Selective mono-fluorination of diols *via* a cyclic acetal of *N,N*-diethyl-4-methoxybenzamide

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Abstract

Selective mono-fluorination of 1,2- and 1,3-diols was achieved using *N,N*-diethyl-4-methoxybenzamide diethyl acetal and Et_3N-3HF. The reaction proceeds through a cyclic acetal of the benzamide, and only one hydroxy group was fluorinated and another one was acylated.

Keywords: Mono-fluorination of diol; Benzamide acetal; Triethylamine trishydrogen fluoride

1. Introduction

Recently, we succeeded in the selective mono-fluorination of 1,2- and 1,3-diols using *N,N*-diethyl-α,α-difluoro-4-methylbenzylamine (DFMBA), and a cyclic acetal of the benzamide was expected to be formed as an intermediate from DFMBA and the diol [1]. In this paper, we prepared the cyclic amide acetals from amide diethyl acetals and diols, and converted them to the mono-fluorination products by Et_3N-3HF.

2. Result and discussion

The cyclic acetal of *N,N*-diethyl-3-methylbenzamide (**1a**), which is an expected

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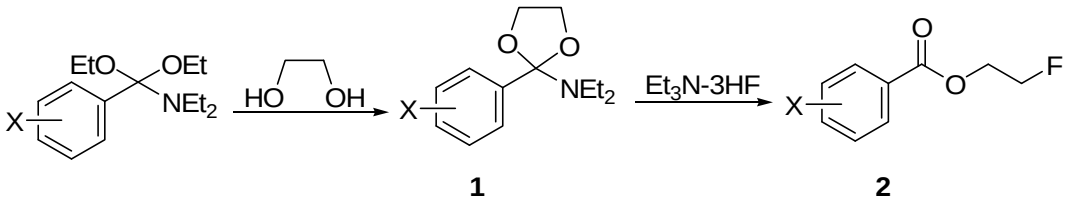
intermediate in the reaction of ethylene glycol with DFMBA [1], was prepared by transacetalization from *N*,*N*-diethyl-3-methylbenzamide diethyl acetal and ethylene glycol [2], and was applied to the fluorination without isolation. When the reaction of **1a** with Et_3N-3HF was carried out at 140 °C for 30 min, 2-fluoroethyl 3-methylbenzoate (**2a**), which is the same product as in the reaction of ethylene glycol with DFMBA [1], was obtained in 66% yield. Similarly, the cyclic acetal of *N*,*N*-diethylbenzamide (**1b**), *N*,*N*-diethyl-4-chlorobenzamide (**1c**), and *N*,*N*-diethyl-4-methoxybenzamide (**1d**) were prepared from the corresponding bezamide diethyl acetal and ethylene glycol, and used for the fluorination reaction under the same conditions. Among them, **1d** gave the best result and 2-fluoroethyl 4-methoxybenzoate (**2d**) was obtained in 80% yield (Table 1). From the cyclic acetals of DMF and DMA, the corresponding fluorination products could not be obtained under the same conditions.

Table 1 Fluorination of ethylene glycol using benzamide diethyl acetals[a]



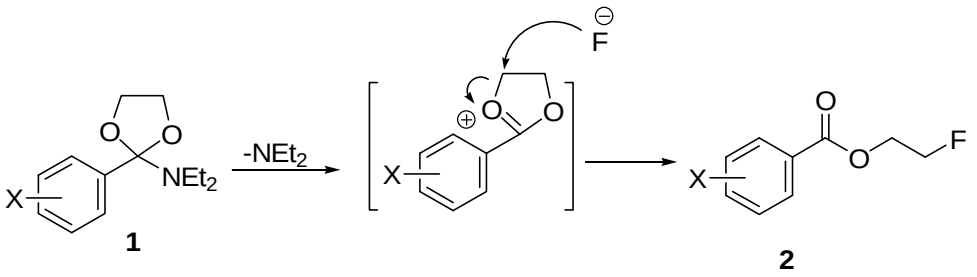
1 **2**

1 (X)	Product **2** (X)	Yield (%)[b]
1a (3-Me)	**2a** (3-Me)	66
1b (H)	**2b** (H)	54
1c (4-Cl)	**2c** (4-Cl)	57
1d (4-MeO)	**2d** (4-MeO)	80

[a] Transacetalization was carried out using 1.1 eq of acetal under reduced pressure at 50°C for 1h. Fluorination was carried out at 140 °C for 30 min using 2 eq of Et_3N-3HF.
[b] Isolated yield based on ethylene glycohol .

