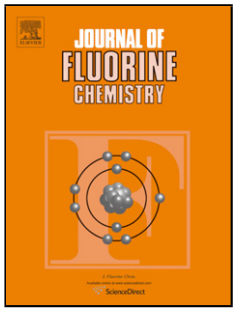

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Synthesis of tetrafluoroethyl- and tetrafluoroethylene-containing amines by the reaction of silanes with enamines under acidic conditions

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Keywords

Nucleophilic addition; Enamines; Iminium salts; Tetrafluoroethyl; Tetrafluoroethylene

Abstract

Enamines with in situ formed hydrogen fluoride underwent efficient reaction with trimethyl(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)silane and trimethyl(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)silane. Radical or reductive desulfurization of the addition products provided amines containing the tetrafluoroethyl group.

1. Introduction

Fluoroalkyl-containing silanes are widely used and versatile reagents for the introduction of fluoroalkyl groups. The most extensively studied member of the family – trimethyl (trifluoromethyl)silane – represents not only a very useful nucleophilic trifluoromethylating reagent [1] but also the source of trifluoromethyl radicals [2] and difluorocarbene [3]. Carbon or heteroatom-substituted examples include RCF_2SiMe_3 (R = PhS [4], $PhSO_2$ [**Error! Bookmark not defined.**j, [5], PO_3Et_2 [**Error! Bookmark not defined.**e, **Error! Bookmark not defined.**j, [6], CO_2Et [7], Ar [8], ArO [**Error! Bookmark not defined.**b], CN [9]) which after activation by a Lewis base (typically fluoride anions) act as equivalents of fluorinated carbanions. We have recently shown that $PhSCF_2CF_2SiMe_3$ (**1**) can be used as a tandem radical and anion synthon [$^{\bullet}CF_2CF_2^{-}$] for the synthesis of tetrafluoroethyl-containing alcohols, pyrrolidinones and isoindolinones, and tetrafluoroethylene-containing tetrahydropyrans and 1-azabicyclic compounds [10]. The intermediate in the synthesis of **1**,

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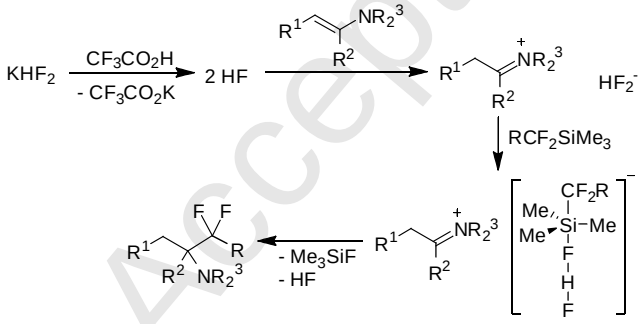
$PhSCF_2CF_2Br$, can serve as a [$PhSCF_2CF_2^{\bullet}$], [$HCF_2CF_2^{\bullet}$], and [$^{\bullet}CF_2CF_2^{\bullet}$] synthon in radical additions to alkenes [11].

Fluorinated amines are very important in pharmaceutical research [12] and one of the ways to their synthesis is nucleophilic fluoroalkyl addition of C=N bonds of imines, iminium ions, nitrones or hydrazones [13]. Imines including activated imines such as *N*-sulfinyl or *N*-sulfonylimines are widely used electrophilic substrates for nucleophilic additions [14]. They have been successfully used as electrophilic partners in some nucleophilic fluoroalkylations with fluorinated silanes (Me_3SiCF_3, Me_3SiCF_2CN, $PhSCF_2SiMe_3$, $PhSO_2CF_2SiMe_3$) in the presence of Lewis bases or under acidic conditions [**Error! Bookmark not defined.**d, **Error! Bookmark not defined.**j, **Error! Bookmark not defined.**e, **Error! Bookmark not defined.**, **Error! Bookmark not defined.**, [15,16] while the reaction of $Me_3SiCF_2PO_3Et_2$ with imines under acidic conditions was inefficient [**Error! Bookmark not defined.**j]. In contrast to electrophilic imines, enamines are typical nucleophilic reagents. However, in the presence of hydrogen fluoride generated in situ from KHF_2 and either trifluoroacetic or triflic acid, enamines are converted to electrophilic iminium salts. The bifluoride counterion is capable to activate the silicon reagent, followed by the transfer of the fluorinated group onto the C=N bond. This process has been successfully demonstrated in the reaction of enamines with the following fluorinated silanes: RCF_2SiMe_3 (R = F, CN, SPh, SO_2Ph, PO_3Et_2) (Scheme 1) [**Error! Bookmark not defined.**j, **Error! Bookmark not defined.**,17].



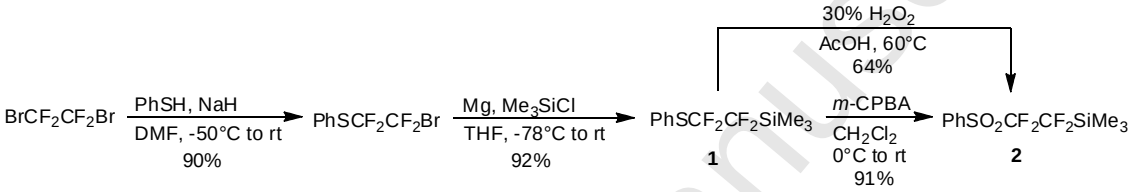
Scheme 1: Mechanism of nucleophilic fluoroalkyl group transfer to enamines under acidic conditions [**Error! Bookmark not defined.**j, **Error! Bookmark not defined.**, **Error! Bookmark not defined.**].

In this paper, we investigate reactions of sulfur-containing silanes $PhSCF_2CF_2SiMe_3$ (**1**) and $PhSO_2CF_2CF_2SiMe_3$ (**2**) with imines and enamines under acidic conditions providing amines with the CF_2CF_2 moiety in α-position. There is one precedence to the synthesis of

fluoroalkyl-containing (CF_3, C_2F_5, CF_2CF_2H) amines by asymmetric addition of enantiomerically pure lithium methyl or benzyl *p*-tolyl sulfoxides to fluorinated aldimines [18].

