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POLYFLUOROALKYLATION OF CARBONYL COMPOUNDS BY POLYFLUOROALKYL ANIONS GENERATED FROM POLYFLUOROCARBOXAMIDES

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Abstract Polyfluoroalkyl anions, generated by reduction of (polyfluoroalkanoyl)piperidines with Et_3BHK, were used for the polyfluoroalkylation of carbonyl compounds. Trifluoromethylation of aromatic aldehydes proceeded in good yields, and that of aliphatic aldehydes afforded a moderate yield. In contrast, the yield was low when the reaction involved benzophenone. Pentafluoroethylation and octafluorobutylation of aldehydes were also carried out by using the corresponding (polyfluoroalkanoyl)piperidines, which were prepared from commercially available polyfluorocompounds. The (polyfluoroalkanoyl)piperidines were also prepared through polyfluorination, and were used in the polyfluoroalkylation of aldehydes.

INTRODUCTION

Nucleophilic trifluoromethylation of carbonyl compounds has been widely performed to introduce a trifluoromethyl group into the substrate.[1] The trifluoromethyl anion is unstable. Therefore, it is generated from the precursor in the presence of an electrophile such as a carbonyl compound. Although a number of various trifluoromethyl compounds have been used as precursors, trifluoromethyltrimethylsilane has been most frequently used and is well-studied.[1c,1d,2]

Recently, trifluoroacetaldehyde hemiaminals (**1**) have attracted much attention as an accessible trifluoromethyl source, because they can be prepared from economical materials such as fluoroform[1j,3] and trifluoroacetaldehyde hemiacetal.[1j,4] They are converted to their metal salts (**2**) to generate the trifluoromethyl anion.[5] We can obtain **2** by the reduction of trifluoroacetamide (**3**).[6] Moreover, various (polyfluoroalkanoyl)amides are obtainable from either commercially available

polyfluorocompounds or through polyfluorination reactions, and they can be used as a source for polyfluoroalkyl anions (Scheme 1).
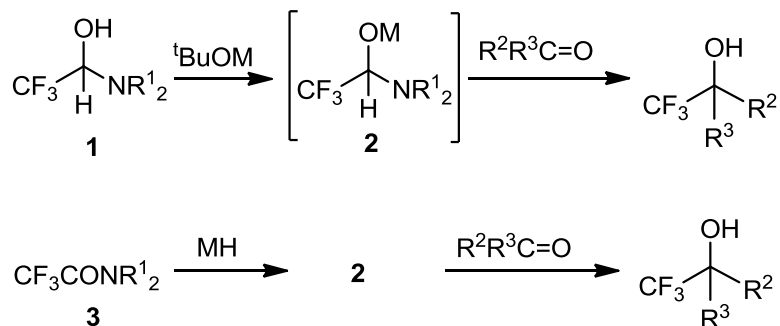
Scheme 1

RESULTS AND DISCUSSION

Trifluoromethylation of benzaldehyde was carried out using N-(trifluoroacetyl)piperidine, N-(trifluoroacetyl)pyrrolidine, and N,N-diethyl trifluoroacetamide as trifluoromethyl anion sources, and potassium triethylborohydride, DIBAH and potassium triisopropoxyborohydride as reducing reagents under various conditions (Table 1). A reducing reagent and benzaldehyde were successively added to the amide in THF at -78 °C (Entries 1−5) or at room temperature (Entry 6), and the resulting mixture was stirred for 24 h at 50 °C. Maintaining an interval between each addition of the reagents did not improve the results. The expected trifluoromethylated product (**2a**) was formed, only when N-(trifluoroacetyl)piperidine or N-(trifluoroacetyl)pyrrolidine was treated with potassium triethylborohydride (Entries 1, 4, and 6). The best yield was obtained by adding potassium triethylborohydride and benzaldehyde to N-(trifluoroacetyl)piperidine at room temperature (Entry 6).

Table 1. Trifluoromethylation of benzaldehyde under various conditions[a]

$$CF_3-C(=O)-NR^1_2 \xrightarrow[\text{2) PhCHO}]{\text{1) MH}} CF_3-CH(OH)-Ph$$

Entry	NR$_2$	MH	Yield (%)[b]
1	N⟨piperidine⟩	KBEt$_3$H	57
2	N⟨piperidine⟩	DIBAH	0
3	N⟨piperidine⟩	KB(OPr-i)$_3$	0
4	N⟨pyrrolidine⟩	KBEt$_3$H	47
5	NEt$_2$	KBEt$_3$H	0
6	N⟨piperidine⟩	KBEt$_3$H	99[c]

a. If otherwise not mentioned, 2 eq of the amide and MH to benzaldehyde
were used. The reagents were added at -78 °C, and the mixture was
stirred at 50 °C for 24h. b. ^{19}F NMR yield based on benzaldehyde.
c. The reagents were added at room temperature.