The cyclic acetal intermediate **1d** is isolable by distillation after the transacetalization, and from the isolated **1d**, **2d** could be obtained in 83 % yield by the reaction with Et_3N-3HF at 140 ºC for 30 min. These results showed that the reaction

proceeds through the cyclic acetal intermediate **1** as expected. The reaction from **1** to **2** must be proceeding as follows: Elimination of diethylamine from **1** took place to give a dioxolenium intermediate [3], and subsequent fluoride attack, generated from DFMBA or Et_3N-3HF, on the dioxolenium intermediate gave the fluoroethyl benzoate **2** (Scheme 1).

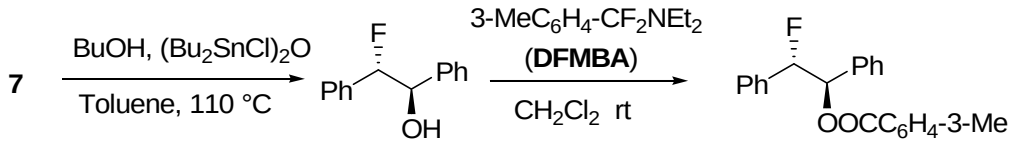


1 **2**

Scheme 1

In order to optimize the reaction conditions, the fluorination reaction of **1d** was carried out under various conditions. Lower temperature (120 °C) or shorter reaction time (10 min) caused the decrease of the yield. On the other hand, higher temperature (160 °C) or longer reaction time (1 h) could not improve the result. We also applied various fluoride sources such as KF, TBAF, Et_3N-2HF, and Et_3N-4HF, but the results could not be improved. The present method was applied to the reaction with various 1,2- and 1,3-diols (Table 2). From *cis*-1,2-cyclohexanediol, *trans*-2-fluorocyclohexyl 4-methoxybenzoate (**3**) was obtained in 75% yield (Entry 1). The reaction proceeded with inversion of the stereochemistry. On the other hand, from *trans*-1,2-cyclohexanediol, *trans*-2-fluorocyclohexanol was obtained in low yield and the expected methoxybenzoyl ester of *cis*-2-fluorocyclohexanol was not formed. In this case, the formation of the cyclic acetal is slow due to the steric effect and a cyclohexene oxide must be initially formed by the reaction of the *trans*-cyclohexanediol with amide acetal [4]. The subsequent ring opening fluorination of the epoxide by Et_3N-3HF provided *trans*-2-fluorocyclohexanol [5]. In the reaction with 1,2-dodecanediol, the fluorination took place non-regioselectively to give a mixture of 1- and 2-fluorinated products (**4a** : **4b** = 71 : 29) (Entry 2). In the reaction of *cis*-1,2-cyclododecandiol, the resulting *trans*-2-fluorocyclododecyl 4-methoxybenzoate was subjected to the transesterification reaction without isolation [6] and

trans-2-fluorocyclododecanol (**5**) was obtained in 56% overall yield from cyclododecandiol (Entry 3). As the reaction proceeds stereoselectively, the optically active fluorohydrin derivatives could be selectively prepared from optically active diols without losing their original enantiomeric purity. For instance, when (*R,R*)-hydrobenzoin was subjected to the reaction, (*1R, 2S*)-2-fluoro-1,2-diphenylethyl 4-methoxybenzoate (**7**) was obtained in 77% yield (>95%de) (Entry 5). Its absolute stereochemistry was determined by comparison of its optical rotation with the product from DFMBA after converting to the 3-methylbenzoic acid ester (Scheme 2). Similarly, from (*R, R*)-2,3-butanediol, (*2R, 3S*)-3-fluoro-2-butyl 4-methoxybenzoate (**6**) was obtained in 79 % yield (>95%de) (Entry 4).