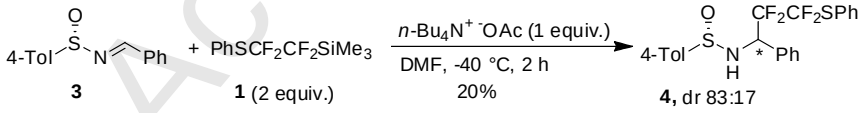
2. Results and discussion

Synthesis of silane **1** was described in literature [**Error! Bookmark not defined.**f] and silane **2** is available in high yield by simple oxidation of **1** with aqueous hydrogen peroxide solution in acetic acid (in 64% yield) or with mCPBA (in 91% yield) (Scheme 2).



Scheme 2: Synthesis of silanes **1** and **2**.

The investigations were started with the reaction of (*S*)-*N*-benzylidene-4-toluenesulfinamide (**3**) with **1** under various conditions. At best, 20% yield of the adduct **4** was achieved using tetrabutylammonium acetate in DMF (Scheme 3). Other initiators (TMAF, TBAF, TBAT, CsF in THF or DMF) provided low yields (0–14%) of **4** often accompanied by the product of protodesilylation of **1** ($PhSCF_2CF_2H$). Similarly, reaction of **1** with 2-(benzylideneamino)phenol in the presence of TFA or TfOH and KHF_2 in MeCN provided only traces of expected addition product. Therefore attention was turned to reactions of highly electrophilic iminium salts formed from enamines.

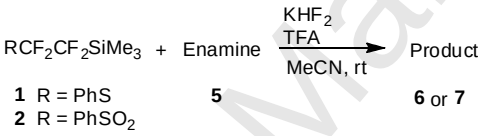


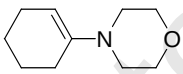
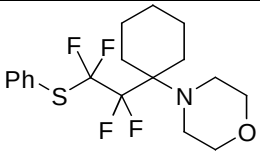
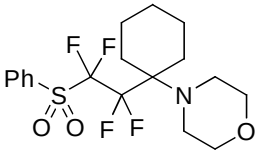
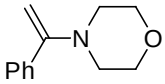
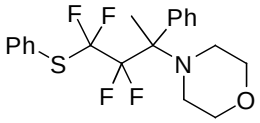
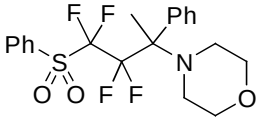
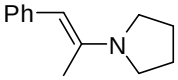
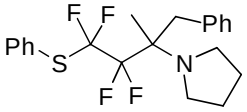
Scheme 3: Nucleophilic addition of silane **1** to (*S*)-*N*-benzylidene-4-toluenesulfinamide (**3**).

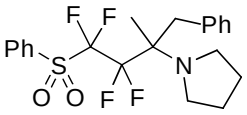
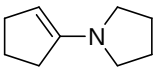
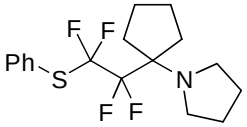
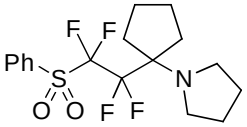
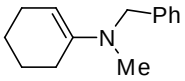
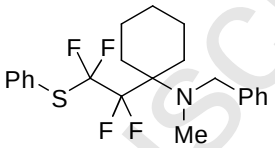
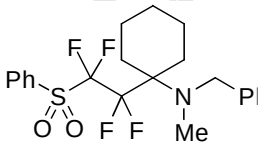
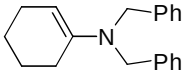
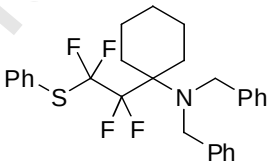
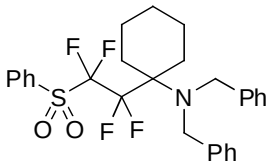
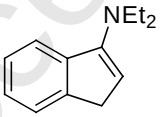
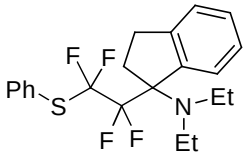
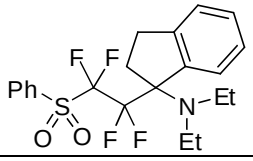
We found that enamines **5** derived from enolizable ketones such as cyclopentanone, cyclohexanone, acetophenone, 1-phenylpropan-2-one and 2,3-dihydro-1*H*-inden-1-one and secondary amines such as morpholine, pyrrolidine, *N*-methyl-1-phenylmethanamine and dibenzylamine react with both fluorinated silanes **1** and **2** in the presence of potassium hydrogenfluoride and trifluoroacetic acid in acetonitrile to form addition products **6** or **7**

(Table 1). Conditions described by Dilman and co-workers (1.5 equiv. of silane and TFA, 0.75 equiv. of KHF_2 in MeCN) [**Error! Bookmark not defined.**j] were found to be optimal in the reaction of **1** with **5a**, therefore, they were used in the reaction scope study. Yields were substrate dependent and ranged from modest to high. Bulky enamines **5f** and **5g** gave the lowest yields. Silane **2** was less reactive than silane **1** in most cases. This can be explained by lower nucleophilicity of the respective fluorinated carbanion species because of stronger electron acceptor character of the phenylsulfonyl moiety compared to the phenylsulfanyl group. Employment of enamines derived from morpholine and enolizable aldehydes such as propionaldehyde or 2-phenylacetaldehyde did not lead to expected products **6** in reactions with **1** or **2**. In the latter case, the presence of product of acid catalyzed aldol condensation – 2,4-diphenylbut-2-enal – was identified by GCMS analysis of the reaction mixture.

Table 1: Addition of silanes **1** and **2** to enamines under acidic conditions[a]



Entry	Silane	**5**	Enamine	Time (h)	Product	Yields[b] (%)
1	**1**	**5a**		1	**6a**	 68
2	**2**	**5a**		2	**7a**	 93
3	**1**	**5b**		2.5	**6b**	 43
4	**2**	**5b**		4	**7b**	 40
5	**1**	**5c**		2	**6c**	 91

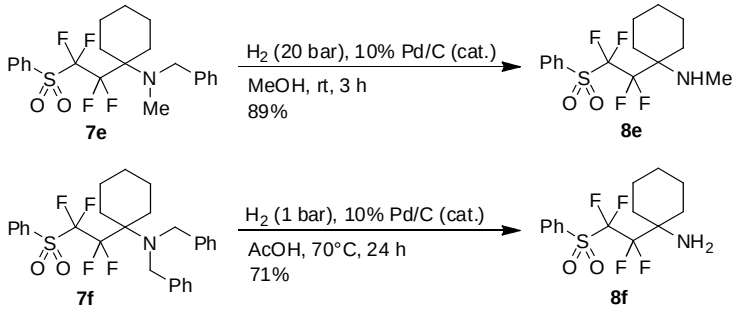
6	**2**	**5c**		1	**7c**		45
7	**1**	**5d**		4	**6d**		68
8	**2**	**5d**		1.5	**7d**		41
9	**1**	**5e**		2	**6e**		70
10	**2**	**5e**		1	**7e**		66
11	**1**	**5f**		4	**6f**		28
12	**2**	**5f**		1.5	**7f**		20
13	**1**	**5g**		4	**6g**		38
14	**2**	**5g**		1	**7g**		20

[a] Reactions were performed with **1** or **2** (1.5 equiv.), **5** (1 equiv.), KHF_2 (0.75 equiv.), TFA (1.5 equiv.) in MeCN at rt.