The present trifluoromethylation reaction was applied to various carbonyl compounds. In the reaction with aromatic aldehydes and cinnamaldehyde, the corresponding trifluoromethylated products were obtained in good yield (Entries 1-5 in Table 2). From adamantane-1-carbaldehyde that has no α-proton, the trifluoromethylated product was obtained in 60% yield (Entry 6). In contrast, the reaction with cyclohexanecarbaldehyde that has α-proton, afforded an aldol reaction product as the main product. However, when the reaction was carried out in CH$_2$Cl$_2$ instead of THF, the trifluoromethylated product was obtained in 45% yield (Entry 7). In the reaction with benzophenone, most of the starting material remained unchanged (Entry 8).

Table 2. Trifluoromethylation of carbonyl compounds[a]

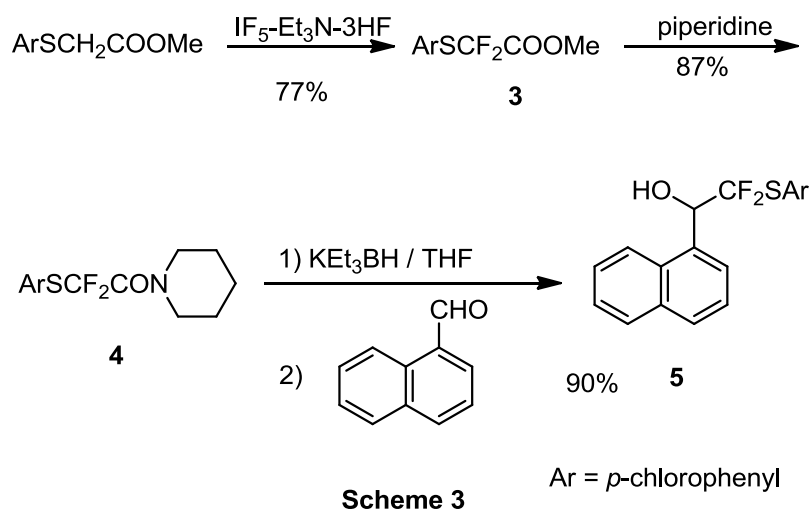| Entry	Carbonyl compound	Product	Yield (%)[b]
1	PhCHO	**2a**	(99)
2	Br—C₆H₄—CHO	**2b**	83
3	Ph—CH=CH—CHO	**2c**	84
4	naphthalene-1-CHO	**2d**	89
5	furan-2-CHO	**2e**	(81)
6	adamantyl-CHO	**2f**	60
7	cyclohexyl-CHO	**2g**	45[c]
8	Ph₂C=O	**2h**	14

a. If otherwise not mentioned, the reaction was carried out in THF using 2 eq of KBEt₃H and amide to carbonyl compound. The reagents were mixed at room temperature and stirred at 50 °C for 24 h. b. Isolated yield base on carbonyl compound used. In parentheses, ^{19}FNMR yield. c. CH₂Cl₂ was used as solvent.

