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Article

Synthesis of 5-Fluoroalkyl Isoxazolidines via 1,3-Dipolar Cycloaddition of Ethyl 2-Hydropolyfluoroalk-2-enoates with Nitrones†

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1,3-Dipolar cycloaddition reactions of ethyl 2-hydropolyfluoroalk-2-enoates (**1**) with some nitrones were described. The reaction of 3,4-dihydroisoquinoline *N*-oxide (**2**) with **1** took place readily in methylene chloride at room temperature to give the corresponding 5-fluoroalkylisoxazolidines regioselectively as a mixture of two diastereoisomers (*trans* and *cis*) in high yields, while longer reaction time and higher temperature were needed in the case of non-cyclic nitrones. Under similar conditions the reaction of quinoline *N*-oxide (**14**) with **1** did not give the expected adducts and a ring-opening product was obtained.

Keywords 5-fluoroalkyl isoxazolidine, ethyl 2-hydropolyfluoroalk-2-enoate, nitrone, cycloaddition, synthesis

Introduction

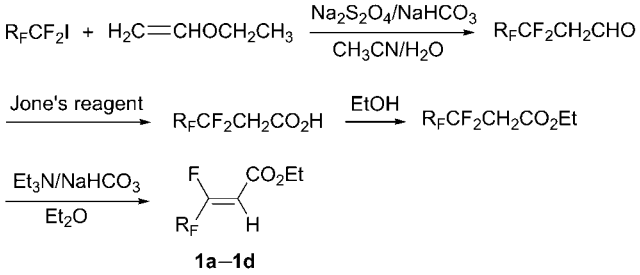
Recently, fluorine-containing heterocyclic compounds have received much attention and are of current interest in both academic and industrial fields due to their potential biological activities,[1] and the development of synthetic strategies for fluorine-containing heterocycles has been the subject of many research works. Among the large variety of strategies available for the synthesis of five-numbered heterocycles, 1,3-dipolar cycloaddition reaction of nitrones with olefins is an extremely powerful one,[2] which usually occurs under mild conditions to give the corresponding isoxazolidines efficiently with good regio- and stereo-selectivity.

In our continuous study on the synthesis of fluorine-containing heterocycles, a number of versatile fluorine-containing building blocks were developed. Among them, ethyl 2-hydropolyfluoroalk-2-enoates (**1**), $R_FCF{=}CHCO_2Et$ (R_F=polyfluoroalkyl or perfluoroalkyl), have been under research in our laboratory for several years. Previous papers reported the reaction of **1** generated *in situ* from $R_FCF_2CH_2CO_2Et$ with various *N*-ylides.[3] Further studies showed that **1** could also react with some nitrones and the corresponding 1,3-dipolar cycloadducts were obtained in high yields.[4] The results are reported in detail in this paper.

Results and discussion

Ethyl 2-hydropolyfluoroalk-2-enoates (**1a—1d**) were prepared in *Z*-form conveniently from per(poly)-fluoroalkyl iodides as outlined in Scheme 1.[5] Nitrones were prepared according to literature procedures.[6]

Scheme 1



1a—1d

R_F = $(CF_2)_3Cl$, **a**; CF_2Br, **b**; $(CF_2)_5Cl$, **c**; $(CF_2)_4CF_3$, **d**

The cycloaddition reaction was carried out in methylene chloride. At room temperature **1** reacted readily with 3,4-dihydroisoquinoline *N*-oxide (**2**) to give the corresponding 5-fluoroalkylisoxazolidines **3** and **4** in high yields (Scheme 2). The reaction was very fast and usually completed in 0.5 h (monitored by TLC or ^{19}F NMR). The results were summarized in Table 1.