[b] Isolated yield.

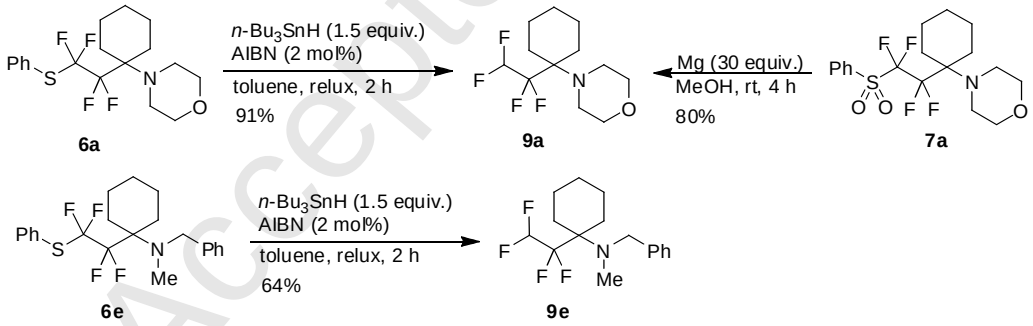
The nucleophilic fluoroalkylation reactions gave access to fluorinated tertiary amines **6** and **7**. In order to prepare primary or secondary amines we envisioned hydrogenolysis of benzyl

groups in adducts formed from *N*-benzyl enamines **5e** and **5f**. Debenzylation of **7** with hydrogen and catalytic palladium on charcoal provided *N*-methylamines **8** in high yields (Scheme 4). Debenzylation of **7f** required the use of acidic medium and elevated temperature (Scheme 4). On the other hand, analogous reaction with sulfide **6e** was not successful presumably because of the catalyst poisoning with sulfur of the phenylsulfanyl moiety.



Scheme 4: Debenzylation of adducts **7**.

Next, we investigated substitutions of the phenylsulfanyl group in compounds **6** or phenylsulfonyl group in compounds **7** for hydrogen atom. Substitution of phenylsulfanyl group of **6a** and **6e** was achieved under radical conditions giving tetrafluoroethyl-substituted amines **9** in good yields (Scheme 5). Reductive desulfonylation of **7a** provided **9a** also in good yield (Scheme 5).



Scheme 5: Radical and reductive desulfurization to provide tetrafluoroethyl-substituted amines **9**.

3. Conclusion

In conclusion, we demonstrated application of silanes **1** and **2** in hydrogen fluoride-mediated nucleophilic tetrafluoroalkyl transfer to enamines giving adducts **6** and **7**. Further chemical modifications included desulfurization of adducts **6** and **7** and hydrogenolysis of *N*-benzyl-

containing adducts **7**. This method provided easy access to primary, secondary and tertiary amines containing the tetrafluoroethyl group.

4. Experimental

4.1 General information

^{1}H and ^{19}F NMR spectra were recorded on a Bruker 400 MHz instrument at ambient temperature in $CDCl_3$ at 400 and 376 MHz, respectively. ^{13}C NMR spectra were recorded on a Bruker 400 MHz, 500 MHz or 600 MHz at 100, 125 and 150 MHz, respectively. The chemical shifts (δ) are reported in parts per million (ppm) relative to Me_4Si (0 ppm, for ^{1}H NMR), residual $CHCl_3$ (7.26 ppm for ^{1}H NMR), $CDCl_3$ (77.0 ppm for ^{13}C NMR), internal $CFCl_3$ (0 ppm for ^{19}F NMR). Coupling constants (J) are given in Hertz. ^{13}C and ^{19}F NMR spectra were proton decoupled. GCMS spectra were recorded on an Agilent 7890A gas chromatograph coupled with a 5975C quadrupole mass-selective electron impact (EI) detector (70 eV). High-resolution mass spectra (HRMS) were recorded on an Agilent 7890A gas chromatograph coupled with a Waters GCT Premier orthogonal acceleration time-of-flight detector using electron impact (EI) or chemical (CI) ionizations or on a LTQ Orbitrap XL instrument using electrospray (ESI) ionization. Infrared spectra were measured on a FTIR instrument. Reactions were conducted under the atmosphere of dry argon. Toluene and THF were dried by distillation with sodium/benzophenone before the use. MeOH, DMF and MeCN were dried using activated molecular sieves (3 Å). CH_2Cl_2 and AcOH were used without purification. Enamines **5** were prepared according to literature procedure [19]. All other chemicals obtained from commercial suppliers and were used as received. PE refers to petroleum ether with bp of 40−60 °C. Purifications of products were performed by flash chromatography using silica gel 60. TLC plates were visualized with ultraviolet light (254 nm) and/or with $KMnO_4$ staining solution.

*4.2 Synthesis of trimethyl(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)silane (**2**)*

Method A. m-CPBA (2.16 g, 12.5 mmol) was added to a solution of silane **1** (1.41 g, 5 mmol) in CH_2Cl_2 (50 mL) at 0 °C and the mixture was stirred 2 h at 0 °C. Cooling bath was removed and the mixture was stirred for 24 h at room temperature. Saturated $Na_2S_2O_3$ (20 mL) was

added at 0°C, the mixture was filtered, extracted into CH_2Cl_2 and the organic extract was washed with aqueous $NaHCO_3$. The combined organic phase was dried ($MgSO_4$), filtered and concentrated under vacuum. Resulting mixture was dissolved in PE−EtOAc (90:10), filtered and concentrated under vacuum to give 1.43 g (91% yield) of **2**.

