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Fluorination of alcohols and diols with a novel fluorous deoxy-fluorination reagent

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ABSTRACT

We prepared a novel fluorous deoxy-fluorination reagent *N*,*N*-diethyl-α,α-difluoro-[3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzyl]amine (**1b**) from 3,5-diiodobenzoic acid (**3b**) via *N*,*N*-diethyl-3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzamide (**2b**) in four steps and used it for the fluorination of alcohols and diols. After the fluorination reactions, the isolation of the products and recovery of **2b** was performed by extraction with a fluorous/organic solvent system.

1. Introduction

Recently, fluorous chemistry using a fluorous/organic biphasic system has been developing as an environmentally friendly technology. The highly fluorinated compounds are selectively soluble in fluorocarbon solvents and separable from other organic compounds by simple extraction with a fluorous/organic biphasic solvent systems. Many fluorous reagents having fluorous tags have been prepared and successfully applied to organic synthesis [1]. The deoxy-fluorination reaction is a useful method for the selective introduction of one or two fluorine atoms into molecules and many deoxy-fluorination reagents such as DAST and deoxofluor have been developed and used [2]. However, to our knowledge, no recyclable fluorous deoxy-fluorination reagents have been reported so far. Recently we reported the fluorination of alcohols [3], aldehydes [4], diols [5], amino alcohols [6], and epoxides [7] using a novel deoxy-fluorination reagent, *N*,*N*-diethyl-α,α-difluoro-3-methylbenzylamine (DFMBA) **1a**, which is prepared from *N*,*N*-diethyl-3-methylbenzamide **2a** and returns to **2a** after the fluorination reaction. Therefore, we planned to prepare the fluorous deoxy-fluorination reagent, *N*,*N*-diethyl-α,α-difluoro-[3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzyl]amine **1b**, and apply it to the fluorination of alcohols. After the fluorination reaction, **1b** will return to **2b**, and the recovery of **2b** as well as isolation of products could be performed by simple extraction with a fluorous/organic solvent system (Scheme 1).

2. Result and discussion

2.1. Preparation of fluorous fluorination reagent 1b

We prepared a fluorous deoxy-fluorination reagent, *N*,*N*-diethyl-α,α-difluoro-[3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzyl]amine **1b**, from 3,5-diiodobenzoic acid **3b** [8] in four steps via *N*,*N*-diethyl-3,5-diiodobenzamide **4b**. Introduction of the fluorous tags was performed by a Heck-type reaction of **4b** with 1*H*,1*H*,2*H*-perfluorodec-1-ene, followed by hydrogenation [9]. The resulting *N*,*N*-diethyl-3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzamide **2b** was converted to **1b** by deoxychlorination with oxalyl chloride, followed by a halogen-exchange reaction with Et_3N–3HF [10]. The fluorous fluorination reagent **1b** is a moisture sensitive white solid and can be kept in a Teflon™ PFA bottle with a tight screw cap under inert atmosphere (Scheme 2).

2.2. Fluorination of alcohols with the fluorous deoxy-fluorination reagent 1b and the separation of products and recovery of 2b by extraction with a fluorous/organic solvent system

Initially, we examined the fluorination ability of **1b** by applying it for the deoxy-fluorination of 1-dodecanol and butyl 5-hydroxypentanoate **6**. The reactions were completed at 98 °C in 3 h, and the corresponding fluorinated products, 1-fluorododecane and

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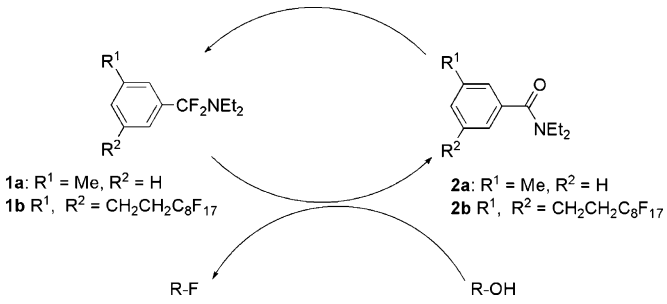
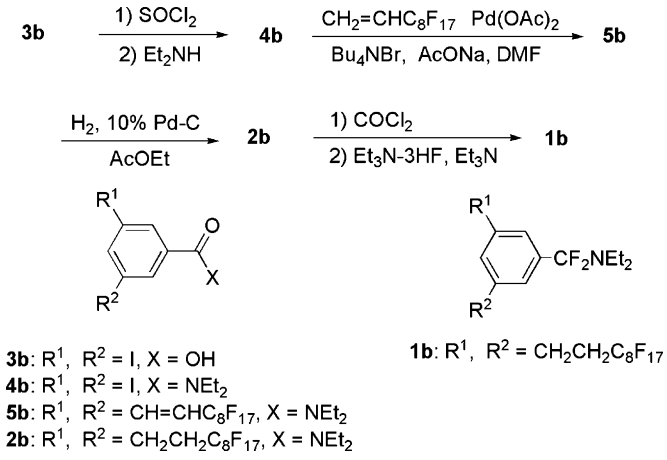