The two isomeric products **3** and **4** could be separated easily by column chromatography. Their ^1H NMR spectra showed that the CO_2Et and R_F groups in both compounds were at C-4 and C-5 positions of the isoxazolidine ring respectively, indicating a good regioselectivity of this reaction. It was caused mainly by the elec-

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Scheme 2

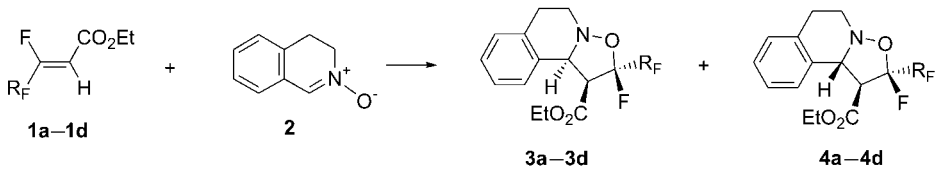


Table 1 1,3-Diploar cycloaddation reaction of **1** with nitrones

Entry	Nitrone	R_F	Conditions	Product (isolated yield/%)
			Nitrone∶**1**/Time/Temp.	
1	**2**	$CF_2CF_2CF_2Cl$	1∶1/0.5 h/r.t.	**3a** (40.0)+**4a** (60.0)
2	**2**	CF_2Br	1∶1/0.5 h/r.t.	**3b** (59.4)+**4b** (40.4)
3	**2**	$CF_2(CF_2)_3CF_2Cl$	1∶1/0.5 h/r.t.	**3c** (44.7)+**4c** (44.7)
4	**2**	$CF_2(CF_2)_3CF_3$	1∶1/0.5 h/r.t.	**3d** (32.6)+**4d** (56.3)
5	**5**	$CF_2CF_2CF_2Cl$	2∶1/3 d/r.t.	**6a** (47.9)+**7a** (47.9)
6	**5**	$CF_2(CF_2)_3CF_3$	2∶1/3 d/r.t.	**6d** (48.1)+**7d** (35.3)
7	**8**	$CF_2CF_2CF_2Cl$	2∶1/3 d/r.t.	**9a**+**10a** (4∶96, 77.6)[a]
8	**8**	$CF_2(CF_2)_3CF_3$	2∶1/3 d/r.t.	**9d**+**10d** (20∶80, 78.1)[a]
9	**11**	$CF_2CF_2CF_2Cl$	1∶1/6 d/reflux	**12a** (26.5)+**13a** (68.3)
10	**11**	$CF_2(CF_2)_3CF_2Cl$	1∶1/6 d/reflux	**12c** (23.0)+**13c** (63.8)

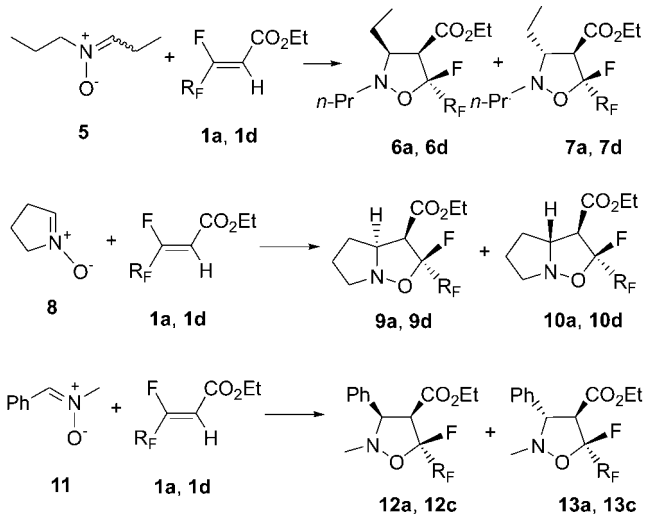
[a] The ratio was determined by GC and ^{19}F NMR.

tronic factor: the more electron-deficient end (C-2) of the dipolarophile preferred to add to the nitrone oxygen atom. Taking compound **3a** as an example, the presence of a doublet-doublet peak at δ 4.42 for the proton next to ester group indicated that the proton was coupled by both a neighboring fluorine atom and a neighboring proton. This was consistent with the assigned structure of compound **3a** in which the ester group connected to C-4 of the isoxazolidine ring and the proton at C-4 had a fluorine atom and a proton at its neighboring C-5 and C-3 positions.

