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Silicon Reagent with Functionalized Tetrafluoroethylene Fragments: Preparation and Coupling with Aldehydes

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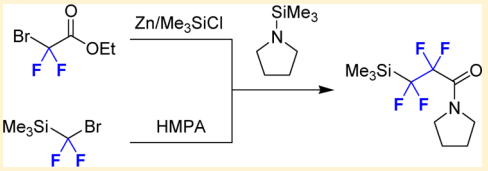
Supporting Information

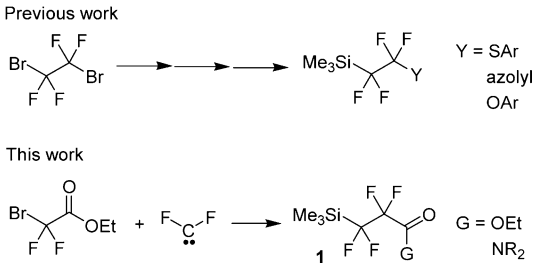
ABSTRACT: A new fluorinated silicon reagent bearing a functionalized tetrafluoroethylene fragment was prepared from two CF_2 building blocks: ethyl bromodifluoroacetate and (bromodifluoromethyl)trimethylsilane. The key C−C bond-forming step involves a difluorocarbene addition/cyclopropane rearrangement sequence. The silicon reagent was coupled with aldehydes and reactive azomethines in the presence of potassium fluoride.



Fluorinated silanes constitute an important class of reagents for the synthesis of valuable organofluorine compounds.[1,2] While these reagents are typically air-stable and themselves are unreactive toward electrophiles, they display nucleophilic reactivity when activated by a suitable Lewis base. As a consequence, fluorinated silanes have found widespread applications as a source of nucleophilic fluorinated fragment in reactions with C=O, C=N, and C=C bonds[2] as well as in transition-metal catalyzed cross-couplings.[3]

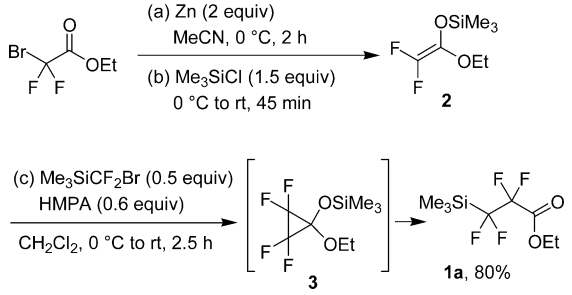
The Ruppert-Prakash reagent (Me_3SiCF_3) and its homologues ($Me_3SiC_nF_{2n+2}$) are the most frequently employed silanes and are quite well-studied.[2a,b] At the same time, functionalized silanes containing a CF_2CF_2 unit are rare, which may be associated with limited approaches for their synthesis.[4] Indeed, a general method for the preparation of such silanes relies on dibromotetrafluoroethane as a starting compound and involves substitution of one bromine and reductive silylation of the other[4,5] (Scheme 1). Given the growing interest toward compounds with tetrafluoroethylene fragments,[6−8] the elaboration of fluorinated silanes bearing a modifiable functional group is important. Herein, we describe new silicon reagents, ester and amido substituted silanes **1**, which can be readily obtained from ethyl bromodifluoroactetate and a source of difluorocarbene. This process constitutes a rare example of C−C bond forming process between two different CF_2 fragments.[9] Our concept is based on the difluorohomologation approach recently reported by our group.[10,11]

Scheme 1. Functionalized Silicon Reagents



Ethyl bromodifluoroactetate was first converted into silyl ketene acetal **2** by treatment with zinc and chlorosilane in acetonitrile (Scheme 2). This reaction proceeds with the yield around 40%. Furthermore, compound **2** is prone to transformation into thermodynamically more stable C-silyl tautomer.[12] The crude material was dissolved in dichloromethane and reacted with (bromodifluoromethyl)trimethylsilane (Me_3SiCF_2Br) and hexamethylphosphoramide (HMPA), affording, after distillation, product **1a** in 80% yield based on Me_3SiCF_2Br. Concerning the mechanism, the combination of Me_3SiCF_2Br and HMPA generates difluorocarbene,[13] which easily adds to electron-rich double bond of **2**.[10,14,15] Cyclopropane **3** is unstable and cannot be detected by monitoring of the reaction by ^{19}F NMR spectroscopy. As it is formed, it rapidly rearranges into product **1a**, similar to cyclopropanes derived from nonfluorinated ketene acetals.[10a] The mechanism of the rearrangement of **3** into **1a** is not clear at present, but dissociative C−C bond-breaking owing to strongly donating oxygen atoms seems likely.

Scheme 2. Synthesis of Reagent 1a



As a fluorinated silicon reagent, silane **1a** was first tested in fluoride-mediated reaction with benzaldehyde **4a** (Scheme 3). Under various conditions, complex mixtures containing small amounts of expected product **5a** were formed. Iminium ions are