Scheme 1.



Scheme 2.

butyl 5-fluoropentanoate **7**, were obtained in 88% and 87% yields, respectively. These results indicated that the fluorination ability of **1b** is comparable to that of DFMBA **1a** [3], as shown in Table 1.

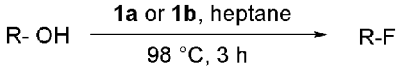
To separate the product and the amide **2b**, their partition ratios in various fluorous and organic solvent systems were examined (Table 2). When FC-77 (a mixture of perfluoroalkanes and pefluorocyclic ethers) was used as the fluorous solvent, an appropriate organic solvent could not be found for their separations (entries 1 and 2). However, better results were obtained with perfluoromethylcyclohexane (PFMC). When **2b** and the product were dissolved in a mixture of PFMC and toluene, the product came to the toluene phase exclusively (>99%), and **2b** was present in PFMC phase selectively (89%) (entry 3). For the separation of **2b** and **7**, the solvent system of FC-77 + HFE-7100 (nonafluorobutyl methyl ether)/CH_3CN (5% H_2O) was superior to the PFMC/toluene system. Thus, when **2b** and **7** were dissolved in that solvent system, **2b** came to the fluorous phase exclusively (>99%), and **7** was predominantly present in the organic phase (97%) (entry 4).

After the reaction of 1-dodecanol with **1b**, the solvent was removed under reduced pressure and the residue was dissolved in the solvent system of PFMC/toluene (2:1). The separated toluene phase was washed with PFMC once and 1-fluorododecane was obtained in a 75% yield (>99% purity) from the toluene phase. On the other hand, GC analysis showed that the PFMC phase contains **2b**, 1-fluorododecane and dodecyl 3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzoate **8** in a ratio of 87:7:6 (Scheme 3) [11]. Benzoate **8** was generated by the hydrolysis of the intermediate derived from 1-dodecanol and **1b** [3], and found only in the PFMC phase. The recovered **2b** and **8** can be converted to **1b**.

In the reaction of **6** with **1b**, the concentrated reaction mixture was dissolved in the solvent system of FC-77 and HFE-7100/CH_3CN (5% H_2O) (2:1). The separated organic layer was washed with a mixture of FC-77 and HFE-7100. From the organic phase, **7** was obtained in a 72% yield (>99% purity). In the fluorous phase, **2b**, **7**, and 4-butoxycarbonylbutyl 3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-benzoate **9** were present in a ratio of 95:2:3 (Scheme 4).

Thus, the fluorination of alcohols **3** and **6** can be achieved with **1b**, and separation of the fluorinated product and recovery of **2b** and the ester (**8** or **9**) are possible by simple extraction with a fluorous/organic solvent systems.

Table 1
Fluorination of alcohols with **1a** or **1b**[a].



Alcohol	Fluorination reagent	Product	Yield (%)[b]
$C_{12}H_{25}$–OH	**1a**	$C_{12}H_{25}$–F	86[c]
$C_{12}H_{25}$–OH	**1b**	$C_{12}H_{25}$–F	88
$BuOOC(CH_2)_4-OH$ 6	**1b**	$BuOOC(CH_2)_4-F$ 7	87

[a] 1.2 equiv. of **1a** or **1b** to alcohol was used.
[b] Isolation yield based on alcohol used.
[c] Ref. [3].

