

HETEROCYCLES, Vol. 88, No. 2, 2014, pp. 1201 - 1212. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 4th July, 2013, Accepted, 26th September, 2013, Published online, 4th October, 2013
DOI: 10.3987/COM-13-S(S)84

POLYFLUOROALKYLATION OF CARBONYL COMPOUNDS BY POLYFLUOROALKYL ANIONS GENERATED FROM POLYFLUOROCARBOXAMIDES

Natshumi Wakita and Shoji Hara*

Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

E-mail: shara@eng.hokudai.ac.jp

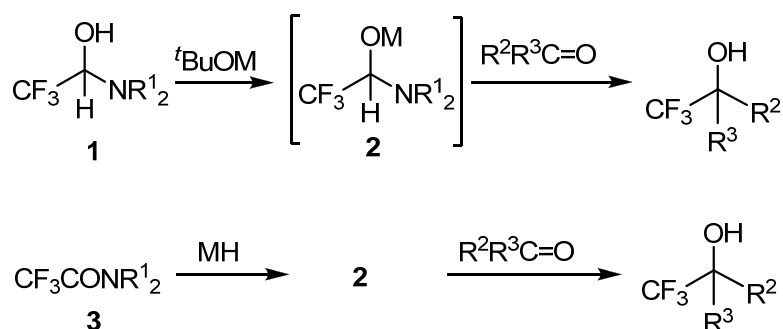
Abstract – Polyfluoroalkyl anions, generated by reduction of (polyfluoroalkanoyl)piperidines with Et_3BHK , were used for the polyfluoroalkylation of carbonyl compounds. Trifluoromethylation of aromatic aldehydes proceeded in good yields, and that of aliphatic aldehydes afforded a moderate yield. In 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}

Dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

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 polyfluoro compounds 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*-diethyltrifluoroacetamide 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 $-78\text{ }^\circ\text{C}$ (Entries 1–5) or at room temperature (Entry 6), and the resulting mixture was stirred for 24 h at $50\text{ }^\circ\text{C}$. 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

Entry	NR ₂	MH	Yield (%) ^b
1		KBEt ₃ H	57
2		DIBAH	0
3		KB(OPr- <i>i</i>) ₃	0
4		KBEt ₃ H	47
5	NEt ₂	KBEt ₃ H	0
6		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 24 h. b. ¹⁹F NMR yield based on benzaldehyde. c. The reagents were added at room temperature.

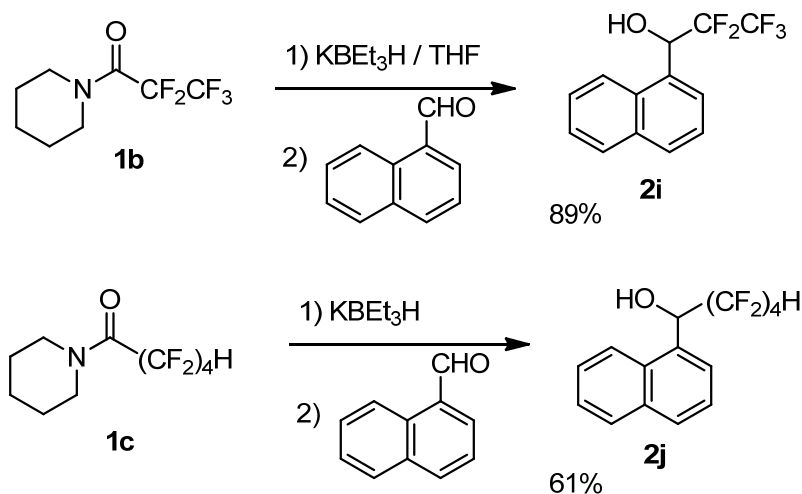
The present trifluoromethylation reaction was applied to various carbonyl compounds. In the reaction with aromatic aldehydes and cinnamaldehyde, the corresponding trifluoromethylated products were obtained in good yield (Entries 1-5 in Table 2). From adamantane-1-carbaldehyde that has no α -proton, the 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 CH₂Cl₂ 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		(99)
2			83
3			84
4			89
5			(81)
6			60
7			45 ^c
8			14