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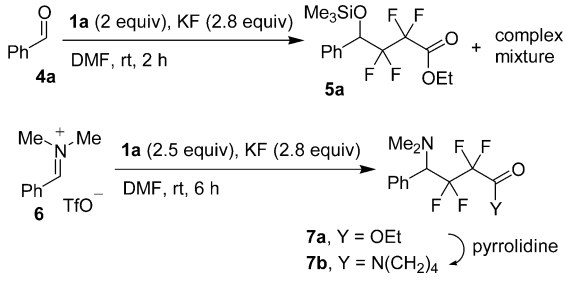
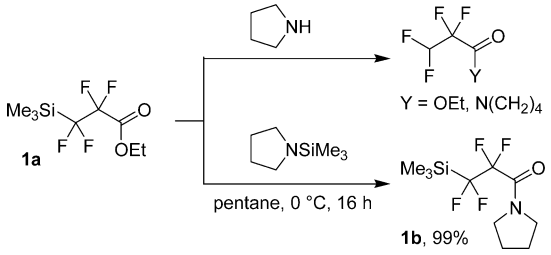
Scheme 3. Reactions of Silane 1a



also good substrates for coupling with fluorinated nucleophiles.[16] When iminium salt **6** was coupled with silane **1a**, addition product **7a** was cleanly formed, as evidenced by ^{19}F NMR, but we could not isolate it by silica gel chromatography. These facts may be associated with the high electrophilic activity of the ester carbonyl group, which causes cyclization of **5a** (or its alkoxide form) or decomposition of **7a** on silica gel. Correspondingly, when crude material containing **7a** was treated with pyrrolidine, amide **7b** was formed, and it was easily isolated after conventional chromatography in 46% yield.

The increased stability of the amide **7b** compared to ester **7a** prompted us to modify the silane **1a** by converting the ester into an amide group. It should be pointed out that modifications of side chains of fluorinated silanes under nucleophilic conditions is problematic owing to facile cleavage of the C−Si bond. Indeed, interaction of silane **1a** with pyrrolidine provided a mixture of protodesilylated products (Scheme 4). Rewardingly, reaction of **1a** with *N*-silylpyrrolidine

Scheme 4. Synthesis of Silane 1b

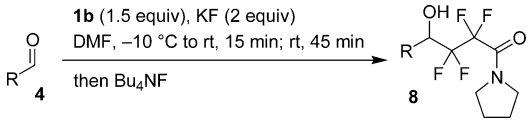


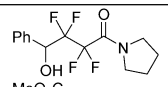
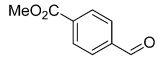
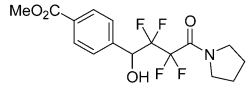
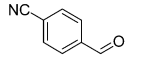
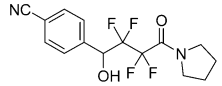
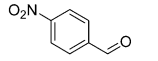
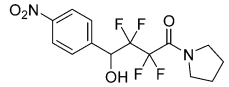
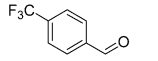
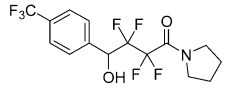
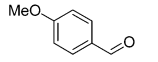
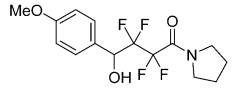
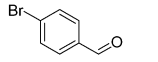
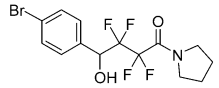
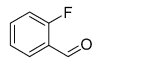
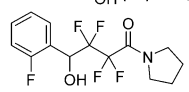
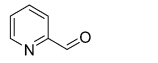
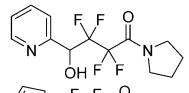
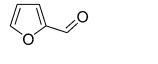
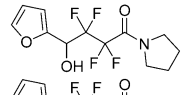
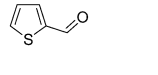
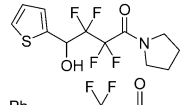
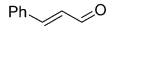
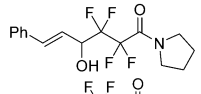
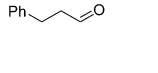
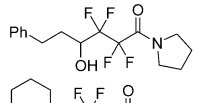
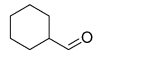
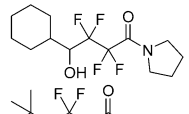
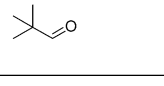
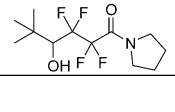
proceeded cleanly in pentane, furnishing silane **1b** in 99% isolated yield. Attempted preparation of silane **1b** directly from *N*-(bromodifluoroacetyl)pyrrolidine was unsuccessful presumably because of difficulties with generation of intermediate silyl ketene aminal.

A series of aldehydes **4** were coupled with silane **1b** (Table 1). Under the optimized conditions, 2 equiv of potassium fluoride in dimethylformamide (DMF) was used with reaction time of 1 h followed by desilylation.[17] Aromatic and heteroaromatic aldehydes gave good yields of products. Cinnamaldehyde and enolizable substrates also worked well (entries 12−14). Only *p*-methoxybenzaldehyde exhibited decreased reactivity and afforded addition product in moderate yield (entry 6).

Acetophenone turned out to be unreactive, and self-condensation of the silicon reagent proceeded faster than that of the carbonyl addition reaction. Thus, when silane **1b** was subjected to potassium fluoride without carbonyl substrate, compound **9** was formed in 63% yield (determined by ^{19}F NMR) along with other byproducts (Scheme 5). From the complex mixture, compound **9** was isolated in individual form

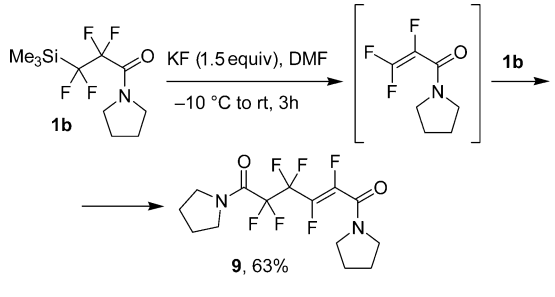
Table 1. Reactions of Aldehydes with Silane 1b



no.	Aldehyde	Product		Yield of **8**, %[a]
1			**8a**	76
2			**8b**	85
3			**8c**	81
4			**8d**	73
5			**8e**	78
6			**8f**	50
7			**8g**	74
8			**8h**	73
9			**8i**	89
10			**8j**	83
11			**8k**	81
12			**8l**	68
13			**8m**	66
14			**8n**	79
15			**8o**	70

[a]Isolated yield.