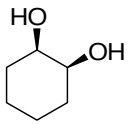
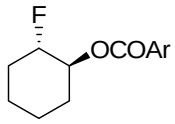
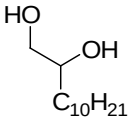
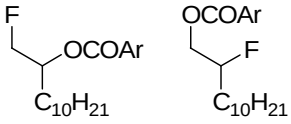
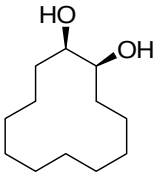
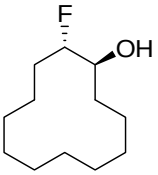
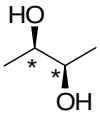
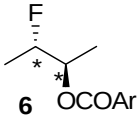
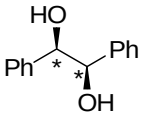
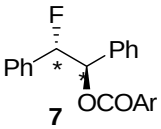
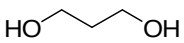
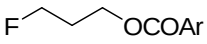
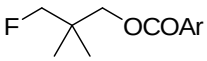
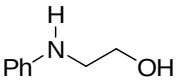
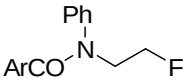
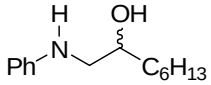
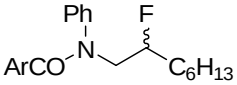
$[\alpha]^{24}_{D}$ = +60.7 (c =1.00, MeOH)

{lit[1] $[\alpha]^{21}_{D}$ = +61.3 (c =1.02, MeOH)}

Scheme 2

The reaction of 1,3-diols is sluggish and higher temperature (160 ºC) was required to complete the reaction (Entries 6 and 7). Recently, we found that the reaction of β-amino alcohols with DFMBA also proceeds through the similar cyclic intermediate to give fluoroalkylamides [7]. The reaction of *N*-phenyl-2-aminoethanol and *N*-phenyl-1-amino-2-octanol with the benzamide diethyl acetal and Et_3N-3HF proceeded as in the case of DFMBA and *N*-acylated 2-fluoroethylamine (**10**) and 2-fluorooctylamine (**11**) were obtained, respectively (Entries 8 and 9).

Table 2 Fluorination of diols and amino alcohol using *p*-methoxybenzamide diethyl acetal and Et_3N-3HF[a]

Entry	Substrate	Product	Yield(%)[b]
1		 **3**	75
2		 **4a** 71 : 29 **4b**	83
3		 **5**	56[c]
4		 **6**	79 (>95)
5		 **7**	77 (>95)
6		 **8**	60[d]
7		 **9**	66[d]
8		 **10**	72[e]
9		 **11**	72[e]

[a]If otherwise not mentioned, the reaction was carried out at 140 °C for 30 min. Ar = *p*-$MeOC_6H_4$.
[b]Isolated yield based on diol or amino alcohol used and in paretheses, diasteromeric excess.
[c]1,2-Dichloroethane was used as solvent and the product was converted to fluorohydrin before isolation.
[d]The reaction was carried out at 160 °C for 30 min. [e]The reaction was carried out at 100 °C for 30 min.

3. Experimental

3.1. General methods

The melting points were measured with a Yanagimoto micro melting-point apparatus and uncorrected. 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) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (^{1}H, ^{13}C) and $CFCl_3$ (^{19}F), respectively. The ^{1}H NMR (270 MHz) spectra and ^{13}C NMR (68 MHz) spectra were recorded on a JEOL JNM-A270II FT NMR. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. Optical rotation was measured with a Horiba High Sensitive Polarimeter. *cis*-1,2-Cyclohexanediol, 1,2-dodecanediol, (*R*,*R*)-2,3-butanediol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, *N*-phenyl-2-ethanolamine *N*,*N*-diethylbenzamide, *N*,*N*-diethyl-4-methyoxybenzamide, *N*,*N*-diethyl-3-methylbenzamide, and *N*,*N*-diethyl-4-chlorobenzamide were purchased from Tokyo Chemical Industry Co., Ltd. *cis*-1,2-Cyclododecanediol was separated by column chromatography from a mixture of the stereoisomers obtained from Tokyo Chemical Industry Co., Ltd. (*R, R*)-Hydrobenzoin (99%ee) was obtained from Aldrich. Et_3N-3HF was prepared according to the literature [8]. Dichlorotetrabutyldistannoxane was prepared according to the literature [9]. A 30 ml-Teflon FEP centrifuge tube with screw cup was obtained from Flon Industry and used as a reaction vessel in fluorination reaction.