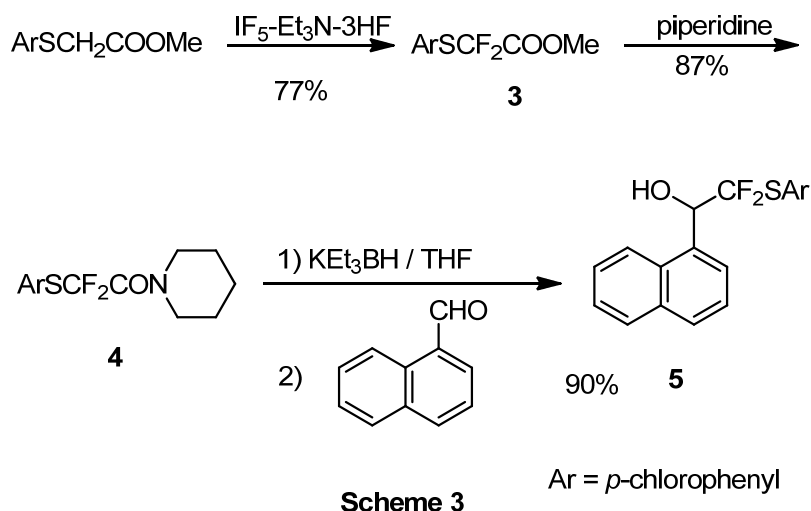
a. If otherwise not mentioned, the reaction was carried out in THF using 2 eq of KBET_3H and amide to carbonyl compound. The reagents were mixed at room temperature and stirred at 50 °C for 24 h. b. Isolated yield base on carbonyl compound used. In parentheses, ^{19}F NMR yield. c. CH_2Cl_2 was used as solvent.

As various (polyfluoroalkanoyl)piperidines are obtainable from commercially available polyfluoro-compounds, the present method is applicable to the various polyfluoroalkylation of carbonyl compounds. For example, *N*-(pentafluoropropanoyl)piperidine (**1b**) was prepared from methyl pentafluoropropionate⁷ 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-Octafluoropentanoyl)piperidine (**1c**) was prepared from commercially available 2,2,3,3,4,4,5,5-octafluoropentanol in three steps⁷⁻⁹ 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 24 h using 4 equivalents of **1c** and KBEt_3H to 1-naphthaldehyde without solvent (Scheme 2).

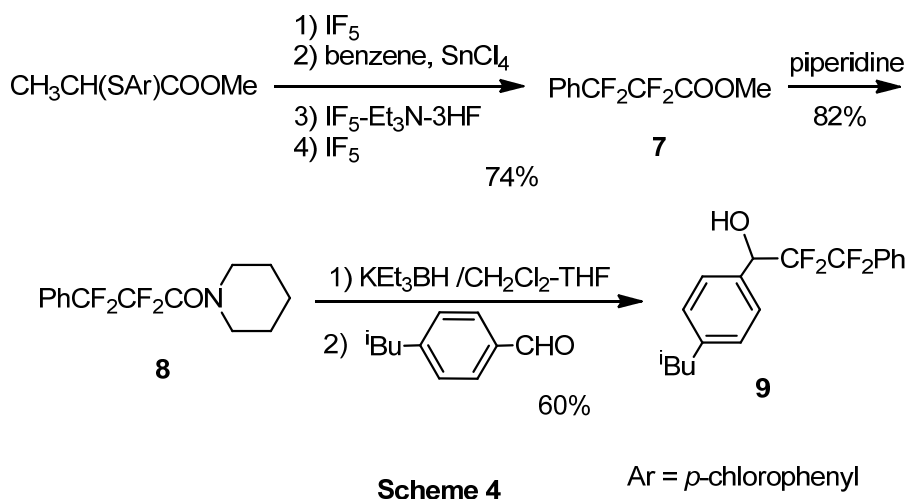


Scheme 2

(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 $\text{IF}_5\text{-Et}_3\text{N}\cdot 3\text{HF}$,¹⁰ and then converted to *N*-2-(arylsulfanyl)-2,2-difluoroacetyl piperidine (**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).



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 KEt₃BH to the aldehyde (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 ¹H NMR (400 MHz) spectra, ¹⁹F NMR (376 MHz) spectra, and ¹³C NMR (100 MHz) were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS (¹H, ¹³C) and CFCl₃ (¹⁹F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. KBEt₃H (1.0 M in THF) was purchased from Aldrich Chemical and

