CF_2^-$) would improve the difluoromethylation reaction. As expected, the reaction with benzophenone (**7a**) at room temperature afforded the desired product **10a** in 77% yield (Eq. (3)).

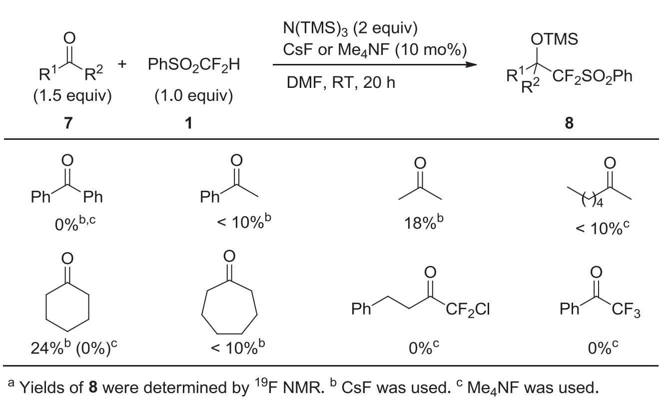


(3)

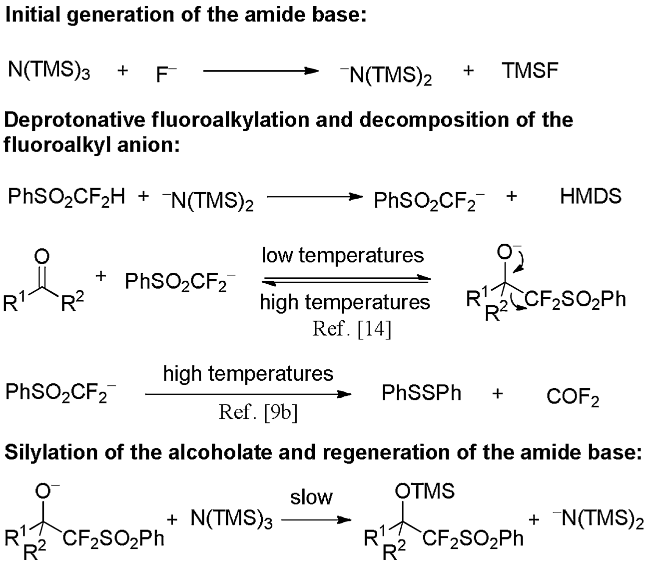


Scheme 2. Imination of aromatic aldehydes.

Table 3
Investigation on nucleophilic difluoro(phenylsulfonyl)methylation of various ketones with reagent **1**.[a].



[a] Yields of **8** were determined by ^{19}F NMR.
[b] CsF was used.
[c] Me_4NF was used.



Scheme 3. Nucleophilic difluoro(phenylsulfonyl)methylation of ketones with $PhSO_2CF_2H$ and the reversibility of the addition reaction.

3. Conclusion

We have investigated the reaction between carbonyls and $PhSO_2CF_2H$ using substoichiometric amount of base in situ generated from tris(trimethylsilyl)amine and catalytic tetramethylamonium fluoride. This research has led to the discovery of an efficient nucleophilic difluoro(phenylsulfonyl)methylation of both enolizable and non-enolizable aldehydes. Moreover, the reactivity difference of $PhSO_2CF_2H$ and CF_3H toward carbonyls has been rationalized, and the difluoromethylation of ketones with $PhSCF_2H$ using the in situ generated base has been developed.

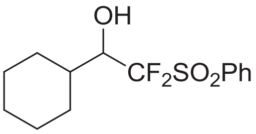
4. Experimental

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. DMF was distilled from CaH_2. Commercially available chemicals were used without further purification. Column chromatography was performed on silica gel 300–400 (0.038–0.048 mm). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$, chemical shifts (δ) are given in ppm and spin–spin coupling constants (J) are given in Hz. ^{1}H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of a residual protonated solvent: $CDCl_3$ δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0. Mass spectra were obtained on a mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI or ESI mode. Melting points are uncorrected.