3.2. Preparation of N,N-diethyl-4-methoxybenzamide diethyl acetal

To a 300 ml three-necked glass flask equipped with mechanical stirrer, a reflux

condenser, and a dropping funnel were introduced *N,N*-diethyl-4-methoxybenzamide (20.73 g, 100 mmol) and CH_2Cl_2 (50 ml) under N_2 atmosphere. After addition of oxalyl chloride (12.95 g, 102 mmol) from the dropping funnel at room temperature, the reaction mixture was stirred under reflux for 90 min. The mixture was cooled to -40 ºC, and a dry ethanol (27.64 g, 600 mmol) and Et_3N (20.60 g, 204 mmol) were added successively. Then, the temperature was allowed to rise up to room temperature and CH_2Cl_2 was carefully removed under reduced pressure. After the addition of hexane (100 ml), the precipitate was removed by filtration under N_2 atmosphere. The filtrate was concentrated under reduced pressure and the residue was distilled to give *N,N*-diethyl-4-methoxybenzamide diethyl acetal (14.08 g, 50 mmol) in 50% yield (bp 94 ºC/0.42 mmHg**)**. As it is moisture sensitive, it was kept and used as 1M CH_2Cl_2 solution under N_2. IR: (neat) ν 2972, 1609, 1509, 1244, 1083 cm^{-1}. ^1H NMR (270 MHz) δ 0.97 (t, *J* = 7.1 Hz, 6H), 1.17 (t, *J* = 7.1 Hz, 6H), 2.60 (q, *J* = 7.1 Hz, 4H), 3.25 – 3.37 (m, 2H), 3.45 – 3.56 (m, 2H), 3.80 (s, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (68MHz) δ 15.05 (2C), 16.05 (2C), 42.37 (2C), 55.14, 56.37 (2C), 109.02, 112.59 (2C), 128.37 (2C), 132.71, 158.67. HRMS (EI): calc. for $C_{16}H_{27}NO_3$: 281.1991 found: 281.1990.

*3.2.1. N,N-Diethyl 4-methoxybenzamide ethylene acetal (**1d**)*

bp 85 ºC/0.28 mmHg. IR (neat): 2968, 1509, 1246 cm^{-1}. ^1H NMR (270 MHz) δ 0.98 (t, *J* = 7.16, 6H), 2.71 (q, *J* = 7.11, 4H), 3.73 – 3.78 (m, 2H), 3.82 (s, 3H), 4.01 – 4.06 (m, 2H), 6.84 – 6.89 (m, 2H), 7.45 – 7.48 (m, 2H). ^{13}C NMR δ 14.18 (2C), 40.34 (2C), 55.20, 63.85 (2C), 113.07 (2C), 119.75, 128.31 (2C), 133.13, 159.38. HRMS (EI): calc. for $C_{14}H_{20}NO_3$ (M^+-H): 250.1443 found: 250.1447.