As various (polyfluoroalkanoyl)piperidines are obtainable from commercially available polyfluorocompounds, the present method is applicable to the various polyfluoroalkylation of carbonyl compounds. For example, *N*-(pentafluoropropanoyl)piperidine (**1b**) was prepared from methyl pentafluoropropionate[7] and was used for the pentafluoroethylation of 1-naphthaldehyde. The reaction proceeded similar to trifluoromethylation, and the pentafluoroethylated product (**2i**) was obtained in high yield. *N*-(2,2,3,3,4,4,5,5-Octafluoropetanoyl)piperidine (**1c**) was prepared from commercially available 2,2,3,3,4,4,5,5-octafluoropentanol in three steps[7-9] and was used in the reaction with 1-naphthaldehyde. The reaction of **1c** with aldehyde was sluggish and the octafluorobutylated product **2j** was formed in poor yield under the trifluoromethylation conditions. However, **2j** was obtained in 61% yield by carrying the reaction at 40 °C for 24h using 4 equivalents of **1c** and KBEt₃H to 1-naphthaldehyde without solvent (Scheme 2).
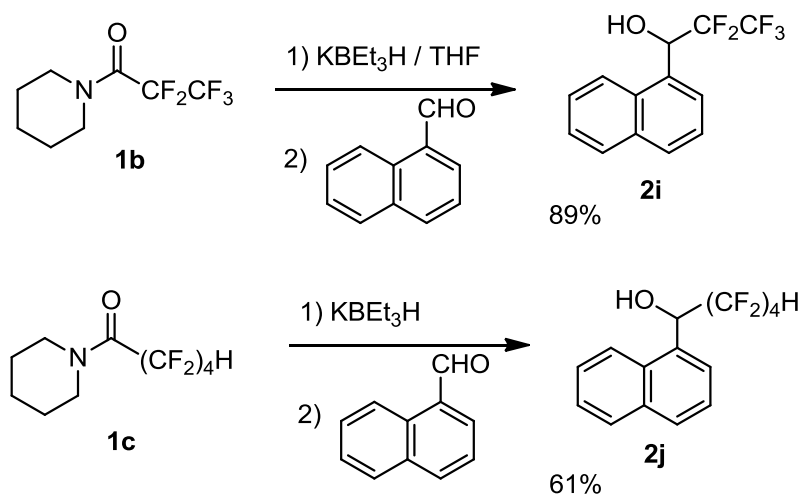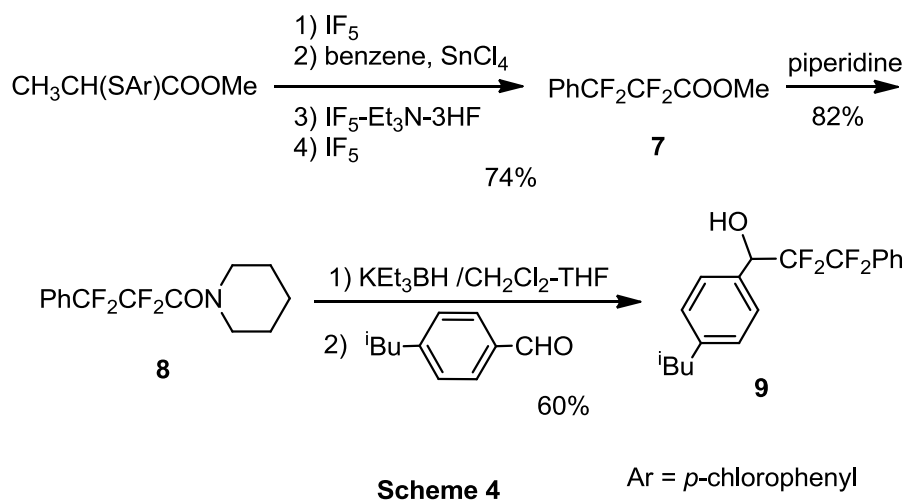

Scheme 2

(Polyfluoroalkanoyl)piperidines can be also prepared through polyfluorination reactions. For example, methyl 2-(arylsulfanyl)-2,2-difluoroacetate (**3**) was prepared by difluorination of methyl 2-(arylsulfanyl)acetate using IF₅-Et₃N-3HF,[10] and then converted to *N*-2-(arylsulfanyl)-2,2-difluoroacetylpiperidine (**4**).[7] The reaction of **4** with an aldehyde was performed as in the case of **2a**, and the (arylsulfanyl)difluoromethylated product (**5**) was obtained in high yield (Scheme 3).

ArSCH$_2$COOMe $\xrightarrow[\text{77\%}]{\text{IF}_5\text{-Et}_3\text{N-3HF}}$ ArSCF$_2$COOMe $\xrightarrow[\text{87\%}]{\text{piperidine}}$

3

ArSCF$_2$CON$\bigcirc$ $\xrightarrow[\text{2)}]{\text{1) KEt}_3\text{BH / THF}}$

4

2) (naphthalene-CHO)

90%   **5**

HO—CH—CF$_2$SAr (on naphthalene)

Ar = p-chlorophenyl

Scheme 3

Methyl 2,2,3,3-tetrafluoro-3-phenylpropionate (**7**) was prepared from methyl 2-(arylsulfanyl)propionate in 74% yield by using our recently developed method,[11] and the resulting **7** was converted to the amide (**8**).[7] Although the reaction of **8** with aldehyde was sluggish, the expected polyfluoroalkylated product (**9**) was obtained in 60% yield by performing the reaction at 40 °C for 24 h using 4 equivalents of **8** and KEt$_3$BH to the aldehyde (Scheme 4).