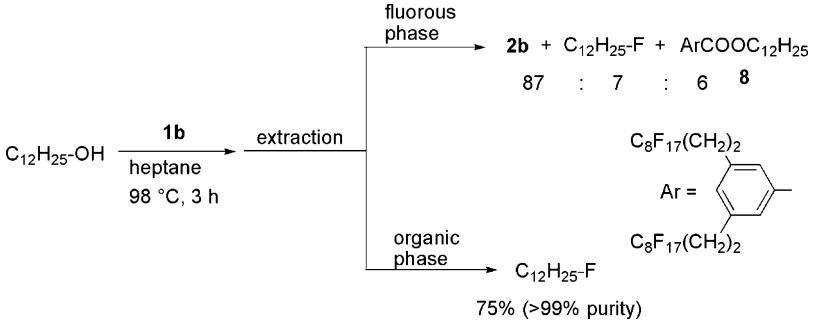
Table 2
Fluorous organic liquid/liquid partition of amide (**2b**) and products.

Entry	Solvent	Partition (fluorous organic)[a]		
		2b	$C_{12}H_{25}$–F	**7**
1	FC-77:hexane (2:1)	89:11	20:80	19:81
2	FC-77:toluene (2:1)	80:20	<1:>99	
3	PFMC:toluene (2:1)	89:11	<1:>99	<1:>99
4	FC-77 + HFE-7100:CH_3CN (5% H_2O) (2:1)[b]	>99:<1	38:62	3:97

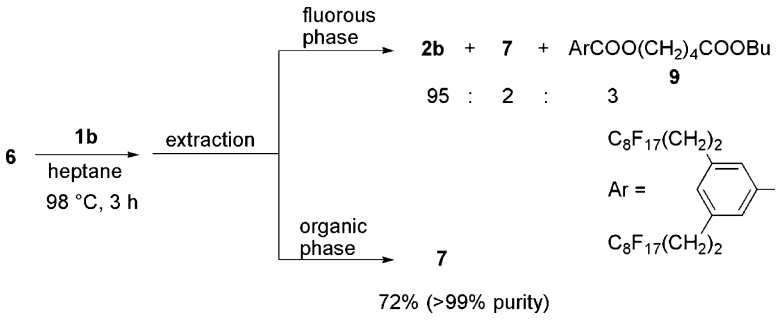
[a] Determined by GC.
[b] FC-77:HFE-7100 = 1:1.

2.3. Fluorination of diols with 1b

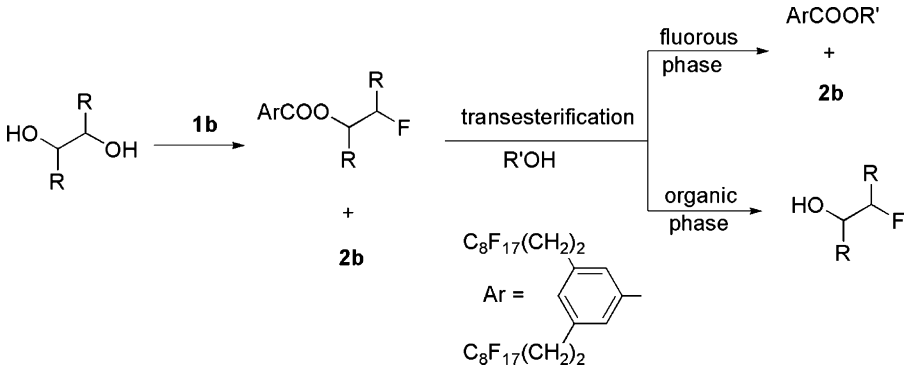
Next, we applied **1b** for the fluorination of 1,2-diols. In the reaction of DFMBA with 1,2- or 1,3-diols, selective monofluorina-



Scheme 3.



Scheme 4.



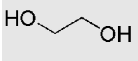
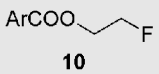
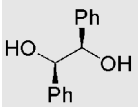
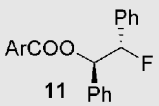
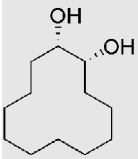
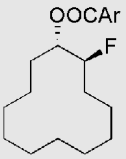
Scheme 5.

tion occurred and 3-methylbenzoates of the corresponding fluorohydrins were formed [5]. The perfluoroalkylated benzoates of fluorohydrins, generated by the reaction of **1b** with 1,2-diols, would be convertible to the corresponding fluorohydrins by transesterification. The separation of the generated fluorohydrins and recovery of the fluorous reagent would be possible by extraction with a fluorous/organic solvent system (Scheme 5).