3.3. Fluorination of diols

*3.3.1. 2-Fluoroethyl 4-methoxybenzoate (**2d**)*

A mixture of ethylene glycol (62 mg, 1 mmol) and a CH_2Cl_2 solution of *N*,*N*-diethyl-4-methoxybenzamide diethyl acetal (1.2 ml of 1 M solution, 1.2 mmol) in a 30 ml-Teflon FEP tube was stirred at 50 ºC under reduced pressure for 1 h to remove the generate ethanol and complete the transacetalization. To the crude **1d**, Et_3N-3HF (322 mg, 2 mmol) was added and the mixture was stirred at 140 ºC for 30 min. The reaction mixture was cooled to room temperature and aq $NaHCO_3$ (6 ml) was added. The product was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-ether) gave **2d** (158 mg, 0.8 mmol) in 80 % yield. IR: (neat) ν 2959, 1715, 1607, 1511, 1258, 1169 cm^{-1}. ^1H NMR (400 MHz) δ 3.87 (s, 3H), 4.59 (dt, *J* = 28.8, *J* = 4.2 Hz, 2H), 4.68 (dt, *J* = 47.4, *J* = 4.2 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz) δ 55.42, 63.54 (d, *J* = 19.9 Hz), 81.55 (d, *J* = 170.4 Hz), 113.64 (2C), 122.03 (2C), 131.79, 163.55, 166.08. ^{19}F NMR (376 MHz) δ -225.01 (tt, *J* = 47.6, *J* = 28.7 Hz, 1F). HRMS (EI): calc. for $C_{10}H_{11}FO_3$: 198.0686 found 198.0692.

*3.3.2. 2-Fluoroethyl 3-methylbenzoate (**2a**)*

IR: (neat) ν 2958, 1725, 1596, 1276 cm^{-1}. ^1H NMR (400 MHz) δ 2.40 (s, 3H), 4.52 – 4.80 (m, 4H) 7.31 – 7.38 (m, 2H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H). ^{13}C NMR (100 MHz) δ 21.12, 63.70 (d, *J* = 20.7 Hz), 81.39 (d, *J* = 171.0 Hz), 126.80, 128.23, 129.50, 130.15, 133.91, 138.14, 166.43. ^{19}F NMR (376 MHz) δ -225.03 (tt, *J* = 47.6, *J* = 28.7 Hz, 1F). HRMS (EI): calc. for $C_{10}H_{11}FO_2$: 182.0743 found 182.0743.

*3.3.3. 2-Fluoroethyl benzoate (**2b**)*

IR: (neat) ν 2958, 1724, 1276 cm^{-1}. ^1H NMR δ 4.53 – 4.81 (m, 4H), 7.26 – 7.48 (m, 2H), 7.56 – 7.60 (m, 1H), 8.07 – 8.10 (m, 2H). ^{13}C NMR (100 MHz) δ 63.83 (d, *J* = 19.9 Hz), 81.43 (d, *J* = 170.9 Hz), 128.42 (2C), 129.66, 129.75 (2C), 133.24, 166.37.

^{19}F NMR (376 MHz) δ -225.09 (tt, *J* = 47.6, *J* = 28.6 Hz, 1F). HRMS (EI): calc. for $C_9H_9FO_2$: 168.0586 found 168.0589.

*3.3.4. 2-Fluoroethyl 4-chlorobenzoate (**2c**)*

IR: (neat) ν 2958, 1725, 1596, 1276 cm^{-1}. ^{1}H NMR (400 MHz) δ 4.52 – 4.80 (m, 4H), 7.42 – 7.45 (m, 2H), 8.00 – 8.03 (m, 2H). ^{13}C NMR (100 MHz) δ 64.03 (d, *J* = 19.8 Hz), 81.31 (d, *J* = 170.9 Hz), 128.06, 128.78 (2C), 131.13 (2C), 139.72, 165.49. ^{19}F NMR (376 MHz) δ -225.13 (tt, *J* = 47.6, *J* = 28.7 Hz, 1F). HRMS (EI): calc. for $C_9H_8ClFO_2$: 202.0197 found 202.0181.

*3.3.5. trans-2-Fluorocyclohexyl 4-methoxybenzoate (**3**)*

IR: (neat) ν 2994, 1713, 1607, 1259, 1103 cm^{-1}. ^{1}H NMR (400 MHz) δ 1.34 – 1.81 (m, 6H), 2.12 – 2.20 (m, 2H), 3.86 (s, 3H), 4.59 (dm, *J* = 50.3 Hz, 1H), 5.05 – 5.13 (m, 1H), 6.91 – 6.94 (m, 2H), 8.00 – 8.03 (m, 2H). ^{13}C NMR (100 MHz) δ 22.76 (d, *J* = 9.5 Hz), 22.99, 29.38 (d, *J* = 6.1 Hz), 30.40 (d, *J* = 18.3 Hz), 55.43, 74.03 (d, *J* = 19.5 Hz), 91.93 (d, *J* = 178.5 Hz), 113.55 (2C), 122.73, 131.70 (2C), 163.37, 165.62. ^{19}F NMR (376 MHz) δ -182.11 (brd, *J* = 45.2 Hz, 1F). HRMS (EI): calc. for $C_{14}H_{17}FO_3$: 252.1162 found 252.1162.