Method B. Silane **1** (1.41 g, 5 mmol) was added to a solution of 30% aqueous H_2O_2 (16 mL, 150 mmol) in AcOH (30 mL), the mixture was heated to 60 °C and stirred for 25 h. Water (15 mL) was added, the mixture was extracted into Et_2O and the organic extract was washed with brine. The combined organic phase was dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by column chromatography eluting with PE−EtOAc (95:5) to give 1.00 g (64% yield) of **2**. White solid, R_f 0.32 (PE−EtOAc, 95:5); mp 37−39 °C; ^{1}H NMR δ_H 0.28 (s, 9H), 7.58−7.71 (m, 3H), 7.98−8.08 (m, 2H); ^{19}F NMR δ_F −126.1 (s, 2F), −109.2 (s, 2F); ^{13}C NMR (100 MHz) δ_C −4.4, 117.3 (tt, J = 291.5, 32.6 Hz), 123.5 (tt, J = 273.4, 41.4 Hz), 129.3, 130.7, 135.6; MS (EI) *m/z* (rel. int.) 299 (15), 214 (14), 166 (50), 141

(14), 135 (100), 77 (65), 73 (93); HRMS (CI) *m/z* calcd for $C_{11}H_{15}F_4O_2SSi$ $[M + H]^+$ 315.0498, found 315.0496.

*4.3 Synthesis of 4-methyl-N-(2,2,3,3-tetrafluoro-1-phenyl-3-(phenylthio)propyl)benzenesulfinamide (**4**)*

A solution of $AcONBu_4$ (302 mg, 1 mmol) in dry DMF (2 mL) was added to (*S*)-*N*-benzylidene-4-toluenesulfinamide (**3) (**243 mg, 1 mmol) and **1** (565 mg, 2 mmol) in dry DMF (8 mL) at −40 °C. The reaction mixture was stirred at this temperature for 2 h, and then allowed to warm up to room temperature within 1 h. Aqueous saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with Et_2O, the combined organic phase was washed with brine, water, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (dr 85:15) was purified by column chromatography eluting with PE−EtOAc (95:5) to give 90 mg (20% yield, dr 83:17) of **4**. Pale yellow solid, R_f 0.04 (PE−EtOAc, 95:5); ^{1}H NMR δ_H 2.37 (s, 3H, major), 2.43 (s, 3H, minor), 4.58−4.72 (m, 1H, major), 4.72−4.78 (m, 1H, minor), 4.98−5.12 (m, 2H, major + minor), 7.10−7.70 (m, 28H, major +

minor); ^{19}F NMR δ_F −117.5 (dt, J = 266.0, 4.5 Hz, 1F, minor), −115.5 (dt, J = 268.4, 4.5 Hz, 1F, major), −114.5 (dt, J = 268.4, 4.5 Hz, 1F, major), −113.8 (dt, J = 266.0, 4.5 Hz, 1F, minor), −85.3 (t, J = 4.5 Hz, 2F, minor), −84.8 (t, J = 4.5 Hz, 2F, major); ^{13}C NMR (100 MHz) δ_C (major) 21.3, 58.6 (dd, J = 24.4, 22.5 Hz), 125.6, 128.4, 128.6, 128.9, 129.2, 129.4, 130.5, 134.6, 137.2, 141.3, 141.7; MS (EI) *m/z* (rel. int.) 436 (15), 416 (11), 294 (12), 153 (11), 139 (12), 125 (100), 111 (50), 104 (30); HRMS (EI) *m/z* calcd for $C_{22}H_{19}F_4NaOS_2$ $[M + Na]^+$ 476.07364, found 476.07365.

*4.4 General procedure for the synthesis of compounds **6** and **7***

TFA (93 mL, 1.25 mmol) was added to a Schlenk flask containing a solution of **5** (1 mmol) and KHF_2 (59 mg, 0.75 mmol) in dry MeCN (2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 5 min, and then **1** or **2** (1.5 mmol) was added to the reaction mixture. Ice bath was removed and the reaction mixture was stirred for appropriate time. Aqueous saturated Na_2CO_3 solution (5 mL) was added and the reaction mixture was extracted with Et_2O. The combined organic phase was washed with brine and water, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash or column chromatography eluting with PE−EtOAc to give pure product **6** or **7**.

*4.4.1. 4-(1-(1,1,2,2-Tetrafluoro-2-(phenylthio)ethyl)cyclohexyl)morpholine (**6a**)*

White solid (208 mg, 68% yield), R_f 0.28 (PE–EtOAc, 98:2); mp 82–84 °C; ^{1}H NMR δ_H 1.11–1.31 (m, 1H), 1.36–1.65 (m, 6H), 1.65–1.75 (m, 1H), 1.96–2.12 (m, 2H), 2.77–2.98 (m, 4H), 3.28–3.96 (m, 4H), 7.32–7.51 (m, 3H), 7.57–7.69 (m, 2H); ^{19}F NMR δ_F −110.3 (s, 2F), −82.4 (s, 2F); ^{13}C NMR (100 MHz) δ_C 20.5, 25.9, 28.1 (t, J = 3.3 Hz), 46.7 (t, J = 2.7 Hz), 63.8 (t, J = 19.7 Hz), 68.4, 124.7, 129.0, 130.3, 137.3, CF_2CF_2 carbons were not observed; MS (EI) *m/z* (rel. int.) 168 (100), 109 (4); HRMS (EI) *m/z* calcd for $C_{18}H_{24}F_4S$ $[M + H]^+$ 378.1515, found 378.1515.

*4.4.2. 4-(1-(1,1,2,2-Tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexyl)morpholine (**7a**)*

White solid (341 mg, 93% yield), R_f 0.07 (PE–EtOAc, 98:2); mp 98–100 °C; ^{1}H NMR δ_H 1.11–1.28 (m, 1H), 1.38–1.63 (m, 6H), 1.65–1.75 (m, 1H), 1.94–2.10 (m, 2H), 2.77–2.98 (m,

4H), 3.17−4.00 (m, 4H), 7.56−7.66 (m, 2H), 7.71−7.81 (m, 1H), 7.93−8.05 (m, 2H); ^{19}F NMR δ_F −112.2 to −111.9 (m, 2F), −107.9 to −107.7 (m, 2F); ^{13}C NMR (100 MHz) δ_C 20.3, 25.6, 27.7 (t, J = 3.2 Hz), 46.6 (t, J = 2.5 Hz), 64.7 (tt, J = 19.4, 2.6 Hz), 68.4, 117.0 (tt, J = 300.0, 43.0 Hz), 122.2 (tt, J = 264.0, 31.8 Hz), 129.3, 130.9, 134.8, 135.6; MS (CI) *m/z* (rel. int.) 168 (100), 77 (7); HRMS (EI) *m/z* calcd for $C_{18}H_{23}F_4NO_3S$ $[M + H]^+$ 410.1413, found 410.1404.