Under similar conditions, *N*-propylidene propanamine *N*-oxide (**5**), nitrones **8** and **11** could also react with **1** and the corresponding 5-fluoroalkylisoxazolidines were obtained as final products (Scheme 3). Compared to **2**, these nitrones were less reactive and the reaction usually took a few days to go completion. The reaction of nitrone **11** with **1** was carried out under reflux. In the case of nitrone **8**, the two isomeric products (**9** and **10**) obtained could not be separated by column chromatography, and the ratio was evaluated by GC and ^{19}F NMR.

As shown in Table 1, all reactions gave two diastereoisomeric cycloadducts with the two protons at C-3 and C-4 in *cis* and *trans* configurations respectively. The ratio of *cis* to *trans* isomers varied from 50∶50 to 4∶96 and better stereoselectivity was obtained with less reactive nitrones. The relative configurations of H-3 and H-4 in cycloadducts were determined by means of their NMR spectra and X-ray crystallography. In the case of isoxazolidines **3** and **4**, the structure of *cis*-isomer **3** was confirmed by the X-ray crystallography of compound **3a** (Figure 1).[7] In ^1H NMR spectra these *cis* isomers showed lower chemical shifts for H-3 due to the deshielding effect of the neighboring ester group and higher chemical shifts for H-4 than their *trans* counterparts **4**. The rule was applied to other fluoroalkylated isoxazolidines: the isomers with lower chemical shifts for H-3 and higher chemical shifts for H-4 being assigned as *cis* isomers. This was further proved by the NOESY experiment of compound **6a**. 4-H and 5-F in both isomers were in *trans* configuration which was controlled by the stereochemistry of ester **1**.

Scheme 3



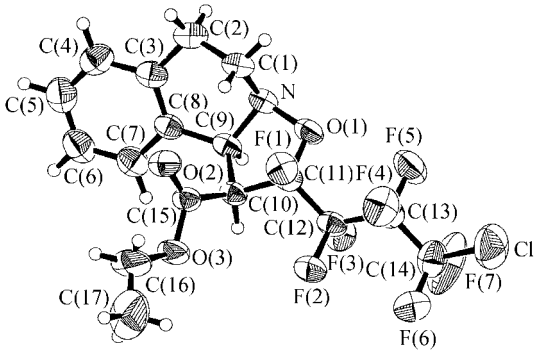
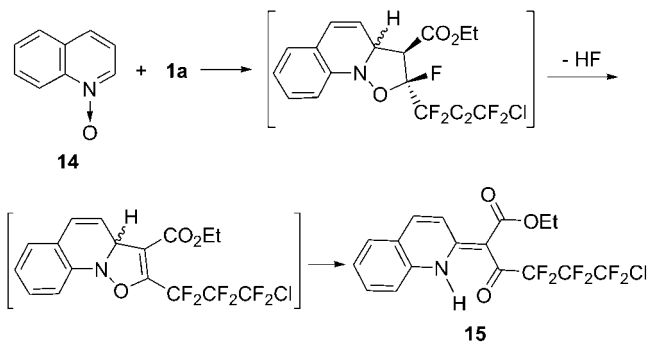


Figure 1 Crystal structure of **3a**.

When quinoline *N*-oxide **14** was allowed to react with **1**, no expected cycloadduct was obtained. However the ring-opening product **15** was isolated from the reaction (Scheme 4), which was consistent with the reported results.[8]

Scheme 4



In summary, the regiospecific 1,3-dipolar cycloaddition reaction of ethyl 2-hydropolyfluoroalk-2-enoates with nitrones was achieved under mild conditions, providing a convenient and efficient method for the synthesis of 5-fluoroalkyl isoxazolidines.