CH$_3$CH(SAr)COOMe $\xrightarrow[\substack{\text{3) IF}_5\text{-Et}_3\text{N-3HF} \\ \text{4) IF}_5 \\ \text{74\%}}]{\substack{\text{1) IF}_5 \\ \text{2) benzene, SnCl}_4}}$ PhCF$_2$CF$_2$COOMe $\xrightarrow[\text{82\%}]{\text{piperidine}}$

7

PhCF$_2$CF$_2$CON$\bigcirc$ $\xrightarrow[\text{2) }^i\text{Bu}—\bigcirc—\text{CHO}]{\text{1) KEt}_3\text{BH /CH}_2\text{Cl}_2\text{-THF}}$

8

60%

HO—CH—CF$_2$CF$_2$Ph (on ^{i}Bu-phenyl)

9

Ar = p-chlorophenyl

Scheme 4

EXPERIMENTAL

4.1. General

The melting points were measured with a Yanagimoto micro melting-point apparatus.   The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) spectra, ^{19}F NMR (376 MHz) spectra, and ^{13}C NMR (100 MHz) were recorded in CDCl$_3$ on a JEOL JNM-A400II FT NMR and the chemical

shift, δ, is referred to TMS (^{1}H, ^{13}C) and CFCl$_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. KBEt$_3$H (1.0 M in THF) was purchased from Aldrich Chemica and KB(OPr^i)$_3$H was prepared from B(OPr^i)$_3$ and KH according to the literature.[12] IF$_5$ in a stainless-steel cylinder was supplied by Asahi Glass Co., Ltd. IF$_5$ was transferred through a Teflon™ tube into a Teflon™FEP bottle from the cylinder under an N$_2$ atmosphere. IF$_5$ was transferred quickly from the bottle to the reaction vessel made of Teflon ™ FEP in open air. IF$_5$ decomposes in air emitting HF fume, and, therefore, it should be carefully handled in a bench hood with rubber-gloved hands.[11] 2,2,3,3,4,4,5,5-Octafluoropentanol was donated from Daikin Industries, Ltd.

4.2. Preparation of *N*-(polyfluoroalkanoyl)piperidine

N-(Polyfluoroalkanoyl)piperidines were prepared from the corresponding ethyl or methyl polyfluoroalkanoate with piperidine according to the literature.[7]

4.2.1. *N*-(Trifluoroacetyl)piperidine (1a)

IR (neat) 2945, 1691, 1193, 1128 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 1.65-1.71 (6H, m), 3.54-3.63 (4H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 23.8, 25.1, 26.0, 44.2, 46.5 (t, $^4J_{C\text{-}F}$ = 3.5 Hz), 116.4 (t, $^1J_{C\text{-}F}$ = 287.8 Hz), 154.9 (t, $^2J_{C\text{-}F}$ = 35.3 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -69.49 (3F, s) (lit.[13] -68.02).

4.2.2. *N*-(2,2,3,3,3-Pentafluoropropanoyl)piperidine (1b)

IR (neat) 2947, 1684, 1175 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 1.64-1.71 (6H, m), 3.61 (4H, brs). ^{13}C NMR (100MHz, CDCl$_3$) δ 23.7, 25.0, 26.0, 44.0, 46.2, 108.3 (tq, $^1J_{C\text{-}F}$ = 270.6 Hz, $^2J_{C\text{-}F}$ = 36.0 Hz), 117.9 (tq, $^2J_{C\text{-}F}$ = 34.4 Hz, $^1J_{C\text{-}F}$ = 285.6 Hz), 155.6 (t, $^2J_{C\text{-}F}$ = 24.8 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -82.77 (3F, s), -115.44 (2F, s). HRMS (EI) calcd for C$_8$H$_{10}$F$_5$NO (M$^+$) 231.06825, found 231.06888.

4.2.3. *N*-(2,2,3,3,4,4,5,5-Octafluoropentanoyl)piperidine (1c)

Ethyl 2,2,3,3,4,4,5,5-octafluoropentanoate was prepared from 2,2,3,3,4,4,5,5-octafluoropentanol according to the literature,[8,9] and then converted to **1c** according to the literature.[7]

IR (neat) 2950, 1682, 1450, 1166 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 1.65-1.71 (6H, m), 3.61-3.63 (4H, m), 6.33 (1H, tt, J = 52.3, 5.7 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 23.7, 25.1, 26.0, 44.5, 46.5 (t, $^4J_{C\text{-}F}$ = 6.3 Hz), 105.0-114.1 (4C, m), 156.3 (t, $^2J_{C\text{-}F}$ = 24.6 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -112.13 (2F, t, J = 9.0 Hz), -124.50 to -124.56 (2F, m), -129.02 to -129.12 (2F, m), -138.17 (2F, dm, J = 52.0 Hz). HRMS (EI) calcd for C$_{10}$H$_{11}$F$_8$NO (M$^+$) 313.07129, found 313.07058.