*4.4.3. 4-(3,3,4,4-Tetrafluoro-2-phenyl-4-(phenylthio)butan-2-yl)morpholine (**6b**)*

Colorless oil (138 mg, 43% yield), R_f 0.24 (PE−EtOAc, 98:2); ^{1}H NMR δ_H 1.74 (s, 3H), 2.52−2.78 (m, 4H), 3.71−3.79 (m, 4H), 7.28−7.48 (m, 6H), 7.53−7.61 (m, 2H), 7.64−7.74 (m, 2H); ^{19}F NMR δ_F −102.3 (d, J = 268.1 Hz, 1F), −81.6 to −80.4 (m, 3F); ^{13}C NMR (100 MHz) δ_C 13.8, 48.2, 67.4, 68.1 (t, J = 19.8 Hz), 119.2 (tt, J = 270.4, 30.0 Hz), 124.8, 126.0 (tt, J = 292.5, 40.0 Hz), 127.8, 128.0, 128.9, 129.0, 130.1, 137.1, 138.5; MS (EI) *m/z* (rel.

int.) 190 (100), 159 (6), 109 (3), 105 (4), 77 (6); HRMS (EI) *m/z* calcd for $C_{20}H_{22}F_4NOS$ [M + H]$^+$ 400.1358, found 400.1356.

*4.4.4. 4-(3,3,4,4-Tetrafluoro-2-phenyl-4-(phenylsulfonyl)butan-2-yl)morpholine (**7b**)*

Pale yellow solid (135 mg, 40% yield), R_f 0.29 (PE–EtOAc, 98:2); mp 88–90 °C; ^{1}H NMR δ_H 1.61 (s, 3H), 2.38–2.68 (m, 4H), 3.56–3.66 (m, 4H), 7.18–7.28 (m, 3H), 7.45–7.58 (m, 4H), 7.63–7.72 (m, 1H), 7.82–7.92 (m, 2H); ^{19}F NMR δ_F −112.0 to −110.0 (m, 1F), −108.3 to −104.4 (m, 2F), −102.4 (d, J = 281.6, 1F); ^{13}C NMR (125 MHz) δ_C 13.2, 47.9, 67.4, 68.9 (t, J = 18.7 Hz), 116.8 (tdd, J = 303.5.5, 44.2, 40.0 Hz), 119.7 (tt, J = 262.7.5, 27.6 Hz), 128.0, 128.2, 129.3, 130.9, 133.5, 137.6; MS (EI) *m/z* (rel. int.) 190 (100), 105 (5), 77 (8); HRMS (CI) *m/z* calcd for $C_{20}H_{22}F_4NO_3S$ [M + H]$^+$ 432.1257, found 432.1255.

*4.4.5. 1-(3,3,4,4-Tetrafluoro-2-methyl-1-phenyl-4-(phenylthio)butan-2-yl)pyrrolidine (**6c**)*

Pale yellow oil (174 mg, 91% yield), R_f 0.71 (PE–EtOAc, 95:5); ^{1}H NMR δ_H 1.29 (d, J = 3.6 Hz, 3H), 1.59–1.84 (m, 4H), 2.70–2.92 (m, 3H), 3.03–3.18 (m, 2H), 3.24–3.37 (m, 1H), 7.13–7.29 (m, 5H), 7.34–7.48 (m, 3H), 7.57–7.70 (m, 2H); ^{19}F NMR δ_F –112.6 (dd, J = 266.7, 7.5 Hz, 1F), –111.5 (ddd, J = 266.7, 10.7, 6.1 Hz, 1F), –85.8, (ddd, J = 219.9, 10.7, 7.5 Hz, 1F), –78.1 (dd, J = 219.9, 6.1 Hz, 1F); ^{13}C NMR (100 MHz) δ_C 19.7, 24.9, 35.6, 46.6, 62.8 (t, J = 20.6 Hz), 120.0 (tt, J = 271.2, 26.7 Hz), 125.5 (tt, J = 295.5, 37.0 Hz), 126.3, 127.8, 128.9, 129.9, 131.2, 136.9; MS (EI) *m/z* (rel. int.) 306 (100), 188 (35), 159 (4), 116 (15), 109 (3), 91 (6), 77 (3); HRMS (EI) *m/z* calcd for $C_{21}H_{24}F_4NS$ $[M + H]^+$ 398.1566, found 398.1552.

*4.4.6. 1-(3,3,4,4-Tetrafluoro-2-methyl-1-phenyl-4-(phenylsulfonyl)butan-2-yl)pyrrolidine (**7c**)*

White solid (110 mg, 45% yield), R_f 0.8 (PE−EtOAc, 80:20); mp 71−73 °C; ^{1}H NMR δ_H 1.19 (d, J = 1.12 Hz, 3H), 1.62−1.80 (m, 4H), 2.70−2.78 (m, 1H), 2.78−2.88 (m, 2H), 3.00−3.10 (m, 2H), 3.22−3.32 (m, 1H), 7.09−7.30 (m, 5H), 7.58−7.68 (m, 2H), 7.73−7.82 (m, 1H), 7.98−8.10 (m, 2H); ^{19}F NMR δ_F −111.2 (ddd, J = 286.0, 14.9, 7.2 Hz, 1F), −109.0 (ddd, J = 251.3, 14.9, 6.2 Hz, 1F), −107.3, (ddd, J = 286.0, 11.0, 6.2 Hz, 1F), −106.3 (ddd, J = 251.3, 11.0, 7.2 Hz, 1F); ^{13}C NMR (150 MHz) δ_C 19.3, 24.4, 36.4, 46.6, 64.3 (t, J = 20.0 Hz), 117.3 (tt, J = 302.0, 40.3 Hz), 121.4 (tdd, J = 267.0, 30.9, 26.9 Hz), 126.4, 127.9, 129.3, 130.9, 131.0, 133.9, 136.4, 135.5; MS (EI) *m/z* (rel. int.) 338 (100), 281 (13), 207 (40), 188 (45), 146 (23), 91 (12), 77 (18), 68 (17); HRMS (ESI) *m/z* calcd for $C_{21}H_{24}F_4NO_2S$ $[M + H]^+$ 430.1458, found 430.1458.