Experimental

Melting points were uncorrected. IR spectra were recorded with an FTS-185 spectrometer. ^{1}H NMR spectra were measured on a Bruker AM 300 (300 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were recorded on a Varian EM-360L spectrometer (56.4 MHz) using TFA as external standard. The values are reported as δ_{CFCl_3} ($\delta_{CFCl_3}=\delta_{TFA}+76.8$), positive for upfield shifts. Mass spectra were obtained on an HP 5989A spectrometer. Gas chromatography (GC) was performed on an HP 6890 spectrometer.

Typical procedure for the synthesis of 5-fluoroalkyl isoxazolidines

A solution of **1** (1.0 mmol) and 3,4-dihydroisoquinoline *N*-oxide (**2**, 1.0 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 0.5 h (monitored by TLC or ^{19}F NMR). After reaction the solvent was removed under reduced pressure and the residue was purified by column chromatography using petrolum ether and ethyl acetate (50∶1) as eluent to give the corresponding adducts **3** and **4**.

3a: White solid, m.p. 57.5—59.5 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.16 (m, 3H), 7.02 (d, J=7.1 Hz, 1H), 5.11 (d, J=9.5 Hz, 1H), 4.42 (dd, J_{HF}=15.5 Hz, J_{HH}=9.5 Hz, 1H), 4.03—3.91 (m, 3H), 3.65—3.62 (m, 1H), 3.18—2.93 (m, 2H), 1.05 (t, J=7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 66.8 (m, 2F), 108.9 (m, 1F), 117.9 (m, 4F); IR (KBr) ν: 1743, 1382, 1205, 1185, 1118, 742 cm^{-1}; MS *m/z* (%): 449 (M^+, 0.57), 404 (M^+-OEt, 1.21), 147 (100). Anal. calcd for $C_{17}H_{15}ClF_7NO_3$: C 45.40, H 3.36, N 3.11; found C 45.40, H 3.20, N 2.98.

4a: White solid, m.p. 91—93 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.30—7.12 (m, 4H), 5.38 (d, J=7.8 Hz, 1H), 4.42—4.28 (m, 2H), 3.99 (dd, J_{HF}=19.5 Hz, J_{HH}=7.8 Hz, 1H), 3.51—3.41 (m, 2H), 2.98—2.87 (m, 2H), 1.35 (t, J=7.8 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 67.3 (m, 2F), 112.2 (m, 1F), 117.0—119.5 (m, 4F); IR (KBr) ν: 1743, 1191, 1124, 748 cm^{-1}; MS *m/z* (%): 450 (M^++1, 5.68), 430 (M^+-F, 5.48), 404 (M^+-OEt, 6.73), 356 (16.83), 264 ($M^+-CF_2CF_2CF_2Cl$, 37.19), 145 (100). Anal. calcd for $C_{17}H_{15}ClF_7NO_3$: C 45.40, H 3.36, N 3.11; found C 45.43, H 3.23, N 3.04.

3b: Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.14 (m, 3H), 7.00 (d, J=6.9 Hz, 1H), 5.16 (d, J=9.5 Hz, 1H), 4.32 (dd, J_{HF}=14.6 Hz, J_{HH}=9.5 Hz, 1H), 4.04—3.90 (m, 3H), 3.65—3.63 (m, 1H), 3.18—2.92 (m, 2H), 1.04 (t, J=7.1 Hz, 3H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 62.0 (s, 2F), 106.3 (m, 1F); IR (film) ν: 1743, 1378, 1191, 1124, 749 cm^{-1}; MS *m/z* (%): 393 (M^+, 0.82), 348 (M^+-OEt, 1.12), 264 (M^+-CF_2Br, 2.53), 147 (100). Anal. calcd for $C_{15}H_{15}BrF_3NO_3$: C 45.71, H 3.84, N 3.55; found C 45.99, H 3.80, N 3.50.