*4.1. General procedures for the reaction of aldehydes with $PhSO_2CF_2H$ (**1**)*

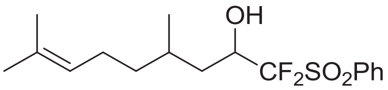
Under a nitrogen atmosphere, into a 20-mL Schlenk flask containing $N(TMS)_3$ (233 mg, 1.0 mmol) and Me_4NF (4 mg, 0.05 mmol) were added $PhSO_2CF_2H$ (96 mg, 0.5 mmol), aldehyde **2** or **5** (0.75 mmol), and DMF (3 mL) at RT. Then the flask was connected with a condenser and heated at 45 °C for 20 h. After the reaction mixture was cooled to RT, TBAF·3H_2O (1.5 mmol) was added and the mixture was stirred at RT for 30 min followed by adding saturated brine (10 mL). The whole mixture was extracted with Et_2O (3× 20 mL). The combined organic phase was washed with water (2× 30 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography (silica gel; petroleum ether/ethyl acetate, 10/1) to give the desired products **4** or **6**.

*4.1.1. 1-Cyclohexyl-2,2-difluoro-2-(phenylsulfonyl)ethanol (**4a**) [13]*



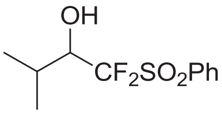
White solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (d, J = 7.2 Hz, 2H), 7.56–7.84 (m, 3H), 4.31 (m, 1H), 2.78 (d, J = 6.5 Hz, 1H), 1.04–1.98 (m, 11H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −106.0 (d, J = 236.0 Hz, 1F), −114.2 (dd, J = 236.0 Hz, J = 22.0 Hz, 1F).

*4.1.2. 1,1-Difluoro-4,8-dimethyl-1-(phenylsulfonyl)non-7-en-2-ol (**4b**)*



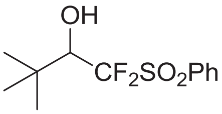
A mixture of diastereomers (dr = 1/1). White solid. IR (film): 3516, 2962, 2921, 2854, 1584, 1449, 1335, 1162, 1104, 717, 686, 600 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99 (d, J = 7.3 Hz, 2H), 7.77 (t, J = 7.3 Hz, 1H), 7.63 (t, J = 7.3 Hz, 2H), 5.09 (s, 1H), 4.55 (m, 1H), 2.67 (t, J = 5.7 Hz, 1H), 2.01–0.96 (m, 16H). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −107.8 (d, J = 265.0 Hz, 0.5F)/−108.2 (d, J = 265.0 Hz, 0.5F), −117.0 (d, J = 265.0 Hz, 0.5F, for one isomer)/−117.0 (dd, J = 265.0 Hz, J = 18.4 Hz, 0.5F, for the other isomer). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.5, 133.1, 131.5 (d, J = 5 Hz), 130.6, 129.3, 124.4, 121.5 (m), 68.1 (t, J = 24.0 Hz)/67.7 (t, J = 24.0 Hz), 37.7/36.6/36.1/35.6 (C-3 and C-5), 28.8/28.1, 25.7, 25.4/25.2, 20.3/18.4, 17.6. MS (EI, m/z, %): 205 ([M−$PhSO_2$]$^+$, 3.22), 69 (100.00). HRMS (EI): Calcd. for $C_{17}H_{24}F_2O_3S$: 346.1414; Found: 346.1411.

*4.1.3. 1,1-Difluoro-3-methyl-1-(phenylsulfonyl)butan-2-ol (**4c**) [9]*



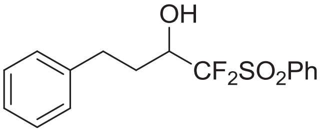
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.99 (d, J = 7.7 Hz, 2H), 7.58–7.82 (m, 3H), 4.36(m, 1H), 2.21 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H), 1.02 (dd, J = 6.7 Hz, J = 0.8 Hz, 3H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −106.8 (d, J = 235.0 Hz, 1F), −115.5 (dd, J = 235.0 Hz, J = 22.0 Hz).