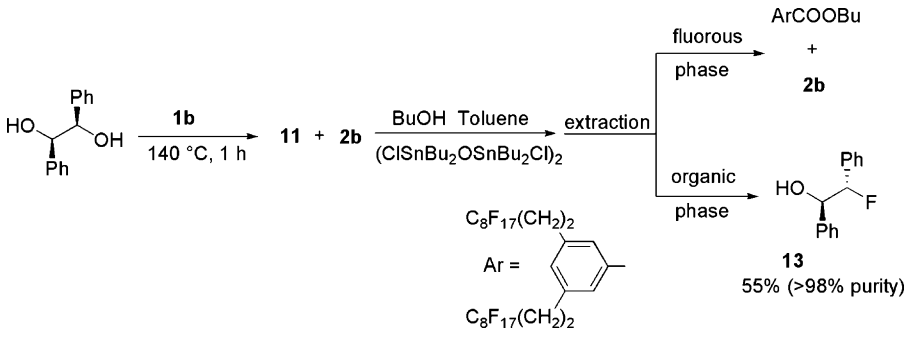
We performed the fluorination of ethylene glycol with 2.4 equiv. of **1b** at 95 °C for 1 h and obtained 2-fluoroethyl 3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzoate **10** in an 84% yield. The reactions of **1b** with (1*R*,2*R*)-1,2-diphenyl-1,2-ethandiol and *cis*-1,2-cyclododecanediol were more sluggish, and higher temperatures (140 and 160 °C, respectively) were required. The resulting perfluoroalkylated benzoates of the corresponding fluorohydrins **11** and **12** were obtained in 74% and 69% yields, respectively (Table 3).

In order to prepare a fluorohydrin, (1*R*,2*S*)-2-fluoro-1,2-diphenylethanol, **11** was subjected to a transesterification reaction after the reaction of **1b** with (1*R*,2*R*)-1,2-diphenyl-1,2-ethandiol without purification. The crude **11**, butanol, and a distannoxane catalyst [12] were dissolved in toluene and the mixture was stirred

Table 3
Fluorination of diols with **1b**[a].

Diol	Reaction cond.	Product	Yield (%)[b]
	95 °C, 1 h	 **10**	84
	140 °C, 1 h	 **11**	74
	160 °C, 1 h	 **12**	69

[a] The reactions were performed using 2.4 equiv. of **1b** to diol without solvent. Ar is 3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl.
[b] Isolation yield based on diol used.



Scheme 6.

under reflux. After the transesterification was completed, the volatile portion was removed under reduced pressure. The residue was dissolved in the solvent system of HFE-7100 and FC-77/CH_3CN (containing 5% H_2O). From the organic phase, (1*R*,2*S*)-2-fluoro-1,2-diphenyl-1-ethanol **13** was obtained in a 55% yield (>98% purity). From the fluorous phase, **2b** (60% based on **1b**) and butyl 3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzoate (38% based on **1b**) were obtained (Scheme 6).

3. Conclusion

We prepared a novel fluorous deoxy-fluorination reagent, *N*,*N*-diethyl-α,α-difluoro-[3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)-benzyl]amine **1b**, and used it for the fluorination of alcohols and diols. The fluorous deoxy-fluorination reagent **1b** has comparable fluorination ability to that of DFMBA, and alcohols can be converted to the corresponding fluorinated products in good yields. After the reaction, the fluorinated products can be isolated in their pure forms by simple extraction with a fluorous/organic solvent system. The amide **2b**, generated from **1b** after fluorination, can be recovered from the fluorous phase of the extract. The fluorous deoxy-fluorination reagent **1b** was also applied to the fluorination of 1,2-diols and the resulting perfluoroalkylated benzoates of the fluorohydrins were converted to the fluorohydrins by the transesterification reaction. The isolation of the fluorohydrins and recovery of the fluorous reagent was achieved by extraction with a fluorous/organic solvent system.

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. Optical rotation was measured with a Horiba High-Sensitive Polarimeter. FC-77 was donated from Central Glass Co. Ltd. PFMC, HFE-7100, and 1*H*,1*H*,2*H*-perfluorodec-1-ene were purchased from Wako Pure Chemical Industries Ltd. 3,5-Diiodobenzoic acid [8], Et_3N–3HF [4], $ClSnBu_2OSnBu_2Cl$ [12] were prepared according to the literatures.