KB(OPr)ⁱ₃H was prepared from B(OPr)ⁱ₃ and KH according to the literature.¹² IF₅ in a stainless-steel cylinder was supplied by Asahi Glass Co., Ltd. IF₅ was transferred through a Teflon™ tube into a Teflon™FEP bottle from the cylinder under an N₂ atmosphere. IF₅ was transferred quickly from the bottle to the reaction vessel made of Teflon™ FEP in open air. IF₅ 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. ¹H NMR (400MHz, CDCl₃) δ 1.65-1.71 (6H, m), 3.54-3.63 (4H, m). ¹³C NMR (100MHz, CDCl₃) δ 23.8, 25.1, 26.0, 44.2, 46.5 (t, ⁴J_{C-F} = 3.5 Hz), 116.4 (t, ¹J_{C-F} = 287.8 Hz), 154.9 (t, ²J_{C-F} = 35.3 Hz). ¹⁹F NMR (373MHz, CDCl₃) 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. ¹H NMR (400MHz, CDCl₃) δ 1.64-1.71 (6H, m), 3.61 (4H, brs). ¹³C NMR (100MHz, CDCl₃) δ 23.7, 25.0, 26.0, 44.0, 46.2, 108.3 (tq, ¹J_{C-F} = 270.6 Hz, ²J_{C-F} = 36.0 Hz), 117.9 (tq, ²J_{C-F} = 34.4 Hz, ¹J_{C-F} = 285.6 Hz), 155.6 (t, ²J_{C-F} = 24.8 Hz). ¹⁹F NMR (373MHz, CDCl₃) δ -82.77 (3F, s), -115.44 (2F, s). HRMS (EI) calcd for C₈H₁₀F₅NO (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. ¹H NMR (400MHz, CDCl₃) δ 1.65-1.71 (6H, m), 3.61-3.63 (4H, m), 6.33 (1H, tt, *J* = 52.3, 5.7 Hz). ¹³C NMR (100MHz, CDCl₃) δ 23.7, 25.1, 26.0, 44.5, 46.5 (t, ⁴J_{C-F} = 6.3 Hz), 105.0-114.1 (4C, m), 156.3 (t, ²J_{C-F} = 24.6 Hz). ¹⁹F NMR (373MHz, CDCl₃) 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 C₁₀H₁₁F₈NO (M⁺) 313.07129, found 313.07058.

4.2.4. *N*-2-{{(4-Chlorophenyl)sulfanyl}-2,2-difluoroacetyl}piperidine (**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. ¹H NMR (400MHz, CDCl₃) 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). ¹³C NMR (100MHz, CDCl₃) δ 24.2, 25.5, 26.3, 44.8, 47.0 (t, ⁴J_{C-F} = 5.0 Hz), 124.2, 124.6 (t, ¹J_{C-F} = 291.4 Hz), 129.2 (2C), 136.8, 137.9 (2C), 159.2 (t, ²J_{C-F} = 26.2 Hz). ¹⁹F NMR (373MHz, CDCl₃) δ -73.52 (2F, s). HRMS (EI)

calcd for C₁₃H₁₄Cl F₂NOS (M⁺) 305.04494, found 305.04527.