4.2.4. *N*-2-{(4-Chlorophenyl)sulfanyl}-2,2-difluoroacetylpiperidine (4)

Methyl 2-{(4-chlorophenyl)sulfanyl}-2,2-difluoroacetate (**3**) was prepared from methyl 2-{(4-Chlorophenyl)sulfanyl}acetate according to the literature,[10] and converted to **4** according to the literature.[7] White solid. Mp 77-79 °C. IR (KBr) 2935, 1671, 1038 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 1.62-1.69 (6H, m), 3.60-3.64 (4H, m), 7.37 (2H, d, J = 8.3 Hz), 7.56 (2H, d, J = 8.3 Hz). ^{13}C NMR

(100MHz, CDCl$_3$) δ 24.2, 25.5, 26.3, 44.8, 47.0 (t, $^4J_{C\text{-}F}$ = 5.0 Hz), 124.2, 124.6 (t, $^1J_{C\text{-}F}$ = 291.4 Hz), 129.2 (2C), 136.8, 137.9 (2C), 159.2 (t, $^2J_{C\text{-}F}$ = 26.2 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -73.52 (2F, s). HRMS (EI) calcd for C$_{13}$H$_{14}$Cl F$_2$NOS (M$^+$) 305.04494, found 305.04527.

4.2.5. *N*-(2,2,3,3-Tetrafluoro-3-phenylpopanoyl)piperidine (8)

Methyl 3-phenyl-2,2,3,3-tetrafluoropropionate (**7**) was prepared from methyl 2-{(4-chlorophenyl)sulfanyl}propionate in three steps according to the literature,[11] and converted to **8** by the reaction with piperidine.[7] IR (neat) 2941, 1675, 1452, 1294, 1120 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 1.63-1.68 (6H, m), 3.59-3.64 (4H, m), 7.45-7.52 (3H, m), 7.62 (2H, d, *J* = 7.5 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 24.2, 25.5, 26.4, 44.8, 46.9-47.1 (m), 111.6 (tt, $^1J_{C\text{-}F}$ = 264.6 Hz, $^2J_{C\text{-}F}$ = 37.4 Hz), 116.1 (tt, $^1J_{C\text{-}F}$ = 253.5 Hz, $^2J_{C\text{-}F}$ = 31.5 Hz) , 126.8 (tt, $^3J_{C\text{-}F}$ = 6.5 Hz, $^4J_{C\text{-}F}$ = 1.5 Hz), 128.1 (2C), 130.3 (t, $^2J_{C\text{-}F}$ = 24.3 Hz), 131.1 (2C, t, $^4J_{C\text{-}F}$ = 1.7 Hz), 157.7 (t, $^2J_{C\text{-}F}$ =26.0 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -110.91 (2F, s), -111.62 (2F, s). HRMS (EI) calcd for C$_{14}$H$_{15}$F$_4$NO (M$^+$) 289.10898, found 289.10820.

4.3. Perfluoroalkylation of carbonyl compounds

4,3,1. 2,2,2-Trifluoro-1-phenylethanol (2a)

To a THF solution (3 mL) of **1a** (181 mg, 1 mmol) were added a 1.0 M THF solution of Et$_3$BHK (1 mL, 1 mmol) and benzaldehyde (53 mg, 0.5 mmol) successively at room temperature under N$_2$ atmosphere. The mixture was stirred at 50 °C for 24 h and then 30% aqueous H$_2$O$_2$ (2 mL) was added at 0 °C. After stirring for 1 h, the mixture was extracted with ether (30 mL X 3). The combined organic phase was dried over MgSO$_4$ and the yield of **2a** was determined by ^{19}F NMR using fluorobenzene as internal standard (99%). Pure **2a** was obtained by column chromatography (silica gel/CH$_2$Cl$_2$:hexane = 4:1). IR (neat) 3397, 1267, 1127 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 5.01-5.06 (1H, m), 7.41-7.49 (5H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 72.8 (q, $^2J_{C\text{-}F}$ = 31.9 Hz), 124.3 (q, $^1J_{C\text{-}F}$ = 282.3 Hz), 127.4, 128.6 (2C), 129.6 (2C), 133.9 (q, $^3J_{C\text{-}F}$ = 0.9 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -78.99 (3F, d, *J* = 7.1 Hz) {lit.[14] -78.77 (d, *J* = 7.6 Hz)}.

4,2,2. 1-(4-Bromophenyl)-2,2,2-trifluoroethanol (2b)

IR (neat) 3397, 1492, 1268, 1173, 1130 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 4.98-5.03 (1H, m), 7.35-7.44 (2H, m), 7.54-7.56 (2H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 72.2 (q, $^2J_{C\text{-}F}$ = 32.2 Hz), 123.8, 123.9 (q, $^1J_{C\text{-}F}$ = 282.1 Hz), 129.0 (2C), 131.8 (2C), 132.7. ^{19}F NMR (373MHz, CDCl$_3$) δ -79.15 (3F, d, *J* = 7.1 Hz) {lit.[14] -78.94 (d, *J* = 6.8 Hz)}.