4.2. *N*,*N*-Diethyl-α,α-difluoro-[3,5-bis(1H,1H,2H,2H-perfluorodecyl)benzyl]amine (1b)

A mixture of 3,5-diiodobenzoic acid [8] (3.75 g, 10 mmol) and thionyl chloride (14.3 g, 120 mmol) was stirred under reflux overnight. Excess thionyl chloride was removed under reduced pressure, and CH_2Cl_2 (10 mL) and Et_2NH (3.65 g, 50 mmol) were added at 0 °C successively. After stirring at 0 °C for 30 min, water (50 mL) was added, and the product was extracted with ether (50 mL × 4). The separated organic phase was washed with water (30 mL × 2), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (silica gel/CH_2Cl_2) gave *N*,*N*-diethyl-3,5-diiodobenzamide **4b** (3.22 g) in 75% yield: **4b**; white solid; mp 68 °C. IR (KBr): 2967, 1619, 1538, 1279, 866 cm^{-1}. ^{1}H NMR δ 8.08 (s, 1H), 7.66 (d, *J* = 1.3 Hz, 2H), 3.50 (brs, 2H), 3.23 (brs, 2H), 1.23 (brs, 3H), 1.12 (brs, 3H). ^{13}C NMR δ 167.56, 145.67, 140.56, 134.31 (2C), 94.72 (2C), 43.32 (brs), 39.45 (brs), 14.13 (brs), 12.78 (brs). HRMS (EI): calcd. for $C_{11}H_{13}I_2NO$ (M^+): 428.9087, found: 428.9078.

A mixture of **4b** (0.215 g, 0.5 mmol), 1*H*,1*H*,2*H*-perfluorodec-1-ene (0.49 g, 1.1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Bu_4NBr (0.26 g, 0.8 mmol), and NaOAc (0.11 g, 1.3 mmol) in DMF (5 mL) was stirred under N_2 atmosphere at 115 °C for 4 days. After cooling to room temperature, CH_2Cl_2 (30 mL) and water (30 mL) were added to the reaction mixture. The separated organic phase was washed with water (30 mL × 2), dried over $MgSO_4$. Purification by column chromatography (silica gel/CH_2Cl_2:ether = 10:1) gave *N*,*N*-diethyl-3,5-bis(1*H*,2*H*-perfluorodec-1-enyl)benzamide **5b** (300 mg, 0.28 mmol) in 56% yield: **5b**; white solid; mp 68 °C. IR (KBr): 2992, 1617, 1241, 1214, 1149, 979 cm^{-1}. ^{1}H NMR δ 7.57 (s, 1H), 7.51 (s, 2H), 7.20 (d, *J* = 16.2 Hz, 2H), 6.29 (dt, *J* = 16.0, 11.8 Hz, 2H), 3.57 (brs, 2H), 3.28 (brs, 2H), 1.28 (brs, 3H), 1.15 (brs, 3H). ^{13}C NMR δ 169.44, 139.10 (2C), 138.15 (t, *J* = 9.1 Hz, 2C), 134.75, 127.48, 126.58 (2C), 116.75 (t, *J* = 23.1 Hz, 2C), 43.41 (brs), 39.50 (brs), 14.25 (brs), 12.87 (brs) [13]. ^{19}F NMR δ −81.31 (t, *J* = 9.7 Hz, 6F), −112.01 (dt, *J* = 12.2, 12.2 Hz, 4F), −121.87 (m, 4F), −122.43 (m, 8F), −123.24 (m, 4F), −123.61 (m, 4F), −126.64 (m, 4F). HRMS (EI): calcd. for $C_{31}H_{17}NOF_{34}Na$ ($(M+Na)^+$): 1088.0675, found: 1088.0670.