*4.1.4. 1,1-Difluoro-3,3-dimethyl-1-(phenylsulfonyl)butan-2-ol (**4d**) [9]*



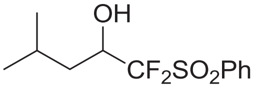
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.99 (d, J = 8.0 Hz, 2H), 7.71 (t, J = 7.7 Hz, 1H), 7.63 (t, J = 7.9 Hz, 2H), 4.22 (m, 1H), 2.83 (d, J = 6.0 Hz, 1H), 1.08 (m, 9H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −108.2 (d, J = 237.0 Hz, 1F), −114.2 (ddd, J = 237.0 Hz, J = 17.6 Hz, J = 7.2 Hz, 1F).

*4.1.5. 1,1-Difluoro-4-phenyl-1-(phenylsulfonyl)butan-2-ol (**4e**) [6]*



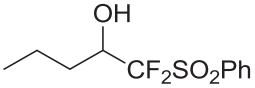
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.98 (d, J = 8.2 Hz, 2H), 7.77 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 8.2 Hz, 2H), 7.32–7.21 (m, 5H), 4.45 (m, 1H), 2.97 (m, 1H), 2.81–2.71 (m, 2H), 2.12–2.03 (m, 2H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −108.2 (d, J = 236.3 Hz, 1F), −116.4 (ddd, J = 236.3 Hz, J = 17.8 Hz, J = 7.2 Hz, 1F).

*4.1.6. 1,1-Difluoro-4-methyl-1-(phenylsulfonyl)pentan-2-ol (**4f**)*



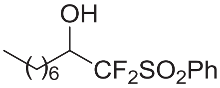
White solid. IR (film): 3512, 3069, 2960, 2872, 1584, 1469, 1388, 1335, 1163, 1137, 718, 685, 598 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.00 (d, J = 7.8 Hz, 2H), 7.78 (t, J = 6.7 Hz, 1H), 7.63 (t, J = 7.2 Hz, 2H), 4.51 (m, 1H), 2.76 (s, 1H), 2.43 (m, 1H), 2.04–0.89 (m, 8H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −108.1 (d, J = 236.4 Hz, 1F), −116.7 (dd, J = 236.4 Hz, J = 17.5 Hz, 1F). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 135.5, 133.1, 130.6, 129.4, 121.4 (t, J = 294.6 Hz), 68.0 (t, J = 21.3 Hz), 37.9, 24.0, 23.5, 21.1 MS (EI, m/z, %): 278 (M$^+$, 2.42), 77 (100.00). HRMS (EI): Calcd. for $C_{12}H_{16}F_2O_3S$: 278.0788; Found: 278.0787.

*4.1.7. 1,1-Difluoro-1-(phenylsulfonyl)pentan-2-ol (**4g**)*



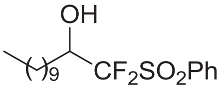
Colorless oil. IR (film): 3508, 2964, 2935, 2875, 1449, 1335, 1164, 1084, 717, 686, 597 cm^{-}1. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.95 (d, J = 7.0 Hz, 2H), 7.78 (t, J = 7.3 Hz, 1H), 7.62 (m, 2H), 4.46 (m, 1H), 3.00–0.89 (m, 9H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −108.1 (d, J = 236.9 Hz, 1F), −116.7 (dd, J = 236.9 Hz, J = 17.9 Hz, 1F). ^{13}C NMR (CDCl$_3$, 100 MHz): 135.5, 133.1, 130.6, 129.3, 121.4 (t, J = 299.1 Hz), 69.2 (t, J = 24.2 Hz), 31.4, 18.3, 13.6 MS (EI, m/z, %): 264 (M$^+$, 1.33), 78 (100.00). HRMS (EI): Calcd. for $C_{11}H_{14}F_2O_3S$: 264.0632; Found: 264.0627.