4,2,3. (*E*)-1,1,1-Trifluoro-4-phenylbut-3-en-2-ol (2c)

White solid. Mp 42-43 °C (lit.[15] 42-43 °C). IR (KBr) 3315, 2924, 1453, 1371 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 4.61-4.68 (1H, m), 6.21 (1H, dd, *J* = 15.9, 6.5 Hz), 6.86 (1H, d, *J* = 15.9 Hz), 7.29-7.44 (5H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 71.6 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 120.5 (q, *J* = 1.9 Hz), 124.2 (q, *J* = 281.8 Hz),

126.9 (2C), 128.7 (2C), 128.8, 135.3, 136.4. ^{19}F NMR (373MHz, CDCl$_3$) δ -79.70 (3F, d, J = 7.2 Hz) {lit.[15] -79.7 (d, J = 6.4 Hz)}.

4,2,4. 2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanol (2d)

IR (neat) 3399, 2941, 1265, 1168, 1126 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 2.69 (1H, d, J = 4.5 Hz), 5.88-5.94 (1H, m), 7.51-7.60 (3H, m), 7.84 (1H, d, J = 7.3 Hz), 7.90-7.93 (2H, m), 8.08 (1H, d, J = 8.4 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 68.8 (q, $^2J_{C\text{-}F}$ = 32.2 Hz), 122.7 (q, $^4J_{C\text{-}F}$ = 0.9 Hz), 124.6 (q, $^1J_{C\text{-}F}$ = 282.5 Hz), 125.1, 125.7 (q, $^3J_{C\text{-}F}$ = 1.2 Hz), 125.9, 126.8, 129.0, 129.8 130.1, 131.0, 133.6. ^{19}F NMR (373MHz, CDCl$_3$) δ -77.48 (3F, d, J = 7.2 Hz) {lit.[14] -77.25 (d, J = 6.5 Hz)}.

4,2,5. 2,2,2-Trifluoro-1-(furan-2-yl)ethanol (2e)

IR (neat) 3399, 1669, 1504, 1152 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 2.59 (1H, d, J = 7.2 Hz), 5.03-5.10 (1H, m), 6.53-6.44 (1H, m), 6.54 (1H, d, J = 3.2 Hz), 7.47-7.48 (1H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 67.1 (q, $^2J_{C\text{-}F}$ = 34.3 Hz), 110.1 (q, $^4J_{C\text{-}F}$ = 0.9 Hz), 110.7, 123.4 (q, $^1J_{C\text{-}F}$ = 282.1 Hz), 143.6, 147.1 (q, $^3J_{C\text{-}F}$ = 1.6 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -78.59 (3F, d, J = 7.2 Hz) {lit.[3c] -78.42 (d, J = 6.4 Hz)}.

4,2,6. 1-(1-Adamantan-1-yl)-2,2,2-trifluoroethanol (2f)

Yellow solid. Mp 47-49 °C. IR (KBr) 3422, 2907, 2851, 1263, 1167, 1120 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 1.68-1.79 (11H, m), 2.02 (3H, brs), 3.44 (1H, q, J = 8.3 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 28.0 (3C), 35.7 (3C), 36.7 (3C), 37.6 (q, $^4J_{C\text{-}F}$ = 1.8 Hz), 77.5 (q, $^2J_{C\text{-}F}$ = 27.9 Hz), 125.6 (q, $^1J_{C\text{-}F}$ = 285.1 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -71.55 (3F, d, J = 8.8 Hz). HRMS (EI) calcd for C$_{12}$H$_{16}$ F$_3$O (M$^+$) 233.11587, found 233.11668.

4,2,7. 1-Cyclohexyl-2,2,2-trifluoroethanol (2g)

IR (neat) 3399, 3055, 1476, 1162, 1060 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 1.10-1.34 (5H, m), 1.67-2.02 (6H, m), 3.68-3.77 (1H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 25.7, 25.9, 26.0, 26.7 (q, $^4J_{C\text{-}F}$ = 1.0 Hz), 29.2 (q, $^3J_{C\text{-}F}$ = 1.2 Hz), 38.1 (q, $^4J_{C\text{-}F}$ = 1.0 Hz), 74.3 (q, $^2J_{C\text{-}F}$ = 29.1 Hz), 125.3 (q, $^1J_{C\text{-}F}$ = 283.3 Hz). ^{19}F NMR (373MHz, CDCl$_3$) δ -76.2 (3F, d, J = 7.1 Hz) {lit.[3c] -75.98 (d, J = 7.5 Hz)}.