A mixture of **5b** (1.2 g, 1.10 mmol) and 10%-Pd/C (0.1983 g) in AcOEt (45 mL) was subjected to a flask equipped with balloon (3 L) filled with H_2. The mixture was stirred at room temperature under H_2 atmosphere for 22 h. The catalyst was removed through celite and washed with ether (20 mL × 2). The filtrate was concentrated under reduced pressure to give pure *N*,*N*-diethyl-3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzamide **2b** (1.2 g) in 99% yield: **2b**; white solid; mp 54 °C. IR (KBr): 2988, 1638, 1437, 1371, 1142, 872, 822, 664 cm^{-1}. ^{1}H NMR δ 7.10 (s, 3H), 3.55 (brs, 2H), 3.23 (brs, 2H), 2.91–2.95 (m, 4H), 2.31–2.45 (m, 4H), 1.26 (brs, 3H), 1.11 (brs, 3H). ^{13}C NMR δ 170.74, 140.15 (2C), 138.57, 129.06, 124.54 (2C), 121.43–105.92 (complex signals of CF_3 and CF_2), 43.26 (brs), 39.29 (brs), 32.72 (t, *J* = 22.2 Hz, 2C), 26.33 (t, *J* = 4.2 Hz, 2C), 14.08 (brs), 12.79 (brs). ^{19}F NMR δ −81.31 (t, *J* = 10.4 Hz, 6F), −115.02 (tt, *J* = 16.5, 14.6 Hz, 4F), −122.20 (m, 4F), −122.43 (m, 8F), −123.24 (m, 4F), −123.96 (m, 4F), −126.64 (m, 4F). HRMS (EI): calcd. for $C_{31}H_{21}NOF_{34}Na$ ($(M+Na)^+$): 1092.0989, found: 1092.0984.

To a CH_2Cl_2 solution (30 mL) of **2b** (15.9 g, 14.9 mmol) was added oxalyl chloride (2.1 g, 16.4 mmol) at room temperature and the mixture was stirred under reflux for 24 h. After cooling to 0 °C, Et_3N–3HF (1.85 g, 11.5 mmol) and Et_3N (2.3 g, 23 mmol) were added successively. The generated precipitate was separated by filtration under N_2 atmosphere and washed with hexane (30 mL). The filtrate was concentrated under reduced pressure, and the generated solid was separated by filtration under N_2 atmosphere again. The filtrate was concentrated under reduced pressure and the distillation of the residue gave *N*,*N*-diethyl-α,α-difluoro-[3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzyl]amine **1b** (13.7 g) in 84% yield (bp 200 °C/0.01 mmHg): **1b**; white solid (moisture sensitive). ^{1}H NMR δ 7.34 (d, *J* = 1.0 Hz, 2H), 7.14 (s, 1H), 2.93–2.97 (m, 4H), 2.87 (q, *J* = 7.1 Hz, 4H), 2.32–2.45 (m, 4H), 1.06 (t, *J* = 7.1 Hz, 6H). ^{19}F NMR δ −73.92 (s, 2F), −81.31 (s, 6F), −114.93 (s, 4F), −122.01 (s, 4F), −122.34 (s, 8F), −123.15 (s, 4F), −123.81 (s, 4F), −128.59 (s, 4F).

4.3. Fluorination of alcohols

4.3.1. 1-Fluorododecane

1-Dodecanol (186 mg, 1 mmol), **1b** (1.34 g, 1.2 mmol), and heptane (1 mL) were introduced into a reaction vessel made of Teflon PFA with a tight screw cap, and the mixture was stirred at 98 °C for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of PFMC (10 mL) and toluene (5 mL), and separated toluene phase was washed with PFMC (10 mL) twice. Concentra-

tion of toluene phase gave pure 1-fluorododecane (141 mg) in 75% yield. On the other hand, GC analysis showed that the PFMC phase contains **2b**, 1-fluorododecane, and dodecyl 3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzoate **8** in a ratio of 87:7:6.

1-Fluorododecane [3b]; IR (neat): 2925, 2855, 1466, 1389, 1050, 1010 cm^{-1}. ^1H NMR δ 4.44 (dt, J = 47.3, 6.3 Hz, 2H), 1.74–1.64 (m, 2H), 1.39–1.26 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR δ 14.07, 22.71, 25.19 (d, J = 5.0 Hz), 29.29, 29.39, 29.56, 29.60, 29.67, 29.69, 30.46 (d, J = 19.0 Hz), 31.96, 84.11 (d, J = 163.8 Hz). ^{19}F NMR δ −218.36 to −218.75 (1F, m).

4.3.2. Butyl 5-fluoropentanoate (7)

The reaction was carried out as in the case of 3.3.1 using butyl 5-hydroxypentanoate **6** (174 mg, 1 mmol) instead of 1-dodecanol. After the reaction, volatile part was removed under reduced pressure, and the residue was dissolved in a mixture of FC-77 (10 mL), HFE-7100 (10 mL), and CH_3CN (containing 5% H_2O) (10 mL). The separated CH_3CN phase was concentrated under reduced pressure to gave pure **7** (127 mg) in 72% yield. GC analysis showed that the fluorous phase contained **2b**, **7**, and 5-butoxycarbonylbutyl 3,5-bis(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)benzoate **9** in a ratio of 95:3:2.