Scheme 5. Self-Condensation of Silane 1b



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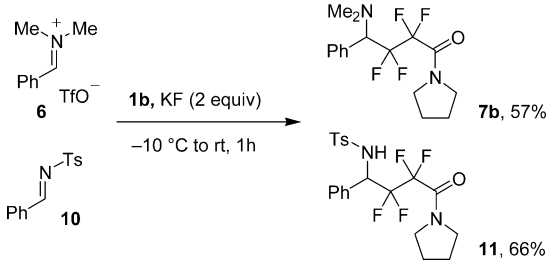
by preparative HPLC. Supposedly, the mechanism of self-condensation involves fluoride-initiated α- or β-elimination of fluorosilane with the generation of trifluoroacrylamide, which reacts with another molecule of **1b**.[18]

Besides aldehydes, iminium salt **6** and *N*-tosyl imine **10** were coupled with silane **1b**, leading to products **7b** and **11**, respectively (Scheme 6).

Scheme 6. Reactions of Azomethine Substrates



In summary, a novel functionalized fluorinated silicon reagent is described. The reagent contains a tetrafluoroethylene fragment which is assembled from two CF_2 building blocks. While coupling of the silane with aldehydes and reactive azomethines proceeds smoothly, its propensity for self-condensation under basic conditions renders problematic nucleophilic fluoroalkylation of less-reactive substrates.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an argon atmosphere. Acetonitrile and HMPA were distilled from CaH_2 and stored over MS 4A. Column chromatography was carried out, employing silica gel (230−400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer. The measurements were done in a positive ion mode (interface capillary voltage −4500 V) or in a negative ion mode (3200 V); mass range from m/z 50 to 3000. Me_3SiCF_2Br[9a] was prepared according to literature procedure.

*Ethyl 2,2,3,3-Tetrafluoro-3-(trimethylsilyl)propanoate (**1a**).* Zinc dust (12.8 g, 200 mmol, 2 equiv) was placed in a Shlenk tube and heated to 100 °C under vacuum (5 Torr). After being cooled to room temperature, the reaction vessel was filled with argon. Then, MeCN (15 mL), Me_3SiCl (763 mg, 7 mmol), and 1,2-dibromoethane (94 mg) were successively added, and the mixture was stirred for 30 min. The mixture was cooled to −10 °C, and a solution of ethyl bromodifluoroacetate (20.2 g, 100 mmol) in MeCN (15 mL) was added over 50 min using the syringe pump. After completion of the addition, the cooling bath was removed, and the mixture was allowed to warm to room temperature and stirred for 1 h. Then, the mixture was cooled to 0 °C; Me_3SiCl (16.4 g, 150 mmol) was added dropwise, and the mixture was allowed to warm to room temperature over 45 min. Under argon atmosphere, the mixture was extracted with pentane (4 × 25 mL, pentane phase was decanted using a cannula). Combined pentane layers were placed in a 250 mL flask, and 75% of the pentane was evaporated under vacuum (40−50 Torr). The residue was diluted with dichloromethane (25 mL), and the mixture was cooled to 0 °C. Then, (bromodifluoromethyl)trimethylsilane (10 g, 50 mmol) and HMPA (11 g, 61 mmol) were successively added dropwise. The cooling bath was removed, and the mixture was stirred for 3 h at room temperature. The mixture was concentrated under vacuum (10−15 Torr); the residue was dissolved in pentane (70 mL), and water (15 mL) was added. The mixture was washed with pentane (3 × 70 mL); the combined pentane extracts were filtered through Na_2SO_4 and concentrated, and the residue was further purified by fractional distillation (55−53 °C/2.6 Torr). Yield: 9.82 g (80%, based on (bromodifluoromethyl)trimethylsilane). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.38 (q, 2H, J = 7.1 Hz), 1.36 (t, 3H, J = 7.1), 0.28 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 161.0 (t, J = 31.3 Hz), 122.4 (tt, J = 271.7, 44.1 Hz), 112.0 (tt, J = 255.2, 32.6 Hz), 63.5, 14.0, −4.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −116.9 (s, 2F), −127.8 (s, 2F). HRMS (ESI): calcd for $C_8H_{14}F_4O_2NaSi$ (M + Na) 269.0591; found 269.0580.

*1-[2,2,3,3-Tetrafluoro-3-(trimethylsilyl)propanoyl]pyrrolidine (**1b**).* *N*-(trimethylsilyl)pyrrolidine (2.91 g., 20.3 mmol) was added dropwise to a solution of silane **1a** (5 g, 20.3 mmol) in pentane (0.5 mL) at 0 °C. The cooling bath was removed, and the mixture was stirred overnight at room temperature. All volatiles were evaporated in vacuum, and the residue was purified by flash chromatography on silica gel (R_f 0.36, hexane/EtOAc, 6/1,). Yield: 5.48 g, 99%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.71 (t, 2H, J = 6.6 Hz), 3.58 (t, 2H, J = 6.9 Hz), 2.01−1.80 (m, 4H), 0.29 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 159.3 (t, J = 27.5 Hz), 123.3 (tt, J = 271.9, 39.0 Hz), 113.5 (tt, J = 258.7, 29.8 Hz), 47.9, 46.9 (m), 26.6, 23.3, −3.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −115.1 (s, 2F), −128.4 (s, 2F). HRMS (ESI): calcd for $C_{10}H_{18}F_4NOSi$ (M + H) 272.1088; found 272.1094.