*3.3.6. 1-Fluoro-2-dodecyl 4-methoxybenzoate (**4a**)*

IR: (neat) ν 2926, 1714, 1607, 1257 cm^{-1}. ^{1}H NMR (400 MHz) δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.24 – 1.43 (m, 16H), 1.67 – 1.83 (m, 2H), 3.36 (s, 3H), 4.56 (dm, *J* = 45.0 Hz, 2H), 5.26 (dm, *J* = 19.2 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (100 MHz) δ 14.10, 22.66, 25.19, 29.29, 29.40 (2C), 29.50, 29.55, 29.71 (d, *J* = 5.5 Hz), 31.87, 55.43, 72.56 (d, *J* = 19.2 Hz), 83.77 (d, *J* = 173.9 Hz), 113.59 (2C), 122.47, 131.74 (2C), 163.45, 165.83. ^{19}F NMR (376 MHz) δ -231.25 (dt, *J* = 22.6, *J* = 47.7 Hz, 1F). HRMS (EI): calc. for $C_{20}H_{31}FO_3$: 338.2257 found: 338.2256.

*3.3.7. 2-Fluoro-1-dodecyl 4-methoxybenzoate (**4b**)*

White solid. mp 36 ºC. IR: (KBr) ν 2926, 1718, 1607, 1257 cm^{-1}. ^{1}H NMR (400 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.26 – 1.84 (m, 18H), 3.87 (s, 3H), 4.29 – 4.50 (m, 2H), 4.79 (dm, *J* = 49.0 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz) δ 14.10, 22.67, 24.81 (d, *J* = 4.3 Hz), 29.31, 29.35, 29.42, 29.51, 29.57, 31.46 (d, *J* = 20.6 Hz), 31.88, 55.43, 66.01 (d, *J* = 22.3 Hz), 91.58 (d, *J* = 172.1 Hz), 113.64 (2C), 122.16, 131.77 (2C), 163.52, 166.06. ^{19}F NMR (376 MHz) δ -187.52 – -187.13 (m, 1F). HRMS (EI): calc. for $C_{20}H_{31}FO_3$: 338.2257 found: 338.2262.

*3.3.8. trans-2-Fluorocyclododecanol (**5**)*

A CH_2Cl_2 solution of *N*,*N*-diethyl-4-methoxybenzamide diethyl acetal (1.2 ml of 1 M solution, 1.2 mmol) and *cis*-1,2-cyclododecanediol (200 mg, 1 mmol) were introduced into a 30 ml-Teflon FEP tube, and a volatile part was removed under reduced pressure. Then 1 ml of 1,2-dichloroethane was added and the reaction mixture was stirred at 50 ºC for 1 h under reduced pressure. To the reaction mixture, Et_3N-3HF (325 mg, 2.1 mmol) was added and the mixture was stirred at 140 ºC for 30 min. The reaction mixture was cooled to room temperature and aq $NaHCO_3$ (6 ml) was added. The product was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product, butanol (10 ml), and dichlorotetrabutyldistannoxane (0.534 mg, 1 mmol), and toluene (5 ml) were introduced into a 25-ml glass flask equipped with a reflux condenser and the mixture was stirred under reflux. The transesterification reaction was monitored by GC and the disappearance of the 2-fluorocyclododecyl 4-methoxybenzoate was confirmed after 160 h. After removal of the volatile part under reduced pressure, 2-fluorocyclododecanol (112 mg, 0.56 mmol) was isolated by column chromatography (silica gel/hexane-ether)