Butyl 5-fluoropentanoate **7** [3b], IR (neat): 2962, 1736, 1172 cm^{-1}. ^1H NMR δ 4.46 (dt, J = 47.6, 5.6 Hz, 2H), 4.08 (t, J = 6.6 Hz, 2H), 2.36 (t, J = 6.3 Hz, 2H), 1.80–1.71 (m, 4H), 1.65–1.56 (m, 2H), 1.43–1.33 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR δ 13.58, 19.04, 20.77 (d, J = 5.0 Hz), 29.69 (d, J = 19.9 Hz), 30.58, 33.64, 64.14, 83.47 (d, J = 165.4 Hz), 173.25. ^{19}F NMR δ −219.25 to −219.66 (m, 1F).

4.4. Fluorination of diols

4.4.1. 2-Fluoroethyl 3,5-bis(1H,1H,2H,2H-perfluorodecyl)benzoate (10)

Ethylene glycol (62 mg, 1 mmol) and **1b** (2.674 g, 2.4 mmol) were introduced into a reaction vessel made of Teflon^{TM} PFA with a tight screw cap and the mixture was stirred at 95 °C for 1 h. The reaction mixture was poured into aqueous 5% NaOH (20 mL) and separated aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated uder reduced pressure. Purification by column chromatography (silica gel/CH_2Cl_2–Et_2O) gave **10** (890 mg) in 84% yield. White solid; mp 62.5–63 °C. IR (KBr): 1725, 1454, 1203 cm^{-1}. ^1H NMR δ 7.82 (s, 2H), 7.30 (s, 1H), 4.76 (dt, J = 47.4, 3.7 Hz, 2H), 4.76 (dt, J = 28.8, 4.2 Hz, 2H), 2.94–3.02 (m, 4H), 2.31–2.48 (m, 4H). ^{13}C NMR δ 165.94, 140.22 (2C), 133.34, 130.78, 128.03 (2C), 81.35 (d, J = 170.6 Hz), 64.08 (d, J = 20.2 Hz), 32.73 (t, J = 22.7 Hz, 2C), 26.26 (t, J = 4.1 Hz, 2C) [13]. ^{19}F NMR δ −81.34 (t, J = 9.8 Hz, 6F), −115.10 (quint, J = 14.0 Hz, 4F), −122.25 (s, 4F), −122.50 (s, 8F), −123.30 (s, 4F), −123.99 (s, 4F), −126.70 (s, 4F), −225.03 (tt, J = 47.6, 28.7 Hz, 1F). HRMS (ESI): calcd. for $C_{29}H_{16}O_2F_{35}$ (M^++H): 1061.0592, found: 1061.0609.

4.4.2. (1R,2S)-2-Fluoro-1,2-diphenylethyl 3,5-bis(1H,1H,2H,2H-perfluorodecyl)benzoate (11)

White solid; mp 81–82 °C, $[\alpha]_D^{21} = +23.1$ (c = 1.00, $CHCl_3$). IR (KBr): 1712, 1456, 1148 cm^{-1}. ^1H NMR δ 7.88 (s, 2H), 7.15–7.35 (m, 11H), 6.29 (dd, J = 17.6, 4.0 Hz, 1H), 5.86 (dd, J = 46.2, 4.1 Hz, 1H), 2.90–3.01 (m, 4H), 2.29–2.39 (m, 4H). ^{13}C NMR δ 164.86, 140.24 (2C), 135.41 (d, J = 20.2 Hz), 134.75 (d, J = 3.4 Hz), 133.34, 130.96, 128.85, 128.68, 128.24 (2C), 128.03 (2C), 128.00 (2C), 127.73 (2C), 126.55 (d, J = 7.3 Hz, 2C), 122.00–108.00 (complex signals of CF_3 and CF_2), 94.51 (d, J = 180.3 Hz), 77.99 (d, J = 25.7 Hz), 32.70 (t, J = 22.1 Hz, 2C), 26.26 (t, J = 3.9 Hz, 2C). ^{19}F NMR δ −81.33 (t, J = 9.8 Hz, 6F), −115.06 (quint, J = 14.0 Hz, 4F), −122.23 (s, 4F), −122.48 (s, 8F), −123.29 (s, 4F), −123.97 (s, 4F), −126.69 (s, 4F), −187.70 (dd, J = 46.4, 17.7 Hz, 1F). HRMS (ESI): calcd. for $C_{41}H_{23}O_2F_{35}Na$ ($(M+Na)^+$): 1235.1033, found: 1235.1018.