*4.1.8. 1,1-Difluoro-1-(phenylsulfonyl)nonan-2-ol (**4h**) [13]*



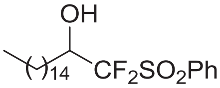
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.00 (d, J = 7.8 Hz, 2H), 7.59–7.83 (m, 3H), 4.43 (m, 1H), 2.57 (d, J = 5.6 Hz, 1H), 1.88–1.20 (m, 12H), 0.88 (t, J = 7.0 Hz, 3H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −108.6 (dd, J = 237.0 Hz, 6.0 Hz, 1F), −117.4 (dd, J = 237.0 Hz, 18.0 Hz, 1F).

*4.1.9. 1,1-Difluoro-1-(phenylsulfonyl)dodecan-2-ol (**4i**)*



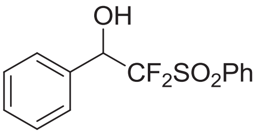
White solid. IR (film): 3508, 3069, 2925, 2855, 1584, 1467, 1336, 1162, 1097, 717, 686, 599 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.99 (d, J = 8.1 Hz, 2H), 7.78–7.63 (m, 3H), 4.43 (m, 1H), 2.69 (s, 1H), 1.75–0.86 (m, 21H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −108.4 (d, J = 237.3 Hz, 1F), −116.9 (ddd, J = 237.3 Hz, J = 17.9 Hz, J = 8.5 Hz, 1F). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 135.5, 133.1, 130.6, 129.3, 121.3 (t, J = 296.2 Hz), 69.5 (t, J = 23.6 Hz), 31.9, 29.56, 29.53, 29.41, 29.31, 29.21, 25.1, 22.7, 14.1 MS (EI, m/z, %): 345 ([M−OH]$^+$, 1.10), 143 (100.00). HRMS (EI): Calcd. for $C_{18}H_{28}F_2O_3S$–OH: 345.1700; Found: 345.1697.

*4.1.10. 1,1-Difluoro-1-(phenylsulfonyl)heptadecan-2-ol (**4j**)*



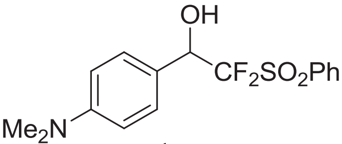
White solid. IR (film): 3550, 3406, 2963, 2918, 2848, 1471, 1449, 1329, 1167, 1128, 1104, 998, 718, 682, 616, 603 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.00 (d, J = 7.4 Hz, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.64 (t, J = 7.4 Hz, 2H), 4.44 (m, 1H), 2.56 (d, J = 5.7 Hz, 1H), 1.85–1.25 (m, 28H), 0.88 (t, J = 6.6 Hz, 3H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −108.1 (d, J = 236.5 Hz, 1F), −116.9 (dd, J = 236.5 Hz, J = 17.4 Hz, 1F). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 135.5, 133.1, 130.6, 129.3, 69.5 (t, J = 25.0 Hz), 31.9, 29.7, 29.65, 29.60, 29.5, 29.3, 29.2, 25.0, 22.7, 14.1 MS (EI, m/z, %): 414 ([M−OH]$^+$, 1.74), 143 (100.00). HRMS (EI): Calcd. for $C_{23}H_{38}F_2O_3S$–OH: 415.2484; Found: 415.2487.

*4.1.11. 2,2-Difluoro-1-phenyl-2-(phenylsulfonyl)ethanol (**6a**) [9]*



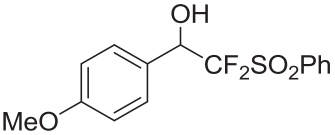
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.00 (d, J = 7.5 Hz, 2H), 7.76 (t, J = 7.1 Hz, 1H), 7.62 (t, J = 7.5 Hz, 2H), 7.48 (s, 1H), 7.38 (m, 3H), 5.57 (m, 1H), 3.29 (m, 1H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −103.8 (d, J = 238.8 Hz, 1F), −119.2 (ddd, J = 238.8 Hz, J = 21.9 Hz, J = 6.1 Hz, 1F).