4b: White solid, m.p. 61—63 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.26—7.10 (m, 4H), 5.44 (d, J=7.7 Hz, 1H), 4.41—4.25 (m, 2H), 3.90 (dd, J_{HF}=18.6 Hz, J_{HH}=7.7 Hz, 1H), 3.48—3.33 (m, 2H), 3.04—2.85 (m, 2H), 1.31 (t, J=7.2 Hz, 3H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 60.1 (m, 2F), 109.6 (m, 1F); IR (KBr) ν: 1746, 1667, 1145, 939 cm^{-1}; MS *m/z* (%): 393 (M^+, 0.53), 348 (M^+-OEt, 4.19), 264 (M^+-CF_2Br), 172 (100). Anal. calcd for $C_{15}H_{15}BrF_3NO_3$: C 45.71, H 3.84, N 3.55; found C 45.79, H 4.09, N 3.47.

3c: White solid, m.p. 67.5—69.5 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.29—7.15 (m, 3H), 7.02 (d, J=7.2 Hz, 1H), 5.10 (d, J=9.4 Hz, 1H), 4.42 (dd, J_{HF}=15.5 Hz, J_{HH}=9.4 Hz, 1H), 3.98—3.91 (m, 3H), 3.65—3.62 (m, 1H), 3.16—2.93 (m, 2H), 1.07 (t, J=7.1 Hz, 3H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 67.0 (m, 2F), 108.6 (m, 1F), 118.4—121.2 (m, 8F); IR (KBr) ν: 1757, 1747, 1219, 1143, 751 cm^{-1}; MS *m/z* (%): 549 (M^+, 0.71), 504 (M^+-OEt, 1.63), 147(100). Anal. calcd for $C_{19}H_{15}ClF_{11}NO_3$: C 41.51, H 2.75, N 2.55; found C 41.34, H 2.90, N 2.40.

4c: White solid, m.p. 111—113 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.11 (m, 4H), 5.36 (d, J=7.7 Hz, 1H), 4.42—4.26 (m, 2H), 3.98 (dd, J_{HF}=19.2

Hz, J_{HH}=7.7 Hz, 1H), 3.48—3.40 (m, 2H), 2.97—2.91 (m, 2H), 1.32 (t, J=7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 67.2 (m, 2F), 111.5 (m, 1F), 117.4—118.5 (m, 2F), 118.7—121.1 (m, 6F); IR (KBr) ν: 1743, 1209, 1114, 749, 675 cm^{-1}; MS *m/z* (%): 550 (M^++1, 2.58), 530 (M^+−F, 4.23), 504 (M^+−OEt, 6.76), 264 (M^+−$C_5F_{10}Cl$, 29.84), 172 (81.23), 145 (100). Anal. calcd for $C_{19}H_{15}ClF_{11}NO_3$: C 41.51, H 2.75, N 2.55; found C 41.79, H 3.06, N 2.58.

3d: White solid, m.p. 56—58 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.15 (m, 3H), 7.01 (d, J=9.0 Hz, 1H), 5.11 (d, J=9.5 Hz, 1H), 4.42 (dd, J_{HF}=15.6 Hz, J_{HH}=9.5 Hz, 1H), 4.03—3.88 (m, 3H), 3.65—3.62 (m, 1H), 3.18—2.93 (m, 2H), 1.05 (t, J=7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 79.8 (t, 3F), 108.4 (m, 1F), 119.4—125.0 (m, 8F); IR (KBr) ν: 1759, 1747, 1242, 1137, 745 cm^{-1}; MS *m/z* (%): 533 (M^+, 0.69), 488 (M^+−OEt, 2.16), 147 (100). Anal. calcd for $C_{19}H_{15}F_{12}NO_3$: C 42.79, H 2.83, N 2.63; found C 42.79, H 2.64, N 2.60.