Reactions of Aldehydes with Silane 1b (General Procedure). A solution of aldehyde **4** (0.5 mmol) and silane **1b** (203 mg, 0.75 mmol) in DMF (0.25 mL) was cooled to −10 °C, and potassium fluoride (58 mg, 1 mmol) was added. The mixture was allowed to warm to room temperature over 15 min and stirred for an additional 45 min. The mixture was treated with $Bu_4NF{\cdot}3H_2O$ (316 mg, 1 mmol) and stirred for 10 min. Then, water (3 mL) was added, and the aqueous phase was extracted with ethyl acetate (3 × 4 mL). The combined organic layers were filtered through Na_2SO_4 and concentrated under vacuum, and the residue was purified by column chromatography.

*2,2,3,3-Tetrafluoro-4-hydroxy-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (**8a**).* Yield 116 mg (76%). Colorless crystals. Mp 76−77 °C. R_f 0.36 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54−7.43 (m, 2H), 7.43−7.31 (m, 3H), 5.27−5.15 (m, 1H), 4.58 (d, 1H, J = 3.8 Hz), 3.88−3.68 (m, 2H), 3.63 (t, 2H, J = 6.9 Hz), 2.11−1.79 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 160.4 (t, J = 27.1 Hz), 135.0, 129.0, 128.32, 128.26, 115.8 (dddd, J = 262.8, 258.2, 29.8, 24.1 Hz), 111.9 (dddd, J = 269.6, 262.8 35.6, 28.7 Hz), 72.0 (dd, J = 28.7, 21.9 Hz), 48.6, 47.5 (t, J = 6.0 Hz), 26.6, 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −114.8 (ddd, 1F, J = 278.2, 13.1, 5.6 Hz), −117.0 (dd, 1F, J = 278.2, 11.0 Hz), −116.3 (dd, 1F, J = 273.0, 11.0 Hz), −130.8 (dddd, 1F, J = 273.2., 21.6, 13.1, 6.7 Hz). HRMS (ESI): calcd for $C_{14}H_{15}F_4NNaO_2$ (M + Na) 328.0931; found 328.0934.

*Methyl 4-(2,2,3,3-Tetrafluoro-1-hydroxy-4-oxo-4-(pyrrolidin-1-yl)butyl)benzoate (**8b**).* Yield 154 mg (85%). Colorless crystals. Mp 129−130 °C. R_f 0.29 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, 2H, J = 8.1 Hz), 7.52 (d, 2H, J = 8.1 Hz), 5.26 (d, 1H, J_{H-F} = 20.7 Hz), 5.01 (s, 1H), 3.86 (s, 3H), 3.74−3.60 (m, 2H), 3.55 (t, 2H, J = 6.8 Hz), 2.04−1.71 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 166.9 (s), 160.2 (t, J = 27.0 Hz), 140.0, 130.7, 129.4, 128.3, 115.5 (m), 111.8 (m), 71.7 (dd, J = 28.5, 22.1 Hz), 52.2, 48.6, 47.4 (t, J = 6.0 Hz), 26.5, 23.2. ^{19}F NMR (300 MHz, $CDCl_3$) δ: −114.8 (dd, 1F, J = 279.7, 10.6 Hz), −116.8 (dd, 1F, J = 279.7, 8.5 Hz), −117.5 (dd, 1F, J = 273.4, 10.6 Hz), −129.9 (dddd, 1F, J = 273.4, 20.7, 10.6, 4.2 Hz). HRMS (ESI): calcd for $C_{16}H_{18}F_4NO_4$ (M + H) 364.1166; found 364.1161.

*4-(2,2,3,3-Tetrafluoro-1-hydroxy-4-oxo-4-(pyrrolidin-1-yl)butyl)-benzonitrile (**8c**).* Yield 134 mg (81%). Colorless crystals. Mp 107−108 °C. R_f 0.30 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (d, 2H, J = 8.4 Hz), 7.57 (d, 2H, J = 8.4 Hz), 5.36−5.16 (m, 2H), 5.20 (s, 1H), 3.70 (t, 2H, J = 6.5 Hz), 3.55 (t, 2H, J = 6.9 Hz), 2.07−1.76 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$), δ: 160.0 (t, J = 27.0 Hz), 140.3, 131.9, 129.1, 118.6, 115.3 (dddd, J = 263.9, 259.3, 29.8, 24.1 Hz), 112.7, 111.5 (dddd, J = 269.6, 263.9, 34.4, 26.7 Hz), 71.3 (dd, J = 28.4, 22.1 Hz), 48.6, 47.4 (m), 26.5, 23.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −114.6 (dd, 1F, J = 280.3, 10.6 Hz), −116.6 (dd, 1F, J = 280.3, 10.6 Hz), −117.2 (dd, 1F, J = 274.1, 10.6 Hz), −130.0 (dddd, 1F, J = 274.1, 21.5, 12.9, 6.8 Hz). HRMS (ESI): calcd for $C_{15}H_{15}F_4N_2O_2$ (M + H) 331.1064; found 331.1058.