*4.4.7. 1-(1-(1,1,2,2-Tetrafluoro-2-(phenylthio)ethyl)cyclopentyl)pyrrolidine (**6d**)*

Colorless oil (304 mg, 68% yield), R_f 0.22 (PE); ^{1}H NMR δ_H 1.54−1.79 (m, 8H), 1.85−2.10 (m, 4H), 2.80−2.95 (m, 4H), 7.34−7.46 (m, 2H), 7.60−7.68 (m, 3H); ^{19}F NMR δ_F −111.3 (t, J = 7.01 Hz, 2F), −83.8 (t, J = 7.01 Hz, 2F); ^{13}C NMR (100 MHz) δ_C 24.4, 24.6, 31.0 (t, J = 1.8 Hz), 46.7 (t, J = 1.7 Hz), 70.2 (t, J = 22.1 Hz), 119.5 (tt, J = 263.6, 29.4 Hz), 125.7 (tt, J = 288.7, 34.8 Hz), 126.6, 128.8, 129.8, 136.8; MS (EI) *m/z* (rel. int.) 159 (1), 138 (100), 109 (5), 77 (3); HRMS (CI) *m/z* calcd for $C_{17}H_{22}F_4NS$ $[M + H]^+$ 348.1409, found 348.1411.

*4.4.8. 1-(1-(1,1,2,2-Tetrafluoro-2-(phenylsulfonyl)ethyl)cyclopentyl)pyrrolidine (**7d**)*

White solid (222 mg, 41% yield), R_f 0.82 (PE–EtOAc, 80:20); mp 118–120 °C; ^{1}H NMR δ_H 1.51−1.75 (m, 8H), 1.82−2.03 (m, 4H), 2.64−2.83 (m, 4H), 7.61−7.72 (m, 2H), 8.00−8.08 (m, 3H); ^{19}F NMR δ_F −108.5 to −108.3 (m, 2F), −108.0 to −107.8 (m, 2F); ^{13}C NMR (100

MHz) δ_C 24.3, 24.7, 30.8, 46.4, 129.2, 129.6, 130.9, 135.4, 136.4, CF_2CF_2 carbons were not observed; MS (EI) *m/z* (rel. int.) 138 (100), 77 (9); HRMS (CI) *m/z* calcd for $C_{17}H_{22}F_4NO_2S$ $[M + H]^+$ 380.1307, found 380.1306.

4.4.9. N-Benzyl-N-methyl-1-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)cyclohexanamine ***(6e)***

Colorless oil (1.20 g, 70% yield), R_f 0.68 (PE−EtOAc, 95:5); ^{1}H NMR δ_H 1.16−1.33 (m, 1H), 1.43−1.57 (m, 2H), 1.60−2.84 (m, 5H), 2.16−2.29 (m, 2H), 2.38 (s, 3H), 3.66 (s, 1H), 4.36 (s, 1H), 7.16−7.26 (m, 1H), 7.28−7.52 (m, 7H), 7.59−7.73 (m, 2H); ^{19}F NMR δ_F −109.0 (s, 2F), −82.8 (d, J = 9.2 Hz, 2F); ^{13}C NMR (100 MHz) δ_C 20.7, 25.8, 29.1 (t, J = 2.6 Hz), 34.4 (t, J = 2.9 Hz), 53.8 (t, J = 3.0 Hz), 64.9 (tt, J = 19.3, 2.3 Hz), 126.3, 127.6, 128.2, 129.1, 130.3, 137.4, 141.2, CF_2CF_2 carbons were not observed; MS (EI) *m/z* (rel. int.) 202 (100), 109 (5), 91 (40), 65 (3); HRMS (CI) *m/z* calcd for $C_{22}H_{26}F_4NS$ $[M + H]^+$ 412.1722, found 412.1730.

4.4.10. N-Benzyl-N-methyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine ***(7e)***

White solid (1.121 g, 66% yield), R_f 0.8 (PE−EtOAc, 80:20); mp 116-118 °C; ^{1}H NMR δ_H 1.10−1.34 (m, 1H), 1.39−1.64 (m, 4H), 1.65−1.87 (m, 3H), 2.13−2.28 (m, 2H), 2.38 (s, 3H), 3.67 (s, 1H), 4.34 (s, 1H), 7.16−7.27 (m, 1H), 7.28−7.39 (m, 4H), 7.57−7.71 (m, 2H), 7.73−7.85 (m, 1H), 8.00−8.10 (m, 2H); ^{19}F NMR δ_F −111.3 (s, 2F), −107.9 (d, J = 88.7 Hz, 2F); ^{13}C NMR (100 MHz) δ_C 20.5, 25.6, 28.7 (t, J = 2.7 Hz), 34.2 (t, J = 2.8 Hz), 53.7 (t, J = 3.0 Hz), 65.7 (tt, J = 19.1, 2.3 Hz), 126.4, 127.5, 128.3, 129.3, 130.9, 133.9, 135.6, 140.7, CF_2CF_2 carbons were not observed; MS (EI) *m/z* (rel. int.) 202 (100), 91 (52); HRMS (CI) *m/z* calcd for $C_{22}H_{26}F_4NO_2S$ $[M + H]^+$ 444.1620, found 444.1628.

*4.4.11. N,N-Dibenzyl-1-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)cyclohexanamine (**6f**)*

Colorless oil (263 mg, 28% yield), R_f 0.18 (PE); ^{1}H NMR δ_H 1.16−1.28 (m, 1H), 1.34−1.42 (m, 2H), 1.57−1.79 (m, 5H), 2.23−2.35 (m, 2H), 3.87 (s, 2H), 4.40 (s, 2H), 6.91−7.14 (m,

10H), 7.34−7.51 (m, 3H), 7.62−7.77 (m, 2H); ^{19}F NMR δ_F −82.5 (s, 2F), −107.1 (s, 2F); ^{13}C NMR (100 MHz) δ_C 20.8, 25.6, 30.1 (t, J = 2.9 Hz), 54.5 (t, J = 2.8 Hz), 67.1 (tt, J = 18.9, 2.2 Hz), 121.7 (tt, J = 265.3, 34.8 Hz), 124.7, 126.1, 126.7 (tt, J = 290.3, 41.3 Hz), 127.6, 128.9, 129.1, 130.3, 137.4, 141.0; MS (EI) *m/z* (rel. int.) 280 (3), 278 (100), 186 (6), 181 (7), 109 (6), 91 (40), 77 (2), 65 (4); HRMS (ESI) *m/z* calcd for $C_{28}H_{30}F_4NS$ $[M + H]^+$ 398.1566, found 488.2022.