4,2,8. 2,2,2-Trifluoro-1,1-diphenylethanol (2h)

IR (neat) 3456, 3063, 1714, 1155 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 7.34-7.38 (6H, m), 7.48-7.50 (4H, m). ^{13}C NMR (100MHz, CDCl$_3$) δ 79.36 (q, $^2J_{C\text{-}F}$ = 28.4 Hz), 125.3 (q, $^1J_{C\text{-}F}$ = 286.1 Hz), 127.4 (2C, q, $^3J_{C\text{-}F}$ = 1.4 Hz), 128.2 (4C), 128.6 (4C), 139.4 (2C). ^{19}F NMR (373MHz, CDCl$_3$) δ -74.91 (3F, s) (lit.[16] -74.21).

4,2,9. 2,2,3,3,3-Pentafluoro-1-(naphthalen-1-yl)propan-1-ol (2i)

The reaction was carried out as in the case of **2a** using **1b** and 1-naphthaldehyde instead of **1a** and benzaldehyde, and **2i** was isolated by column chromatography (silica gel, hexane:CH$_2$Cl$_2$=4:1) in 89% yield. White solid. Mp 44-46 °C. IR (KBr) 3465, 3060, 1185, 1135, 1028 cm^{-1}. ^{1}H NMR (400MHz,

CDCl$_3$) δ 2.49 (1H, d, J = 4.1 Hz), 6.06 (1H, dt, J = 18.3, 4.5 Hz), 7.52-7.61 (3H, m), 7.84 (1H, d, J = 7.2 Hz), 7.90-7.95 (2H, m), 8.03 (1H, d, J = 8.3 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 67.4 (dd, $^2J_{C\text{-}F}$ = 26.3 Hz, $^2J_{C\text{-}F}$ = 21.9 Hz), 113.3 (ddq, $^1J_{C\text{-}F}$ = 262.2 Hz, $^1J_{C\text{-}F}$ = 254.8Hz, $^2J_{C\text{-}F}$ = 35.7 Hz), 119.3 (ddq, $^2J_{C\text{-}F}$ = 36.7 Hz, $^2J_{C\text{-}F}$ = 35.1 Hz, $^1J_{C\text{-}F}$ = 287.1 Hz), 122.6 (dd, $^3J_{C\text{-}F}$ = 2.4 Hz, $^3J_{C\text{-}F}$ = 1.4 Hz), 125.1, 125.9, 126.4, 126.8, 129.0, 130.0, 130.2, 131.2, 133.6. ^{19}F NMR (373MHz, CDCl$_3$) δ -82.19 (3F, s), -120.22 (1F, d, J = 277.6 Hz), -130.51 (1F, dd, J = 276.7, 17.9 Hz){ lit.[17] -81.54 (m, 3F)}, -118.15 (dd, J = 290.4, 20.7 Hz, 1F), -130.24 (dd, J = 290.4, 20.7 Hz, 1F).

4,2,9. 2,2,3,3,4,4,5,5-Octafluoro-1-(naphthalen-1-yl)pentan-1-ol (2j)

To **1c** (626 mg, 2 mmol) were added a 1.0 M THF solution of Et$_3$BHK (2 mL, 2 mmol) and 1-naphthaldehyde (78 mg, 0.5 mmol) successively at room temperature under N$_2$ atmosphere. Then a volatile part was removed under reduced pressure, and the resulting viscous mixture was stirred at 40 °C for 24 h. Then, 30% aqueous H$_2$O$_2$ (2 mL) was added at 0 °C, and after stirring for 1 h, the mixture was extracted with ether (30 mL X 3). The combined organic phase was dried over MgSO$_4$ and **2j** was isolated by column chromatography (silica gel/CH$_2$Cl$_2$:hexane = 1:4) in 61% yield. White solid. Mp 75-77 °C. IR (KBr) 3398, 1175, 1124, 1041 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 2.57 (1H, s), 6.11 (1H, tt, J =52.1, 5.5 Hz), 7.51-7.60 (3H, m), 7.84 (1H, d, J = 7.3 Hz), 7.90-7.94 (2H, m), 8.00 (1H, d, J = 8.4 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 67.3 (dd, $^2J_{C\text{-}F}$ = 21.8 Hz, $^2J_{C\text{-}F}$ = 30.5 Hz), 104.8-118.3 (4C, m), 122.6, 125.1, 125.9, 126.5, 126.9, 129.0, 130.1, 130.2, 131.3, 133.5. ^{19}F NMR (373MHz, CDCl$_3$) δ -116.37 (1F, d, J = 286.6 Hz), -123.50 to -125.38 (2F, m), -127.40 (1F, d, J = 284.8 Hz), -129.7 to -131.90 (2F, m), -136.94 to -138.82 (2F, m). HRMS (ESI) calcd for C$_{15}$H$_9$C F$_8$O (M$^+$) 357.05311, found 357.05331.