4.2.5. *N*-(2,2,3,3-Tetrafluoro-3-phenylpropanoyl)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. ¹H NMR (400MHz, CDCl₃) 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). ¹³C NMR (100MHz, CDCl₃) δ 24.2, 25.5, 26.4, 44.8, 46.9-47.1 (m), 111.6 (tt, ¹*J*_{C-F} = 264.6 Hz, ²*J*_{C-F} = 37.4 Hz), 116.1 (tt, ¹*J*_{C-F} = 253.5 Hz, ²*J*_{C-F} = 31.5 Hz), 126.8 (tt, ³*J*_{C-F} = 6.5 Hz, ⁴*J*_{C-F} = 1.5 Hz), 128.1 (2C), 130.3 (t, ²*J*_{C-F} = 24.3 Hz), 131.1 (2C, t, ⁴*J*_{C-F} = 1.7 Hz), 157.7 (t, ²*J*_{C-F} = 26.0 Hz). ¹⁹F NMR (373MHz, CDCl₃) δ -110.91 (2F, s), -111.62 (2F, s). HRMS (EI) calcd for C₁₄H₁₅F₄NO (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 Et₃BHK (1 mL, 1 mmol) and benzaldehyde (53 mg, 0.5 mmol) successively at room temperature under N₂ atmosphere. The mixture was stirred at 50 °C for 24 h and then 30% aqueous H₂O₂ (2 mL) was added at 0 °C. After stirring for 1 h, the mixture was extracted with Et₂O (30 mL X 3). The combined organic phase was dried over MgSO₄ and the yield of **2a** was determined by ¹⁹F NMR using fluorobenzene as internal standard (99%). Pure **2a** was obtained by column chromatography (silica gel/CH₂Cl₂:hexane = 4:1). IR (neat) 3397, 1267, 1127 cm⁻¹. ¹H NMR (400MHz, CDCl₃) δ 5.01-5.06 (1H, m), 7.41-7.49 (5H, m). ¹³C NMR (100MHz, CDCl₃) δ 72.8 (q, ²*J*_{C-F} = 31.9 Hz), 124.3 (q, ¹*J*_{C-F} = 282.3 Hz), 127.4, 128.6 (2C), 129.6 (2C), 133.9 (q, ³*J*_{C-F} = 0.9 Hz). ¹⁹F NMR (373MHz, CDCl₃) 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. ¹H NMR (400MHz, CDCl₃) δ 4.98-5.03 (1H, m), 7.35-7.44 (2H, m), 7.54-7.56 (2H, m). ¹³C NMR (100MHz, CDCl₃) δ 72.2 (q, ²*J*_{C-F} = 32.2 Hz), 123.8, 123.9 (q, ¹*J*_{C-F} = 282.1 Hz), 129.0 (2C), 131.8 (2C), 132.7. ¹⁹F NMR (373MHz, CDCl₃) 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. ¹H NMR (400MHz, CDCl₃) 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). ¹³C NMR (100MHz, CDCl₃) δ 71.6 (q, ²*J*_{C-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. ¹⁹F NMR (373MHz, CDCl₃) 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} . ^1H 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, $^2J_{\text{C-F}} = 32.2$ Hz), 122.7 (q, $^4J_{\text{C-F}} = 0.9$ Hz), 124.6 (q, $^1J_{\text{C-F}} = 282.5$ Hz), 125.1, 125.7 (q, $^3J_{\text{C-F}} = 1.2$ 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} . ^1H 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, $^2J_{\text{C-F}} = 34.3$ Hz), 110.1 (q, $^4J_{\text{C-F}} = 0.9$ Hz), 110.7, 123.4 (q, $^1J_{\text{C-F}} = 282.1$ Hz), 143.6, 147.1 (q, $^3J_{\text{C-F}} = 1.6$ 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 $^{\circ}\text{C}$. IR (KBr) 3422, 2907, 2851, 1263, 1167, 1120 cm^{-1} . ^1H 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, $^4J_{\text{C-F}} = 1.8$ Hz), 77.5 (q, $^2J_{\text{C-F}} = 27.9$ Hz), 125.6 (q, $^1J_{\text{C-F}} = 285.1$ Hz). ^{19}F NMR (373MHz, CDCl_3) δ -71.55 (3F, d, $J = 8.8$ Hz). HRMS (EI) calcd for $\text{C}_{12}\text{H}_{16}\text{F}_3\text{O}$ (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} . ^1H 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, $^4J_{\text{C-F}} = 1.0$ Hz), 29.2 (q, $^3J_{\text{C-F}} = 1.2$ Hz), 38.1 (q, $^4J_{\text{C-F}} = 1.0$ Hz), 74.3 (q, $^2J_{\text{C-F}} = 29.1$ Hz), 125.3 (q, $^1J_{\text{C-F}} = 283.3$ 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} . ^1H 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, $^2J_{\text{C-F}} = 28.4$ Hz), 125.3 (q, $^1J_{\text{C-F}} = 286.1$ Hz), 127.4 (2C, q, $^3J_{\text{C-F}} = 1.4$ 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_2Cl_2 =4:1) in 89% yield. White solid. Mp 44-46 $^{\circ}\text{C}$. IR (KBr) 3465, 3060, 1185, 1135, 1028 cm^{-1} . ^1H 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, $^2J_{\text{C-F}} = 26.3$ Hz, $^2J_{\text{C-F}} = 21.9$ Hz), 113.3 (ddq, $^1J_{\text{C-F}} = 262.2$ Hz, $^1J_{\text{C-F}} = 254.8$ Hz, $^2J_{\text{C-F}} = 35.7$ Hz), 119.3 (ddq, $^2J_{\text{C-F}} = 36.7$ Hz, $^2J_{\text{C-F}} = 35.1$ Hz, $^1J_{\text{C-F}} = 287.1$ Hz), 122.6 (dd, $^3J_{\text{C-F}} = 2.4$ Hz, $^3J_{\text{C-F}} = 1.4$ 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_3BHK (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_2O_2 (2 mL) was added at 0 °C, and after stirring for 1 h, the mixture was extracted with Et_2O (30 mL X 3). The combined organic phase was dried over MgSO_4 and **2j** was isolated by column chromatography (silica gel/ CH_2Cl_2 :hexane = 1:4) in 61% yield. White solid. Mp 75-77 °C. IR (KBr) 3398, 1175, 1124, 1041 cm^{-1} . ^1H 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, $^2J_{\text{C-F}} = 21.8$ Hz, $^2J_{\text{C-F}} = 30.5$ 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 $\text{C}_{15}\text{H}_9\text{C F}_8\text{O}$ (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_2Cl_2 =4:1). Oil. IR (neat) 3434, 2931, 2857, 1276, 1166 cm^{-1} . ^1H 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, $^2J_{\text{C-F}} = 27.9$ Hz, $^2J_{\text{C-F}} = 26.2$ Hz), 123.1, 124.2, 125.1, 125.7, 126.1, 126.5, 128.9, 129.2 (2C), 129.2 (t, $^1J_{\text{C-F}} = 286.5$ 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 $\text{C}_{18}\text{H}_{13}\text{Cl}_2 \text{F}_2\text{OS}$ ($\text{M}^+\text{+Cl}$) 385.00322, found 385.00203.