*4.4.12 N,N-Dibenzyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine (**7f**)*

White solid (200 mg, 20% yield), R_f 0.47 (PE−EtOAc, 95:5); mp 138-140 °C; ^{1}H NMR δ_H 1.12−1.30 (m, 1H), 1.33−1.47 (m, 2H), 1.53−1.79 (m, 5H), 2.15−2.33 (m, 2H), 3.90 (s, 2H), 4.36 (s, 2H), 6.90−7.16 (m, 10H), 7.58−7.70 (m, 2H), 7.75−7.86 (m, 1H), 7.97−8.12 (m, 2H); ^{19}F NMR δ_F −82.5 to −109.6 (m, 2F), −107.7 to −107.5 (m, 2F); ^{13}C NMR (100 MHz) δ_C 20.6, 25.5, 29.7 (t, J = 2.9 Hz), 54.2 (t, J = 3.1 Hz), 67.8 (tt, J = 18.9, 2.2 Hz), 117.5 (tt, J =300.9, 43.4 Hz), 122.8 (tt, J = 265.6, 32.4), 126.2, 127.7, 128.9, 129.3, 130.9, 133.9, 135.6,

140.5; MS (EI) *m/z* (rel. int.) 277 (11), 244 (8), 207 (12), 186 (94), 140 (34), 106 (11), 105 (3), 91 (100), 77 (58), 65 (17), 51 (19); HRMS (ESI) *m/z* calcd for $C_{28}H_{29}F_4NNaO_2S$ [M + Na]$^+$ 542.1747, found 542.1748.

*4.4.13. N,N-Diethyl-1-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)-2,3-dihydro-1H-inden-1-amine (**6g**)*

Yellow oil (122 mg, 38% yield), R_f 0.36 (PE−EtOAc, 95:5); ^{1}H NMR δ_H 0.80 (t, J = 7.0, 6H), 2.23−2.41 (m, 2H), 2.63−3.07 (m, 6H), 7.03−7.20 (m, 3H), 7.22−7.37 (m, 3H), 7.44−7.59 (m, 3H); ^{19}F NMR δ_F −108.6 (dd, J = 273.6, 7.4, 1F), −106.5 (dd, J = 273.6, 6.3, 1F), −82.3, (dd, J = 217.4, 7.4, 1F), −80.6 (dd, J = 217.4, 6.3, 1F); ^{13}C NMR (150 MHz) δ_C 15.2, 30.5, 32.0 (t, J = 2.2 Hz), 44.0 (t, J = 1.7 Hz), 119.2 (tt, J = 261.7, 29.0 Hz), 120.2 (tt, J = 264.0, 30.9 Hz), 124.6, 125.4, 127.7, 128.3, 129.0, 130.1, 137.2, 140.7, 145.0; MS (EI) *m/z* (rel. int.) 188 (100), 159 (9), 115 (5), 109 (3), 77 (4); HRMS (ESI) *m/z* calcd for $C_{21}H_{24}F_4NS$ [M + H]$^+$ 398.1566, found 398.1557.

*4.4.14. N,N-Diethyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)-2,3-dihydro-1H-inden-1-amine (**7g**)*

Yellow oil (74 mg, 20% yield), R_f 0.8 (PE−EtOAc, 80:20); ^{1}H NMR δ_H 0.82 (t, J = 7.1, 6H), 2.30−2.47 (m, 2H), 2.68−2.93 (m, 5H), 2.96−3.10 (m, 1H), 7.07−7.30 (m, 3H), 7.38−7.47 (m, 1H), 7.54−7.64 (m, 2H), 7.68−7.80 (m, 1H), 7.92−8.04 (m, 2H); ^{19}F NMR δ_F −107.1 (dt, J = 249.7, 3.5, 1F), −106.9 (t, J = 249.7, 3.5, 2F), −105.2, (dt, J = 249.7, 3.5, 1F); ^{13}C NMR (100 MHz) δ_C 15.7, 30.3, 31.6 (t, J = 2.5 Hz), 44.3 (t, J = 2.1 Hz), 78.2 (tt, J = 20.3, 2.2 Hz), 116.9 (tt, J = 301.9, 43.6 Hz), 120.7 (tt, J = 263.2, 33.8 Hz), 124.6, 125.6, 127.1, 128.5, 129.2, 130.8, 133.7, 135.4, 139.7, 145.0; MS (EI) *m/z* (rel. int.) 188 (100), 77 (11); HRMS (ESI) *m/z* calcd for $C_{21}H_{23}F_4NNaO_2S$ $[M + Na]^+$ 452.1278, found 452.1278.

*4.5 Synthesis of compounds **8***

*4.5.1. N-Methyl-1-(1,1,2,2-tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine (**8e**)*

A mixture of 10% Pd/C (10 mg) and **7e** (444 mg, 1 mmol) in MeOH (10 mL) was stirred for 3 h in an autoclave (H_2 20 bar) at room temperature. The solution was then filtered through celite, the filtrate was concentrated under reduced pressure and purified by column chromatography to give 314 mg of **8e** (89% yield). Colorless oil, R_f 0.8 (PE−EtOAc, 80:20);

IR (film) 536, 591, 603, 1105, 1160, 1360, 2817, 2859, 2935, 3103, 3412; ^{1}H NMR δ_H 1.42−1.58 (m, 7H), 1.60−1.70 (m, 2H), 1.75−1.86 (m, 2H), 2.41 (t, J = 1.8 Hz, 3H), 7.58−7.76 (m, 2H), 7.72−7.80 (m, 1H), 7.98−8.06 (m, 2H); ^{19}F NMR δ_F −112.8 (d, J = 2.7 Hz, 2F), −107.9 (d, J = 3.3 Hz, 2F); ^{13}C NMR (100 MHz) δ_C 20.4, 25.2, 27.7 (t, J = 2.5 Hz), 28.9 (t, J = 2.2 Hz), 60.8 (tt, J = 20.1, 1.4 Hz), 118.0 (tt, J = 300.7, 40.5 Hz), 120.4 (tt, J = 265.8, 27.9 Hz), 129.2, 130.9, 133.9, 135.4; MS (EI) *m/z* (rel. int.) 310 (4), 168 (3), 112 (100), 77 (10); HRMS (ESI) *m/z* calcd for $C_{15}H_{20}F_4NO_2S$ $[M + H]^+$ 354.1145, found 354.1145