4,2,10. 2-{(4-Chlorophenyl)sulfanyl}-2,2-difluoro-1-(naphthalen-1-yl)ethanol (5)

The reaction was carried out as in the case of **2i** using **4** instead of **1b**, and **5** was isolated in 90% yield by column chromatography (silica gel, hexane:CH$_2$Cl$_2$=4:1). Oil. IR (neat) 3434, 2931, 2857, 1276, 1166 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 5.89-5.94 (1H, m), 7.26-7.33 (2H, m), 7.48-7.57 (5H, m), 7.88-7.91 (3H, m), 8.01 (1H, d, J = 8.1 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 72.0 (dd, $^2J_{C\text{-}F}$ = 27.9 Hz, $^2J_{C\text{-}F}$ = 26.2 Hz), 123.1, 124.2, 125.1, 125.7, 126.1, 126.5, 128.9, 129.2 (2C), 129.2 (t, $^1J_{C\text{-}F}$ = 286.5 Hz), 129.9 (2C), 131.2, 131.3, 133.6, 136.5, 137.6. ^{19}F NMR (373MHz, CDCl$_3$) δ -79.76 (1F, dd, J = 207.8, 7.2 Hz), -83.60 (1F, dd, J = 207.8, 8.8 Hz). HRMS (ESI) calcd for C$_{18}$H$_{13}$Cl$_2$ F$_2$OS (M$^+$+Cl) 385.00322, found 385.00203

4,2,11. 2,2,3,3-Tetrafluoro-1-(4-isobutylphenyl)-3-phenylpropan-1-ol (9)

To a CH$_2$Cl$_2$ solution (1 mL) of **8** (578 mg, 2 mmol) were added a 1.0 M THF solution of Et$_3$BHK (2 mL, 2 mmol) and 4-Isobutylbenzaldehyde (81 mg, 0.5 mmol) successively at room temperature under N$_2$ atmosphere. The mixture was stirred at 40 °C for 24 h and then 30% aqueous H$_2$O$_2$ (2 mL) was added at

0 °C. After stirring for 1 h, the mixture was extracted with ether (30 mL X 3). The combined organic phase was dried over $MgSO_4$ and **9** was isolated by column chromatography (silica gel/AcOEt:hexane = 1:10) in 60% yield. White solid. Mp 54-55 °C. IR (KBr) 3466, 2960, 1069 cm^{-1}. ^{1}H NMR (400MHz, CDCl$_3$) δ 0.89 (6H, d, J = 6.7 Hz), 1.80-1.91 (1H, m), 2.39 (1H, d, J = 4.7 Hz), 2.47 (1H, d, J = 7.2 Hz), 5.14 (1H, dt, J = 17.3, 5.1 Hz), 7.15 (2H, d, J = 8.1 Hz), 7.34 (2H, d, J = 8.0 Hz), 7.43-7.52 (3H, m), 7.58 (2H, d, J = 7.4 Hz). ^{13}C NMR (100MHz, CDCl$_3$) δ 22.3 (2C), 30.1, 45.1, 72.0 (dd, $^2J_{C\text{-}F}$ = 28.8 Hz, $^2J_{C\text{-}F}$ = 22.4 Hz), 115.4 (tt, $^1J_{C\text{-}F}$ = 260.8 Hz, $^2J_{C\text{-}F}$ = 35.3 Hz), 117.2 (tt, $^1J_{C\text{-}F}$ = 253.0 Hz, $^2J_{C\text{-}F}$ = 34.1 Hz), 126.7 (t, $^3J_{C\text{-}F}$ = 6.7 Hz), 127.8 (2C), 128.2 (2C), 129.1 (2C), 130.9 (2C, t, $^2J_{C\text{-}F}$ = 24.3 Hz), 131.0 (t, $^4J_{C\text{-}F}$ = 1.4 Hz), 132.5, 142.8. ^{19}F NMR (373MHz, CDCl$_3$) δ -109.50 to -110.99 (2F, m), -108.29 (1F, dd, J = 275.5, 6.2 Hz), -108.29 (1F, dd, J = 275.5, 17.6 Hz). HRMS (EI) calcd for $C_{19}H_{19}F_4O$ (M$^+$) 339.13775, found 339.13808.

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