*4.1.12. 1-[4-(Dimethylamino)phenyl]-2,2-difluoro-2-(phenylsulfonyl)ethanol (**6b**) [15]*



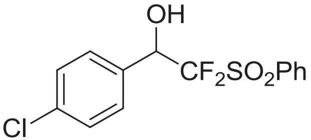
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.99 (d, J = 7.3 Hz, 2H), 7.75 (t, J = 6.4 Hz, 1H), 7.60 (t, J = 7.4 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.68 (d, J = 8.3 Hz, 2H), 5.44 (m, 1H), 2.96 (s, 6H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −103.8 (d, J = 235.3 Hz, 1F), −119.0 (dd, J = 235.3 Hz, J = 20.7 Hz, 1F).

*4.1.13. 2,2-Difluoro-1-(4-methoxyphenyl)-2-(phenylsulfonyl)ethanol (**6c**) [9]*



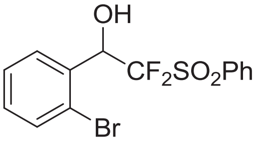
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.98 (d, J = 7.5 Hz, 2H), 7.74 (t, J = 7.0 Hz, 2H), 7.59 (t, J = 7.9 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.52 (dt, J = 21.0 Hz, J = 3.3 Hz, 1H), 3.78 (s, 1H), 3.43 (d, J = 1.7 Hz, 1H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −103.9 (d, J = 239.0 Hz, 1F), −119.0 (dd, J = 239.0 Hz, J = 21.0 Hz, 1F).

*4.1.14. 1-(4-Chlorophenyl)-2,2-difluoro-2-(phenylsulfonyl)ethanol (**6d**) [9]*



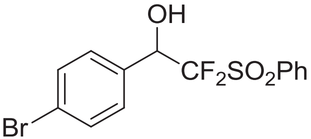
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.96 (d, J = 7.6 Hz, 2H), 7.56–7.76 (m, 3H), 7.41 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 5.58 (d, J = 21.0 Hz, 1H), 3.75 (s, 1H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −104.1 (d, J = 237.0 Hz, 1F), −119.2 (dd, J = 237.0 Hz, J = 21.0 Hz, 1F).

*4.1.15. 1-(2-Bromophenyl)-2,2-difluoro-2-(phenylsulfonyl)ethanol (**6e**)*



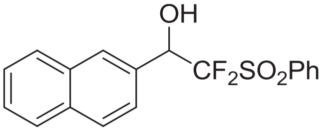
White solid. IR (film): 3478, 3265, 3090, 3063, 1645, 1473, 1451, 1338, 1155, 1121, 1027, 998, 761, 746, 685, 586 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.05 (d, J = 7.7 Hz, 2H), 7.81–7.55 (m, 5H), 7.40–7.18 (m, 3H), 6.16 (dd, J = 19.6 Hz, J = 3.9 Hz, 1H), 3.36 (d, J = 3.2 Hz, 1H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −102.9 (d, J = 239.3 Hz, 1F), −120.1 (dd, J = 239.3 Hz, J = 21.4 Hz, 1F). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 135.7, 133.5, 133.4, 132.9, 132.8, 132.5, 130.9, 130.8, 130.0, 129.8, 129.5, 127.9, 127.7, 124.0, 120.2, 69.5 (t, J = 23.6 Hz). MS (EI, m/z, %): 376 (M$^+$, 4.87), 378 ([M+2]$^+$, 5.83), 187 (100.00). HRMS (EI): Calcd. for $C_{14}H_{11}BrF_2O_3S$: 375.9580; Found: 375.9586.