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*2,2,3,3-Tetrafluoro-4-hydroxy-4-(4-nitrophenyl)-1-(pyrrolidin-1-yl)butan-1-one (**8d**).* Yield 128 mg (73%). Colorless crystals. Mp 132−133 °C. R_f 0.36 (hexane/EtOAc, 1/2). ^{1}H NMR (300 MHz, acetone-d_6) δ: 8.33−8.25 (m, 2H), 7.86−7.79 (m, 2H), 5.86 (d, 1H, J = 5.7 Hz), 5.69 (dt, 1H, J_{H-F} = 19.0 Hz, J = 5.7 Hz), 3.80−3.70 (m, 2H), 3.55 (t, 2H, J = 6.9 Hz), 2.09−1.85 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ: 159.2 (dd, J = 27.2, 26.6 Hz), 149.2, 144.5 (m), 130.4, 123.9, 116.9 (ddt, J = 261.8, 256.1, 27.2 Hz), 112.3 (tdd, J = 266.5, 32.0, 30.4 Hz), 71.7 (dd, J = 27.8, 22.1 Hz), 48.8, 47.6 (t, J = 6.3 Hz), 27.1 (t, J = 1.7), 23.7. ^{19}F NMR (282 MHz, acetone-d_6) δ: −115.6 (m, 2F), −118.7 (d, 1F, J = 270.9 Hz), −128.2 (dd, 1F, J = 270.9, 19.0 Hz). HRMS (ESI): calcd for $C_{14}H_{15}F_4N_2O_4$ (M + H) 351.0962; found 351.0962.

*2,2,3,3-Tetrafluoro-4-hydroxy-1-(pyrrolidin-1-yl)-4-(4-(trifluoromethyl)phenyl)butan-1-one (**8e**).* Yield 146 mg (78%). Colorless crystals. Mp 93−94 °C. R_f 0.35 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67−7.54 (m, 4H), 5.28 (d, 1H, J_{H-F} = 21.1 Hz), 5.04 (d, 1H, J = 3.9 Hz), 3.79−3.69 (m, 2H), 3.61 (t, 2H, J = 6.9 Hz), 2.07−1.83 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 160.1 (t, J = 27.0 Hz), 139.2, 131.1 (q, J = 32.5 Hz), 128.8, 125.1 (q, J = 3.7 Hz), 124.2 (q, J = 272.3 Hz), 115.5 (m), 112.0 (m), 71.5 (dd, J = 28.5, 22.1 Hz), 48.6, 47.4 (m), 26.5, 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: − 63.5 (s, 3F), −114.7 (dd, 1F, J = 280.1, 7.0 Hz), −117.0 (dd, 1F, J = 280.0, 11.2 Hz), −117.2 (dd, 1F, J = 273.6, 12.0 Hz), −130.5 (dddd, 1F, J = 273.6, 21.1, 12.7, 7.0 Hz). HRMS (ESI): calcd for $C_{15}H_{15}F_7NO_2$ (M + H) 374.0986; found 374.0981.

*2,2,3,3-Tetrafluoro-4-hydroxy-4-(4-methoxyphenyl)-1-(pyrrolidin-1-yl)butan-1-one (**8f**).* Yield 84 mg (50%). Colorless crystals. Mp 97−98 °C. R_f 0.30 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.16 (d, J_{H-F} = 21.3 Hz, 1H), 4.45 (d, J = 4.0 Hz, 1H), 3.80 (s, 3H), 3.78−3.68 (m, 2H), 3.62 (t, J = 6.9 Hz, 2H), 2.08−1.80 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.3 (t, J = 26.9 Hz), 160.2, 129.5, 127.0, 115.9 (dddd, J = 261.6, 257.0, 29.8, 24.1 Hz), 113.7, 112.1 (dddd, J = 269.6, 263.9, 35.6, 29.8 Hz), 71.58 (dd, J = 29.0, 21.8 Hz), 55.4, 48.6, 47.5 (t, J = 5.7 Hz), 26.6, 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −114.8 (dd, 1F, J = 278.3, 10.7 Hz), −117.0 (dd, 1F, J = 278.3, 10.8 Hz), −117.4 (dd, 1F, J = 272.0, 11.9 Hz), −131.0 (dddd, 1F, J = 272.0, 21.3, 10.7, 4.7 Hz). HRMS (ESI): calcd for $C_{15}H_{18}F_4NO_3$ (M + H) 336.1217; found 336.1215.

*4-(4-Bromophenyl)-2,2,3,3-tetrafluoro-4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one (**8g**).* Yield 142 mg (74%). Colorless crystals. Mp 119−120 °C. R_f 0.27 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (d, 2H, J = 8.4 Hz), 7.35 (d, 2H, J = 8.4 Hz), 5.17 (d, 1H, J_{H-F} = 21.1 Hz), 4.78 (s, 1H), 3.84−3.70 (m, 2H), 3.63 (t, 2H, J = 6.9 Hz), 2.10−1.83 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 160.4 (t, J = 26.9 Hz), 134.0, 131.5, 130.0, 123.2, 115.6 (m), 111.8 (m), 71.5 (dd, J = 28.7, 22.1 Hz), 48.7, 47.5 (m), 26.6, 23.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −114.7 (ddd, 1F, J = 279.7, 12.6, 5.3 Hz), −116.9 (dd, 1F, J = 279.3, 11.7 Hz), −117.2 (dd, 1F, J = 273.4, 12.6 Hz), −130.9 (dddd, 1F, J = 273.4, 21.1, 12.6, 5.3). HRMS (ESI): calcd for $C_{14}H_{14}BrF_4NNaO_2$ (M + Na) 406.0036, 408.0016; found 406.0029, 408.0007.