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

To a CH_2Cl_2 solution (1 mL) of **8** (578 mg, 2 mmol) were added a 1.0 M THF solution of Et_3BHK (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_2O_2 (2 mL) was added at 0 °C. After stirring for 1 h, the mixture was extracted with Et_2O (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} . ^1H 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, $^2J_{\text{C-F}} = 28.8$ Hz, $^2J_{\text{C-F}} = 22.4$ Hz), 115.4 (tt, $^1J_{\text{C-F}} = 260.8$ Hz, $^2J_{\text{C-F}} = 35.3$ Hz), 117.2 (tt, $^1J_{\text{C-F}} = 253.0$ Hz, $^2J_{\text{C-F}} = 34.1$ Hz), 126.7 (t, $^3J_{\text{C-F}} = 6.7$ Hz), 127.8 (2C), 128.2 (2C), 129.1 (2C), 130.9 (2C, t, $^2J_{\text{C-F}} = 24.3$ Hz), 131.0 (t, $^4J_{\text{C-F}} = 1.4$ 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 $\text{C}_{19}\text{H}_{19}\text{F}_4\text{O}$ (M^+) 339.13775, found 339.13808.

ACKNOWLEDGEMENTS

We are grateful to Asahi Glass Co., Ltd., and Daikin Industries, Ltd., for their donation of IF_5 and 2,2,3,3,4,4,5,5-octafluoropentanol, respectively.

REFERENCES

1. As for reviews and books related to nucleophilic trifluoromethylation, see: (a) D. J. Burton and Z.-Y. Yang, *Tetrahedron*, 1992, **48**, 189; (b) M. A. McClinton and D. A. McClinton, *Tetrahedron*, 1992, **48**, 6555; (c) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757; (d) R. P. Singh and J. M. Shreeve, *Tetrahedron*, 2000, **56**, 7613; (e) G. K. S. Prakash and M. Mandal, *J. Fluorine Chem.*, 2001, **112**, 123; (f) B. R. Langlois and T. Billard, *Synthesis*, 2003, 185; (g) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119; (h) T. Umemoto, 'Fluorine-Containing Synthons: Recent Advances in Perfluoroalkylation Methodology,' ed. by V. A. Soloshonok, American Chemical Society, Washington, DC, 2005, pp. 2-15; (i) G. K. S. Prakash and J. Hu, 'Fluorine-Containing Synthons: New Nucleophilic Fluoroalkylation Chemistry,' ed. by V. A. Soloshonok, American Chemical Society, Washington, DC, 2005, pp. 16-56; (j) B. R. Langlois and T. Billard, 'Fluorine-Containing Synthons: Fluoroform, Fluoral, Trifluoroacetic and Trifluoromethanesulfinic Acids Derivatives as New Reagents for the Introduction of Polyfluorinated Moieties,' ed. by V. A. Soloshonok, American Chemical Society, Washington, DC, 2005, pp. 57-86; (k) B. R. Langlois, T. Billard, and S. Roussel, *J. Fluorine Chem.*, 2005, **126**, 173; (l) G. K. S. Prakash and J. Hu, *Acc. Chem. Res.*, 2007, **40**, 921; (m) M. Médebielle and W. R. Dolbier Jr., *J. Fluorine Chem.*, 2008, **129**, 930; (n) J. Gawronski, N. Wascinska, and J. Gajewy, *Chem. Rev.*, 2008, **108**, 5227; (o) N. Shibata, S. Mizuta, and H. Kawai, *Tetrahedron: Asymmetry*, 2008, **19**, 2633; (p) G. Valero, X. Companyó, and R. Rios, *Chem. Eur. J.*, 2011, **17**, 2018.
2. G. K. S. Prakash, R. Krishnamurti, and G. A. Olah, *J. Am. Chem. Soc.*, 1989, **111**, 393; R. Krishnamurti, D. R. Bellew, and G. K. S. Prakash, *J. Org. Chem.*, 1991, **56**, 984; R. P. Singh, G. Gao, R. L. Kirchmeier, and J. M. Shreeve, *J. Org. Chem.*, 1999, **64**, 2873; J. Kim and J. M. Shreeve, *Org. Biomol. Chem.*, 2004, **2**, 2728; J. J. Song, Z. Tan, J. T. Reeves, F. Gallou, N. K. Yee, and C. H. Senanayake, *Org. Lett.*, 2005, **7**, 2193; S. Mizuta, N. Shibata, S. Ogawa, H. Fujimoto, S. Nakamura, and T. Toru, *Chem. Commun.*, 2006, 2575; V. V. Levin, A. D. Dilman, P. A. Belyakov, M. I. Struchkova, and V. A. Tartakovsky, *Tetrahedron*