4d: White solid, 114.5—116.5 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.27—7.11 (m, 4H), 5.37 (d, J=7.7 Hz, 1H), 4.42—4.26 (m, 2H), 3.79 (dd, J_{HF}=19.2 Hz, J_{HH}=7.7 Hz, 1H), 3.50—3.39 (m, 2H), 3.02—2.87 (m, 2H), 1.32 (t, J=7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 80.4 (t, 3F), 111.3 (m, 1F), 118.0—125.5 (m, 8F); IR (KBr) ν: 1742, 1242, 1197, 1141, 749 cm^{-1}; MS *m/z* (%): 514 (M^+−F, 2.28), 488 (M^+−OEt, 9.51), 264 (M^+−C_5F_{11}, 25.17), 172 (91.44), 145 (100). Anal. calcd for $C_{19}H_{15}F_{12}NO_3$: C 42.79, H 2.83, N 2.63; found C 42.87, H 2.81, N 2.65.

6a: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.32—4.18 (m, 2H), 3.69—3.60 (m, 2H), 3.13—3.06 (m, 1H), 2.98—2.88 (m, 1H), 1.75—1.52 (m, 4H), 1.30 (t, J=7.1 Hz, 3H), 1.00—0.93 (m, 6H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 66.5 (m, 2F), 107.6 (m, 1F), 115.8—118.9 (m, 4F); IR (film) ν: 2973, 1757, 1467, 1188, 1131, 831 cm^{-1}; MS *m/z* (%): 418 (M^++1, 22.02), 398 (M^+−F, 8.26), 388 (M^+−Et, 95.19), 372 (M^+−OEt, 8.34), 232 (M^+−C_3F_5Cl, 5.37), 43 ($C_3H_7^+$, 100). Anal. calcd for $C_{14}H_{19}ClF_7NO_3$: C 40.25, H 4.58, N 3.35; found C 40.14, H 4.50, N 3.51.

7a: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.29—4.19 (m, 2H), 3.94 (dd, J_{HF}=15.6 Hz, J_{HH}=7.4 Hz, 1H), 3.05—2.69 (m, 3H), 1.88—1.56 (m, 4H), 1.30 (t, J=7.1 Hz, 3H), 0.97 (t, J=7.4 Hz, 6H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 66.9 (m, 2F), 112.3 (m, 1F), 116.3—119.8 (m, 4F); IR (film) ν: 2972, 1749, 1190, 1133, 829 cm^{-1}; MS *m/z* (%): 418 (M^++1, 66.93), 417 (M^+, 26.38), 398 (M^+−F, 24.28), 388 (M^+−Et, 53.61), 372 (M^+−OEt, 6.63), 232 (M^+−C_3F_5Cl, 2.41), 156 (100), 43 ($C_3H_7^+$, 20.85). Anal. calcd for $C_{14}H_{19}ClF_7NO_3$: C 40.25, H 4.58, N 3.35; found C 40.18, H 4.37, N 3.68.

6d: Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.33—4.18 (m, 2H), 3.69—3.57 (m, 2H), 3.15—3.07 (m, 1H), 2.99—2.89 (m, 1H), 1.75—1.52 (m, 4H), 1.30 (t, J=7.1 Hz, 3H), 1.00—0.93 (m, 6H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 80.2 (t, 3F), 107.6 (m, 1F), 118.0—125.6 (m, 8F); IR (film) ν: 2973, 1750, 1242, 1206, 1145, 735 cm^{-1}; MS *m/z* (%): 502 (M^++1, 28.38), 482 (M^+−F, 14.40), 472 (M^+−Et, 100), 456 (M^+−OEt, 8.34), 232 (M^+−C_5F_{11}, 4.66), 43 ($C_3H_7^+$, 86.83). Anal. calcd for $C_{16}H_{19}F_{12}NO_3$: C 38.34, H 3.82, N 2.97; found C 38.56, H 3.48, N 2.72.