*2,2,3,3-Tetrafluoro-4-(2-fluorophenyl)-4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one (**8h**).* Yield 118 mg (73%). Colorless oil. R_f 0.26 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (t, 1H, J = 7.4 Hz), 7.41−7.29 (m, 1H), 7.19 (td, 1H, J = 7.5, 0.9 Hz), 7.11−6.97 (m, 1H), 5.64 (d, 1H, J_{H-F} = 21.6 Hz), 4.84 (s, 1H), 3.75 (s, 2H), 3.62 (t, 2H, J = 6.9 Hz), 2.06−1.83 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 160.7 (d, J = 247.2 Hz), 160.2 (t, J = 25.8 Hz), 130.5 (d, J = 8.0 Hz), 129.7 (d, J = 2.0 Hz), 124.2 (d, J = 3.3 Hz), 122.5 (d, J = 13.1 Hz), 115.5 (m), 115.1 (d, J = 22.4 Hz), 111.9 (m), 65.1 (ddd, J = 29.8, 21.8, 4.0 Hz), 48.6, 47.4 (m), 26.5, 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −115.0 (ddd, 1F, J = 279.0, 11.8, 6.8 Hz), −117.7 (dd, 1F, J = 279.0, 12.4 Hz), −118.5 (m, 1F), −118.6 (m, 1F), −131.3 (m, 1F). HRMS (ESI): calcd for $C_{14}H_{14}F_5NNaO_2$ (M + Na) 346.0837; found 346.0833.

*2,2,3,3-Tetrafluoro-4-hydroxy-4-(pyridin-2-yl)-1-(pyrrolidin-1-yl)-butan-1-one (**8i**).* Yield 137 mg (89%). Colorless oil. R_f 0.25 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (d, 1H, J = 4.7 Hz), 7.71 (td, 1H, J = 7.8, 1.6 Hz), 7.46 (d, 1H, J = 7.8 Hz), 7.34−7.24 (m, 1H), 5.40 (s, 1H), 5.43−5.31 (m, 2H), 3.70 (t, 1H, J = 6.7 Hz), 3.56 (t, 1H, J = 6.9 Hz), 2.00−1.77 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 159.0 (t, J = 26.8 Hz), 152.6, 148.3, 136.8, 124.0, 123.3 (d, J = 3.2 Hz), 115.7 (m), 111.3 (m), 71.0 (dd, J = 28.3, 23.0 Hz), 46.9 (t, J = 5.9 Hz), 26.5, 23.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −115.2 (dd, 1F, J = 282.2, 4.2 Hz), −116.6 (d, 1F, J = 283.2 Hz), −118.2 (d, 1F, J = 272.0 Hz), −129.3 (ddd, 1F, J = 272.0, 20.1, 4.2 Hz). HRMS (ESI): calcd for $C_{13}H_{15}F_4N_2O_2$ (M + H) 307.1064; found 307.1068.

*2,2,3,3-Tetrafluoro-4-(furan-2-yl)-4-hydroxy-1-(pyrrolidin-1-yl)-butan-1-one (**8j**).* Yield 123 mg (83%). Colorless oil. R_f 0.32 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 (br s, 1H), 6.50 (d, 1H, J = 3.2 Hz), 6.44−6.33 (m, 1H), 5.32 (d, 1H, J_{H-F} = 19.4 Hz), 4.45 (s, 1H), 3.81−3.66 (m, 2H), 3.60 (t, 2H, J = 6.9 Hz), 2.10−1.78 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 159.9 (t, J = 27.0 Hz), 148.5, 143.3, 115.3 (m), 111.7 (m), 110.6, 110.1, 67.1 (dd, J = 28.7, 23.5 Hz), 48.5. 47.3 (t, J = 6.3 Hz), 26.6, 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −115.4 (dd, 1F, J = 281.8, 10.6 Hz), −117.3 (dd, 1F, J = 281.8, 9.9 Hz), −119.2 (dd, 1F, J = 272.3, 9.9 Hz), −128.4 (ddd, 1F, J = 272.3, 19.4, 10.6 Hz). HRMS (ESI): calcd for $C_{12}H_{14}F_4NO_3$ (M + H) 296.0904; found 296.0911.

*2,2,3,3-Tetrafluoro-4-hydroxy-1-(pyrrolidin-1-yl)-4-(thiophen-2-yl)butan-1-one (**8k**).* Yield 126 mg (81%). Colorless oil. R_f 0.24 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39−7.34 (m, 1H), 7.19−7,14 (m, 1H), 7.03 (dd, 1H, J = 4.9, 3.7 Hz), 5.53 (d, 1H, J_{H-F} = 20.6 Hz), 4.78 (s, 1H), 3.82−3.69 (m, 2H), 3.61 (t, 2H, J = 6.9 Hz), 2.08−1.83 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 160.2 (t, J = 26.9 Hz), 137.3, 127.39 (d, J = 1.4 Hz), 126.7, 126.6, 115.2 (m), 111.8 (m), 69.0 (dd, J = 29.6, 22.8 Hz), 48.7, 47.5 (t, J = 6.0 Hz), 26.6, 23.3 (d, J = 7.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −114.7 (dd, 1F, J = 278.8, 12.7 Hz), −116.8 (dd, 1F, J = 278.8, 11.7 Hz), −117.7 (dd, 1F, J = 270.9, 12.7 Hz), −130.8 (dddd, 1F, J = 20.6, 12.7, 11.7, 5.1 Hz). HRMS (ESI): calcd for $C_{12}H_{14}F_4NO_2S$ (M + H) 312.0676; found 312.0681.