- Lett.*, 2011, **52**, 281.
3. (a) B. Folléas, I. Marek, J.-F. Normant, and L. S. Jalmes, *Tetrahedron Lett.*, 1998, **39**, 2973; (b) J. Russell and N. Roques, *Tetrahedron*, 1998, **54**, 13771; (c) B. Folléas, I. Marek, J.-F. Normant, and L. S. Jalmes, *Tetrahedron*, 2000, **56**, 275; (d) S. Large, N. Roques, and B. R. Langlois, *J. Org. Chem.*, 2000, **65**, 8848; (e) T. Billard, S. Bruns, and B. R. Langlois, *Org. Lett.*, 2000, **2**, 2101.
 4. C. Mispelaere and N. Roques, *Tetrahedron Lett.*, 1999, **40**, 6411; T. Billard, B. R. Langlois, and G. Blond, *Eur. J. Org. Chem.*, 2001, 1467.
 5. Recently, trifluoromethyl anion was generated from fluoroform directly by using organo-superbase, see: H. Kawai, Z. Yuan, E. Tokunaga, and N. Shibata, *Org. Biomol. Chem.*, 2013, **11**, 1446.
 6. Trifluoroacetamides were previously used to generate the trifluoromethyl anion by the reaction with base, but the trifluoromethylation successfully proceeded only in the reaction with aromatic ketones, see: L. Jablonski, J. Joubert, T. Billard, and B. R. Langlois, *Synlett*, 2003, 230.
 7. R. E. Sammelson and J. E. Casida, *J. Org. Chem.*, 2003, **68**, 8075.
 8. T. Hudlicky, R. Fan, J. W. Reed, D. R. Carver, M. Hudlicky, and E. I. Eger II, *J. Fluorine Chem.*, 1992, **59**, 9.
 9. J. Afzal, B. M. Fung, and E. A. O'rear, *J. Fluorine Chem.*, 1987, **34**, 385.
 10. S. Ayuba, N. Yoneda, T. Fukuhara, and S. Hara, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1597.
 11. T. Fukuhara and S. Hara, *J. Org. Chem.*, 2010, **75**, 7393.
 12. H. C. Brown, J. S. Cha, B. Nazer, S.-C. Kim, S. Krishnamurthy, and C. A. Brown, *J. Org. Chem.*, 1984, **49**, 885.
 13. H. A. Schenck, P. W. Lenkowski, I. C. Mukherjee, S.-H. Ko, J. P. Stables, M. K. Patel, and M. L. Brown, *Bioorg. Med. Chem.*, 2004, **12**, 979.
 14. M. Shi, X.-G. Liu, Y.-W. Guo, and W. Zhang, *Tetrahedron*, 2007, **63**, 12731.
 15. M. G. Gorbunova, I. I. Gerus, and V. P. Kukhar, *J. Fluorine Chem.*, 1993, **65**, 25.
 16. J. R. White, G. J. Price, P. K. Plucinski, and C. G. Frost, *Tetrahedron Lett.*, 2009, **50**, 7365.
 17. C. Pooput, W. R. Dolbier, Jr., and M. Médebielle, *J. Org. Chem.*, 2006, **71**, 3564.