7d: Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.29—4.19 (m, 2H), 3.94 (dd, J_{HF}=15.6 Hz, J_{HH}=7.4 Hz, 1H), 3.05—2.71 (m, 3H), 1.88—1.56 (m, 4H), 1.30 (t, J=7.1 Hz, 3H), 0.97 (t, J=7.4 Hz, 6H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 79.9 (t, 3F), 112.1 (m, 1F), 117.8—125.0 (m, 8F); IR (film) ν: 2973, 1757, 1241, 1206, 1145, 702 cm^{-1}; MS *m/z* (%): 502 (M^++1, 41.79), 501 (M^+, 20.31), 482 (M^+−F, 16.36), 472 (M^+−Et, 75.78), 456 (M^+−OEt, 7.72), 232 (M^+−C_5F_{11}, 1.60), 43 ($C_3H_7^+$, 100). HRMS calcd for $C_{14}H_{14}F_{12}NO_3$ (M^+−Et): 472.07821, found 472.07769.

Mixture of 9a and 10a: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.34—4.19 (m, 3H), 3.86 (dd, J_{HF}=17.2 Hz, J_{HH}=2.5 Hz, 1H), 3.65—3.57 (m, 1H), 3.18—3.10 (m, 1H), 2.14—1.72 (m, 4H), 1.30 (t, J=7.1 Hz, 3H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 66.8 (m, 2F), 112.8 (m, 1F), 116.8—119.1 (m, 4F); IR (film) ν: 2988, 1746, 1681, 1182, 1133, 807 cm^{-1}; MS *m/z* (%): 388 (M^++1, 16.88), 358 (M^+−Et, 0.58), 342 (M^+−OEt, 3.56), 202 (M^+−$CF_2CF_2CF_2Cl$, 6.66), 110 (100). Anal. calcd for $C_{12}H_{13}ClF_7NO_3$: C 37.18, H 3.38, N 3.61; found C 37.40, H 3.45, N 3.69.

Mixture of 9d and 10d: Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.37—4.18 (m, 3H), 3.85 (dd, J_{HF}=17.5 Hz, J_{HH}=2.8 Hz, 1H), 3.62—3.56 (m, 1H), 3.22—3.14 (m, 1H), 2.16—1.72 (m, 4H), 1.32—1.26 (m, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 80.3 (m, 3F), 112.3 (m, 1F), 118.0—125.6 (m, 8F); IR (film) ν: 1740, 1683, 1239, 1144 cm^{-1}; MS *m/z* (%): 471 (M^+, 1.07), 452 (M^+−F, 0.64), 426 (M^+−OEt, 6.26), 398 (M^+−CO_2Et, 1.03), 202 (M^+−C_5F_{11}, 13.06), 110 (100). Anal. calcd for $C_{14}H_{13}F_{12}NO_3$: C 35.68, H 2.78, N 2.97; found C 35.45, H 2.78, N 3.04.

12a: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.38—7.29 (m, 5H), 4.19—4.08 (m, 2H), 3.89—3.82 (m, 2H), 2.86 (s, 3H), 0.93 (t, J=7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 67.2 (m, 2F), 115.3 (m, 1F), 118.1—119.7 (m, 4F); IR (film) ν: 1749, 1189, 739, 701 cm^{-1}; MS *m/z* (%): 437 (M^+, 11.86), 418 (M^+−F, 6.63), 392 (M^+−OEt, 5.10), 252 (M^+−C_3F_5Cl, 0.83), 134 (100), 118 (37.85). Anal. calcd for $C_{16}H_{15}ClF_7NO_3$: C 43.90, H 3.45, N 3.20; found C 44.10, H 3.58, N 3.33.

13a: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.54—7.33 (m, 5H), 4.45 (d, J=11.2 Hz, 1H), 4.25—4.17 (m, 1H), 4.14—4.03 (m, 1H), 3.92 (dd, J_{HF}=21.6 Hz, J_{HH}=11.2 Hz, 1H), 2.86 (s, 3H), 1.17 (t, J=7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 66.8 (m, 2F), 108.4 (m, 1F), 118.1 (m, 4F); IR (film) ν: 1758, 1735, 1182, 1131, 700 cm^{-1}; MS *m/z* (%): 438 (M^++1, 26.25), 418 (M^+−F, 7.02), 392 (M^+−OEt, 6.48), 252 (M^+−C_3F_5Cl, 12.86), 118 (100). Anal. calcd for $C_{16}H_{15}ClF_7NO_3$: C 43.90, H 3.45, N 3.20; found C 43.96, H 3.24, N 3.20.