*4.5.1. 1-(1,1,2,2-Tetrafluoro-2-(phenylsulfonyl)ethyl)cyclohexanamine (**8f**)*

A mixture of 10% Pd/C (50 mg) and **7f** (519mg, 1 mmol) in AcOH (30 mL) was stirred at 70 °C for 24 h in a flask under atmospheric hydrogen pressure. The solution was then filtered through celite, the filtrate was concentrated under reduced pressure and purified by column chromatography to give 241 mg of **8f** (71% yield). Colorless oil, R_f 0.14 (PE−EtOAc, 90:10); IR 535, 602, 1104, 1159, 1359, 1450, 2863, 2937, 3068, 3354, 3426; ^{1}H NMR δ_H 1.51−1.76

(m, 10H), 2.08 (s, 2H), 7.60−7.67 (m, 2H), 7.74−7.82 (m, 1H), 7.98−8.08 (m, 2H); ^{19}F NMR δ_F −107.2 (m, 2F), −119.2 (m, 2F); ^{13}C NMR (100 MHz) δ_C 20.2, 25.4, 29.9 (t, J = 2.4 Hz), 58.1 (tt, J = 21.5, 2.2 Hz), 117.7 (tt, J = 300.5, 40.7 Hz), 119.2 (tt, J = 260.6, 27.4 Hz), 129.3, 130.9, 133.5, 135.6; MS (EI) *m/z* (rel. int.) 296 (14), 98 (100), 77 (13); HRMS (CI) *m/z* calcd for $C_{14}H_{18}F_4NO_2S$ $[M + H]^+$ 340.0994, found 340.1001

*4.6 General procedure for the synthesis of compounds **9***

Method A. A solution of *n*-Bu_3SnH (403 μL, 1.5 mmol) and AIBN (3 mg, 0.02 mmol) in dry toluene (2 mL) was added to a refluxing solution of **6a** or **6e** (1 mmol) in dry toluene (3 mL). The resulting mixture was refluxed for 3 h, followed by concentration under reduced pressure and purification by flash column chromatography (PE–EtOAc) to give **9a** (91% yield) and **9e** (64% yield), respectively.

Method B. I_2 (40 mg, cat.) was added to Mg turnings (240 mg, 10 mmol), the mixture was heated up with a heat gun and stirred for 10 minutes. Then, a solution of **7a** (409 mg, 1 mmol) in MeOH (10 mL) was added, and the mixture was stirred for 1.5 h at room temperature. A second portion of Mg (480 mg, 20 mmol) was added, and the reaction mixture was stirred for 2.5 h at room temperature. Aqueous saturated NH_4Cl (15 mL) was added and the reaction mixture was extracted with Et_2O. The combined organic phase was washed with brine and water, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by column chromatography eluting with PE−EtOAc to give **9a** (80% yield).

*4.6.1 4-(1-(1,1,2,2-Tetrafluoroethyl)cyclohexyl)morpholine (**9a**)*

White solid (245 mg, 91% yield from **6a** or 215 mg, 80% yield from **7a**), R_f 0.30 (PE–EtOAc, 95:5); m.p. 56-58°C; ^{1}H NMR δ_H 1.12–1.37 (m, 1H), 1.40–1.67 (m, 6H), 1.69–1.80 (m, 1H), 2.05 (d, J = 13.0 Hz, 2H), 2.87 (s, 4H), 3.66 (s, 4H); ^{19}F NMR $\delta_Ф$ –134.1 (t, J = 4.7 Hz, 2F), –121.0 (s, 2F); ^{13}C NMR (100 MHz) δ_C 20.3, 25.7, 27.4 (t, J = 2.3 Hz), 46.8 (t, J = 2.0 Hz), 61.7 (t, J = 18.9 Hz), 68.4, 110.5 (tt, J = 252.0, 36.3 Hz), 120.5 (tt, J = 260.6, 24.9 Hz); MS (EI) *m/z* (rel. int.) 182 (1), 168 (100), 101 (1); HRMS (CI) *m/z* calcd for $C_{12}H_{20}F_4NO$ $[M + H]^+$ 270.1481, found 270.1486

*4.6.2 N-Benzyl-N-methyl-1-(1,1,2,2-tetrafluoroethyl)cyclohexanamine (**9e**)*

Colorless oil (194 mg, 64% yield), R_f 0.64 (PE); ^{1}H NMR δ_H 1.23–1.35 (m, 2H), 1.45–1.62 (m, 4H), 1.67–1.86 (m, 3H), 2.09–2.28 (m, 2H), 2.37 (s, 3H), 4.0 (s, 2H), 5.82 (tt, J = 52.9, 5.9 Hz, 3H), 7.13–7.52 (m, 5H); ^{19}F NMR δ_F –134.0 (t, J = 4.8 Hz, 2F), –120.8 to –119.6 (m,

2F); ^{13}C NMR (100 MHz) δ_C 20.5, 25.8, 28.5, 34.4 (t, *J* = 2.2 Hz), 54.0 (t, *J* = 2.5 Hz), 62.4 (t, J = 18.7 Hz), 110.6 (tt, *J* = 251.9, 36.1 Hz), 120.9 (tt, *J* = 261.7, 25.0 Hz), 126.5, 127.6, 128.3, 140.7; MS (EI) *m/z* (rel. int.) 202 (100), 91 (64); HRMS (ESI) *m/z* calcd for $C_{16}H_{22}F_4N$ $[M + H]^+$ 304.16829, found 304.1683

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Highlights

- $PhSCF_2CF_2TMS$ and $PhSO_2CF_2CF_2TMS$ react with iminium salts formed from enamines and HF to form products of nucleophilic addition.
- Radical or reductive desulfurization of the adducts affords amines with the tetrafluoroethyl group.
- Primary, secondary and tertiary amines substituted with the CF_2CF_2 group on α-carbon are accessed by this method.