*4.1.16. 1-(4-Bromophenyl)-2,2-difluoro-2-(phenylsulfonyl)ethanol (**6f**) [16]*



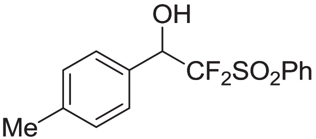
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.99 (d, J = 7.7 Hz, 2H), 7.79 (t, J = 6.6 Hz, 1H), 7.63 (t, J = 8.0 Hz, 2H), 7.53 (s, 1H), 7.51 (s, 1H), 7.36 (d, J = 8.4 Hz, 2H), 5.54 (m, 1H), 3.37 (s, 1H), 1.57 (s, 3H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −104.1 (d, J = 237.9 Hz, 1F), −119.2 (dd, J = 237.9 Hz, J = 21.9 Hz, 1F).

*4.1.17. 2,2-Difluoro-1-(naphthalen-2-yl)-2-(phenylsulfonyl)ethanol (**6g**) [6]*



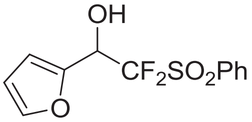
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.01 (d, J = 7.8 Hz, 2H), 7.97 (s, 1H), 7.87–7.73 (m, 4H), 7.63–7.45 (m, 5H), 5.75 (m, 1H), 3.41 (s, 1H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −103.6 (d, J = 236.2 Hz, 1F), −118.8 (dd, J = 236.2 Hz, J = 21.0 Hz, 1F).

*4.1.18. 2,2-Difluoro-2-(phenylsulfonyl)-1-p-tolylethanol (**6h**) [9]*



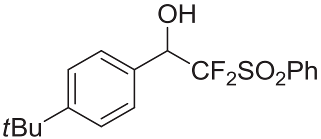
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.00 (d, J = 7.9 Hz, 2H), 7.76 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.2 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 5.53 (m, 1H), 3.17 (d, J = 3.7 Hz, 1H), 2.35 (s, 3H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −103.8 (d, J = 236.3 Hz, 1F), −119.0 (dd, J = 236.3 Hz, J = 20.0 Hz, 1F).

*4.1.19. 2,2-Difluoro-1-(furan-2-yl)-2-(phenylsulfonyl)ethanol (**6i**) [9]*



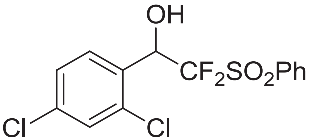
White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.00 (d, J = 7.9 Hz, 2H), 7.77 (t, J = 7.7 Hz, 1H), 7.63 (t, J = 7.6 Hz, 2H), 7.46 (s, 1H), 6.56 (s, 1H), 6.41 (s, 1H), 5.58 (m, 1H), 3.08 (d, J = 6.4 Hz, 1H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −105.9 (dd, J = 237.1 Hz, J = 4.1 Hz, 1F), −115.9 (dd, J = 237.1 Hz, J = 18.5 Hz, 1F).

*4.1.20. 1-(4-tert-Butylphenyl)-2,2-difluoro-2-(phenylsulfonyl)ethanol (**6j**) [17]*



White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.00 (d, J = 7.9 Hz, 2H), 7.76 (t, J = 7.4 Hz, 1H), 7.61 (t, J = 7.4 Hz, 2H), 7.40 (s, 4H), 5.55 (m, 1H), 3.19 (s, 1H), 1.30 (s, 9H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −102.9 (d, J = 239.4 Hz, 1F), −118.7 (dd, J = 239.4 Hz, J = 20.3 Hz, 1F).

*4.1.21. 1-(2,4-Dichlorophenyl)-2,2-difluoro-2-(phenylsulfonyl)ethanol (**6k**) [18]*



White solid. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.02 (d, J = 7.8 Hz, 2H), 7.79 (t, J = 7.4 Hz, 1H), 7.66–7.62 (m, 3H), 7.39 (s, 1H), 7.30 (m, 1H), 6.12 (d, J = 21.8 Hz, 1H), 3.69 (s, 1H). ^{19}F NMR (CDCl$_3$, 282 MHz): δ −103.9 (d, J = 239.3 Hz, 1F), −119.8 (dd, J = 239.3 Hz, J = 21.6 Hz, 1F).

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