*(E)-2,2,3,3-Tetrafluoro-4-hydroxy-6-phenyl-1-(pyrrolidin-1-yl)hex-5-en-1-one (**8l**).* Yield 113 mg (68%). Yellow oil. R_f 0.35 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49−7.25 (m, 5H), 6.85 (d, 1H, J = 15.9 Hz), 6.28 (dd, 1H, J = 15.9, 6.2 Hz), 4.95−4.74 (m, 1H), 4.24 (d, J = 5.3 Hz, 1H), 3.75 (t, 2H, J = 6.7 Hz), 3.60 (t, J = 7.0 Hz, 2H), 2.09−1.79 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0 (t, J = 26.9 Hz), 136.2 (s), 135.0, 128.7, 128.3, 126.9, 121.9, 116.1 (m), 111.7 (m), 71.3 (dd, J = 27.6, 24.0 Hz), 48.5, 47.3 (t, J = 6.3 Hz), 26.5, 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −115.3 (dd, 1F, J = 279.3, 8.3 Hz), −116.4 (d, 1F, J = 279.3 Hz), −119.6 (d, 1F, J = 272.5 Hz), −129.0 (ddd, 1F, J = 272.5, 18.2, 8.3 Hz). HRMS (ESI): calcd for $C_{16}H_{18}F_4NO_2$ (M + H) 332.1268; found 332.1264.

*2,2,3,3-Tetrafluoro-4-hydroxy-6-phenyl-1-(pyrrolidin-1-yl)hexan-1-one (**8m**).* Yield 110 mg (66%). Colorless oil. R_f 0.35 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38−7.16 (m, 5H), 4.10 (ddd, 1H, J_{H-F} = 20.1 Hz, J = 8.8, 4.4 Hz), 3.82 (d, 1H, J = 5.1 Hz), 3.79−3.67 (m, 2H), 3.60 (t, 2H, J = 6.9 Hz), 3.08−2.89 (m, 1H), 2.84−2.59 (m, 1H), 2.14−1.81 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.3 (t, J = 26.9 Hz), 141.4, 128.7, 128.6, 126.2, 116.8 (dddd, J = 261.6, 258.2, 27.9, 26.3 Hz), 111.7 (tdd, J = 264.5, 34.2, 30.2 Hz), 69.3 (dd, J = 27.9, 23.4 Hz), 48.6, 47.4 (t, J = 6.7 Hz), 31.4, 30.5 (s, J = 21.9 Hz), 26.6 (t, J = 1.7 Hz), 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −116.1 (dd, 1F, J = 275.7, 8.2 Hz), −117.2 (d, 1F, J = 275.7 Hz), −121.2 (d, 1F, J = 270.7 Hz), −132.1 (ddd, 1F, J = 270.7, 20.1, 8.2 Hz). HRMS (ESI): calcd for $C_{16}H_{19}F_4NNaO_2$ (M + Na) 356.1244; found 356.1248.

*4-Cyclohexyl-2,2,3,3-tetrafluoro-4-hydroxy-1-(pyrrolidin-1-yl)-butan-1-one (**8n**).* Yield 123 mg (79%). Colorless crystals. Mp 76−77 °C. R_f 0.34 (hexane/EtOAc, 1/1). ^{1}HNMR (300 MHz, $CDCl_3$) δ: 3.99−3.80 (m, 1H), 3.80−3.65 (m, 2H), 3.55 (dd, J = 15.7, 6.5 Hz, 3H), 2.08−1.54 (m, 10H), 1.47−1.05 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 160.3 (t, J = 27.0 Hz), 117.5 (dddd, J = 264.0, 260.0, 28.5, 24.4 Hz), 111.6 (dddd, J = 267.8, 263.1, 34.5, 29.5 Hz), 72.9 (dd, J = 27.1, 21.4 Hz), 48.5, 47.3 (t, J = 6.1 Hz), 38.1, 30.2, 26.8 (d, J = 2.1 Hz), 26.6−26.5 (m), 26.6 (t, J = 2.0 Hz), 26.3, 26.1, 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −116.3 (dd, 1F, J = 275.3, 9.6 Hz), −118.4 (dd,

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1F, J = 275.3, 10.4 Hz), −119.7 (dd, 1F, J = 270.5, 10.4 Hz), −128.6 (ddd, 1F, J = 270.5, 22.3, 9.6 Hz). HRMS (ESI): calcd for $C_{14}H_{22}F_4NO_2$ (M + H) 312.1581; found 312.1586.

*2,2,3,3-Tetrafluoro-4-hydroxy-5,5-dimethyl-1-(pyrrolidin-1-yl)-hexan-1-one (**8o**).* Yield 100 mg (70%). Colorless crystals. Mp 52−53 °C. R_f 0.30 (hexane/EtOAc, 1/1). ^{1}HNMR (300 MHz, $CDCl_3$) δ: 3.84−3.65 (m, 4H), 3.56 (t, 2H, J = 7.0 Hz), 2.04−1.79 (m, 4H), 1.06 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 160.4 (t, J = 27.1 Hz), 118.8 (m), 111.6 (tdd, J = 265.9, 33.0, 29.4 Hz), 75.2 (dd, J = 26.8, 21.1 Hz), 48.4, 47.3 (t, J = 5.9 Hz), 35.4, 26.8 (m), 26.5 (t, J = 2.2 Hz), 23.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −114.5 (d, 1F, J = 268.1 Hz), −117.2 (m, 2F), −129.4 (m, 1F). HRMS (ESI): calcd for $C_{12}H_{20}F_4NO_2$ (M + H) 286.1425; found 286.1423.