12c: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.38—7.33 (m, 5H), 4.20—4.08 (m, 2H), 3.89—3.82 (m, 2H), 2.86 (s, 3H), 0.93 (t, J=7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 69.1 (m, 2F), 115.1 (m, 1F), 118.5—121.4 (m, 8F); IR (film) v: 1758, 1209, 1148 cm^{-1}; MS *m/z* (%): 537 (M^+, 41.83), 518 (M^+—F, 19.29), 492 (M^+—OEt, 7.29), 252 (M^+—$C_5F_{11}Cl$, 1.90), 134 (100), 118 (36.25). Anal. calcd for $C_{18}H_{15}ClF_{11}NO_3$: C 40.20, H 2.81, N 2.60; found C 40.25, H 2.80, N 2.53.

13c: Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.46—7.35 (m, 5H), 4.46 (d, J=11 Hz, 1H), 4.26—4.18 (m, 1H), 4.14—4.06 (m, 1H), 3.93 (dd, J_{HF}=21 Hz, J_{HH}=11 Hz, 1H), 2.86 (s, 3H), 1.17 (t, J=7.3 Hz, 3H); ^{19}F NMR ($CDCl_3$, 56.4 MHz) δ: 67.2 (m, 2F), 108.3 (m, 1F), 117.2—121.8 (m, 8F); IR (film) v: 1749, 1210, 1149 cm^{-1}; MS *m/z* (%): 538 (M^++1, 16.38), 518 (M^+—F, 5.25), 492 (M^+—OEt, 7.69), 252 (M^+—$C_5F_{11}Cl$, 11.85), 118 (100). Anal. calcd for $C_{18}H_{15}ClF_{11}NO_3$: C 40.20, H 2.81, N 2.60; found C 40.36, H 2.76, N 2.74.

Reaction of quinoline *N*-oxide with 1a

A mixture of quinoline *N*-oxide (2 mmol) and **1a** (1 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using petrolum ether and ethyl acetate (50∶1) as eluent to give compound **15** in 28% yield. Yellow solid, m.p. 78—79 ℃. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 16.38 (br, 1H), 8.07 (d, J=9.4 Hz, 1H), 7.76—7.48 (m, 5H), 4.32 (q, J=7.2 Hz, 2H), 1.38 (t, J=7.2 Hz, 3H); ^{19}F NMR (CCl_4, 56.4 MHz) δ: 65.9 (t, 2F), 110.9 (m, 2F), 116.3—118.1 (m, 2F); IR (KBr) v: 1743, 1191, 1124, 1048, 742 cm^{-1}; MS *m/z* (%): 427 (M^+, 13.58), 392 (M^+—Cl, 1.73), 382 (M^+—OEt, 20.30), 242 (M^+—C_3F_5Cl, 99.49), 214 (M^+—COC_3F_5Cl, 26.18), 128 (100). Anal. calcd for $C_{17}H_{12}ClF_6NO_3$: C 47.74, H 2.83, N 3.27; found C 47.83, H 2.70, N 3.24.

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7 X-ray data for compound **3a**: $C_{17}H_{15}ClF_7NO_3$, M=449.75, monoclinic, crystal dimensions 0.2 mm×0.2 mm×0.3 mm, a=0.9926(2) nm, b=1.0660(2) nm, c=1.8251(3) nm, V=1.8788(6) nm^3, D_c=1.590 g/cm^3, Z=4, F_{000}=912.00, μ(Mo Kα)=2.89 cm^{-1}. Data were measured at 293 K on a Bruker SMART CCD diffractometer with graphite monochromated Mo Kα radiation.

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