4.4.3. trans-2-Fluorocyclododecyl 3,5-bis(1H,1H,2H,2H-perfluorodecyl)benzoate (12)

White solid; mp 85.5–86 °C. IR (KBr): 1716, 1469, 1149 cm^{-1}. ^1H NMR δ 7.81 (s, 2H), 7.27 (s, 1H), 5.44–5.55 (m, 1H), 4.85 (ddt, J = 48.6, 8.0, 4.3 Hz, 1H), 2.85–3.07 (m, 4H), 2.27–2.50 (m, 4H), 1.17–1.99 (m, 20H). ^{13}C NMR δ 165.87, 140.08 (2C) 132.96, 131.46, 127.99 (2C), 91.78 (d, J = 175.5 Hz), 72.97 (d, J = 17.0 Hz), 32.76 (t, J = 22.3 Hz, 2C), 28.09 (d, J = 21.2 Hz), 27.31 (d, J = 5.0 Hz), 26.26 (t, J = 3.5 Hz, 2C), 23.87, 23.78, 23.72, 23.68, 22.89, 22.82, 20.65, 20.44 (d, J = 3.5 Hz) [13]. ^{19}F NMR δ −81.34 (t, J = 9.7 Hz, 6F), −115.11 (quint, J = 15.3 Hz, 4F), −122.25 (s, 4F), −122.49 (s, 8F), −123.29 (s, 4F), −123.98 (s, 4F), −126.69 (s, 4F), −193.23 to −193.62 (m, 1F). HRMS (ESI): calcd. for $C_{39}H_{33}O_2F_{35}Na$ ($(M+Na)^+$): 1221.1819, found: 1221.1820.

4.4.4. (1R,2S)-2-Fluoro-1,2-diphenylethanol (13)

A mixture of **1b** (1.337 g, 1.2 mmol) and (1*R*,2*R*)-1,2-diphenyl-1,2-ethandiol (107 mg, 0.5 mmol) was stirred at 140 °C for 1 h. The reaction mixture was cooled to room temperature and 5% aq NaOH (20 mL) was added. The mixture was stirred for 30 min and HFE-7100 (20 mL) was added. The separated aqueous layer was extracted with HFE-7100 (10 mL × 2). The combined HFE-7100 layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in toluene (15 mL) with butanol (1.113 g, 15 mmol) and $ClSnBu_2OSnBu_2Cl$ (553 mg, 1 mmol), and the mixture was stirred under reflux for 8 days. The mixture was cooled to 0 °C and solid part was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in a mixture of FC-77 (20 mL), HFE-7100 (20 mL), and CH_3CN (5% of H_2O) (20 mL). The separated CH_3CN layer was washed with a mixture of FC-77 (20 mL) and HFE-7100 (20 mL), once, and concentrated under reduced pressure to give **13** (60 mg) in 55% yield. ^{19}F NMR analysis of the fluorous layer showed the formation of amide **2b** (60%) and **8** (38%); **13**; white solid; mp 98 °C (lit. [14] 99 °C). $[\alpha]_D^{22.1} = +19.7$ (c = 1.00, MeOH). IR (KBr): 3578, 3033, 2880, 1452, 1050, 965, 706 cm^{-1}. ^1H NMR δ 7.19–7.39 (m, 10H), 5.52 (dd, J = 45.8, 5.6 Hz, 1H), 5.01 (ddd, J = 12.1, 5.5, 4.0 Hz, 1H), 2.11 (d, J = 3.9 Hz 1H). ^{13}C NMR δ 138.82 (d, J = 3.1 Hz), 135.95 (d, J = 19.9 Hz), 128.79 (d, J = 1.7 Hz), 128.25 (2C), 128.19 (2C), 127.00 (2C), 126.98 (2C), 126.78 (d, J = 7.2 Hz), 96.21 (J = 177.8 Hz), 76.31 (d, J = 27.2 Hz). ^{19}F NMR δ −183.83 (dd, J = 45.8, 12.2 Hz, 1F).

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