*(E)-2,3,4,4,5,5-Hexafluoro-1,6-di(pyrrolidin-1-yl)hex-2-ene-1,6-dione (**9**).* KF (87 mg, 1.5 mmol) was added to a mixture of silane **1b** (271 mg, 1 mmol) and DMF (0.2 mL) at 0 °C, and the mixture was allowed to warm to room temperature over 15 min and was then stirred for an additional 3 h. The mixture was quenched with water (4 mL) and extracted with hexane (3 × 4 mL); the combined organic phases were filtered through Na_2SO_4 and concentrated under reduced pressure, and the crude product was subjected to flash chromatography on silica gel eluting with hexane/ethyl acetate, 2/1 (R_f 0.25, hexane/ethyl acetate, 2/1). Further purification was performed by preparative HPLC. Column (21 × 250 mm, 5 μm), flow rate 10 mL min^{-1}, mobile phase: isocratic, ethyl acetate/hexane, 60% ethyl acetate; retention time 7.95 min. Yield 50 mg (28%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.71 (t, 2H, J = 6.8 Hz), 3.64−3.49 (m, 6H), 2.07−1.82 (m, 8H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 157.4 (m), 156.7 (m), 146.7 (dd, J = 267.5, 47.5 Hz), 141.4 (m), 110.7 (m), 48.1, 47.1 (m), 46.8 (m), 46.3, 26.6, 26.00, 24.1, 23.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −118.0 (m, 2F), −119.6 (dtd, 2F, J = 18.5, 12.2, 6.6 Hz), −148.5 (dtt, J = 137.3, 23.3, 6.6 Hz), −160.7 (dtt, J = 137.3, 12.2, 5.8 Hz). HRMS (ESI): calcd for $C_{14}H_{17}F_6N_2O_2$ (M + H) 359.1189; found 359.1184.

*4-(Dimethylamino)-2,2,3,3-tetrafluoro-4-phenyl-1-(pyrrolidin-1-yl)butan-1-one (**7b**).* MeOTf (94 mg, 0.58 mmol) was added to a solution of *N*-(phenylmethylene)methanamine (0.5 mmol, 1 equiv) in dichloromethane (mL) at 0 °C, and the mixture was stirred for 30 min. Dichloromethane was evaporated under vacuum, and the reaction vessel was filled with argon followed by the addition of DMSO (0.5 mL) and silane **1b** (271 mg, 1 mmol). The mixture was cooled to −10 °C, and dry KF (58 mg, 1 mmol) was added. The reaction mixture was slowly warmed to room temperature over 15 min, and the solution was stirred for 45 min at room temperature. The mixture was filtered through a short silica gel pad and washed with small amount of ethyl acetate; the solvent was evaporated under vacuum, and the residue was purified by flash chromatography on silica gel. Yield 95 mg (57%).Yellow crystals. Mp 72−73 °C. R_f 0.29 (hexane/EtOAc, 2/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41−7.29 (m, 5H), 4.38 (dd, 1H, J_{H-F} = 25.2 Hz, J = 8.6 Hz), 3.78−3.60 (m, 2H), 3.55 (t, 2H, J = 6.9 Hz), 2.20 (s, 6H), 2.03−1.78 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 159.2 (t, J = 26.9 Hz), 131.0 (d, J = 2.1 Hz), 129.4, 128.5, 128.1, 118.7 (dddd, J = 262.7, 260.5, 27.5, 25.2 Hz), 111.4 (dddd, J = 261.6, 268.5, 32.1, 28.7 Hz), 67.9 (dd, J = 27.3, 18.4 Hz), 48.1, 46.9 (m), 42.6 (m), 26.8, 23.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −110.7 (d, 1F, J = 267.8 Hz), −114.7 (dd, 1F, J = 273.5, 6.6 Hz), −117.39 (d, 1F, J = 273.5 Hz), −119.8 (ddd, 1F, J = 267.8, 25.2, 5.9 Hz). HRMS (ESI): calcd for $C_{16}H_{20}F_4N_2NaO$ (M + Na) 355.1404; found 355.1406.

*4-Methyl-N-(2,2,3,3-tetrafluoro-4-oxo-1-phenyl-4-[pyrrolidin-1-yl)butyl]benzenesulfonamide (**11**).* KF (58 mg, 1 mmol) was added to a mixture of *N*-tosylimine (130 mg, 0.5 mmol), silane **1b** (203 mg, 0.75 mmol), and dimethylformamide (0.25 mL) at −10 °C. The reaction mixture was slowly warmed to room temperature over 15 min, and the solution was stirred for 45 min at room temperature. The mixture was treated with $Bu_4NF{\cdot}3H_2O$ (316 mg, 1 mmol) and stirred at room temperature for 10 min. The mixture was filtered through a short silica gel pad and washed with a small amount of ethyl acetate; the solvent was evaporated under vacuum, and the residue was purified by flash chromatography on silica gel. Yield 151 mg (66%). Colorless crystals. Mp 201−202 °C. R_f 0.19 (hexane/EtOAc, 1/1). ^{1}H NMR (300 MHz, acetone-d_6) δ: 7.62 (d, 1H, J = 10.6 Hz), 7.48 (d, 2H, J = 8.3 Hz), 7.34−7.07 (m, 7H), 5.61−5.45 (m, 1H), 3.71−3.60 (m, 2H), 2.73 (t, 2H, J = 6.6 Hz), 2.30 (s, 3H), 2.03−1.84 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, acetone-d_6) δ: 158.8 (t, J = 26.3 Hz), 143.7, 139.4, 134.0, 129.9, 129.8, 129.2, 128.9, 127.7, 116.9 (m), 111.9 (m), 59.3 (ddd, J = 27.2, 21.4, 5.9 Hz), 48.7, 47.3 (t, J = 6.7 Hz), 27.0, 23.7, 21.3. ^{19}F NMR (282 MHz, acetone-d_6) δ: −114.1 (d, 1F, J = 287.1 Hz), −115.2 (d, 1F, J = 287.1 Hz), −116.8 (d, 1F, J = 267.8 Hz), −121.3 (dd, 1F, J = 267.8, 17.9 Hz). HRMS (ESI): calcd for $C_{21}H_{23}F_4N_2O_3S$ (M + H) 459.1360; found 459.1367.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01739.

Copies of NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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