in 56 % overall yield from the diol. White solid. mp 65 ºC. IR: (KBr) ν 3366, 2933, 1470, 1022 cm^{-1}. ^{1}H NMR (400 MHz) δ 1.26 – 1.95 (m, 20H), 2.21 (t, *J* = 3.3 Hz, 1H), 3.84 – 3.96 (m, 1H), 4.56 (dm, *J* = 49.5 Hz, 1H). ^{13}C NMR (100 MHz) δ 20.35 (d, *J* = 3.3 Hz), 20.57, 22.55, 22.59, 23.72, 23.76, 23.98, 24.01, 27.83 (d, *J* = 21.7 Hz), 28.73 (d, *J* = 5.6 Hz), 70.44 (d, *J* = 18.4 Hz), 95.31 (d, *J* = 166.1 Hz). ^{19}F NMR (376 MHz) δ -194.02 – -194.32 (m, 1F). HRMS (EI): calc. for $C_{12}H_{23}FO$: 202.1733 found: 202.1726.

*3.3.9. (2R, 3S)-3-Fluoro-2-butyl 4-methoxybenzoate (**6**)*

IR: (neat) ν 2988, 1713, 1258, 1168, 1101 cm^{-1}. ^{1}H NMR (400 MHz) δ 1.35 – 1.44 (m, 6H), 3.86 (s, 3H), 4.78 (dm, *J* = 48.3 Hz, 1H), 5.16 (dm, *J* = 18.3 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 8.01 (d, *J* = 9.1 Hz, 2H). ^{13}C NMR (100 MHz) δ 14.14 (d, *J* = 6.3 Hz), 16.40 (d, *J* = 22.8 Hz), 55.24, 71.94 (d, *J* = 22.4 Hz), 90.83 (d, *J* = 172.3 Hz), 113.49 (2C), 122.50, 131.55 (2C), 163.37, 165.37. ^{19}F NMR (376 MHz) δ -224.81 – -225.21 (m, 1F). (2*R*, 3*R*)-isomer, -186.64 – -186.03 (m, 1F)). HRMS (EI): calc. for $C_{12}H_{15}FO_3$: 226.1005, found 226.1008. $[\alpha]_D^{22.4}$ = -10.0 (c = 1.00, MeOH).

*3.3.10. (1R, 2S)-2-Fluoro-1,2-diphenylethyl 4-methoxybenzoate (**7**)*

White solid. mp 100 ºC. IR: (KBr) ν 1709, 1258, 706 cm^{-1}. ^{1}H NMR (400 MHz) δ 3.87 (s, 3H), 5.85 (dd, *J* = 46.3, *J* = 4.1 Hz, 1H), 6.26 (dd, *J* = 18.1, *J* = 4.2 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 7.18 – 7.32 (m, 10H), 8.02 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (100 MHz) δ 55.36, 77.35 (d, *J* = 25.4 Hz), 94.44 (d, *J* = 81.1 Hz), 113.65 (2C), 122.09, 126.37, 126.44, 127.75 (2C), 127.99 (2C), 128.04 (2C), 128.41, 128.61, 131.76 (2C), 134.97 (d, *J* = 2.9 Hz), 135.59 (d, *J* = 20.6 Hz), 163.57, 164.90. ^{19}F NMR (376 MHz) δ -188.91 (dd, *J* = 46.3, *J* =18.3 Hz, 1F). HRMS (EI): calc. for $C_{22}H_{19}FO_3$: 350.1318 found: 350.1316. $[\alpha]_D^{20.4}$ = +96.0 (c = 1.00, MeOH).

(1R, 2S)-2-Fluoro-1,2-diphenylethanol

Butanol (13 ml), **7** (298 mg, 0.85 mmol), dichlorotetrabutyldistannoxane (578 mg, 1.1 mmol), and toluene (5 ml) were introduced into a 25-ml glass flask equipped with a reflux condenser, and the mixture was stirred under reflux for 90 h. After removal of the volatile part under reduced pressure, (*1R, 2S*)-2-fluoro-1,2-diphenylethanol (330 mg, 0.65 mmol) was isolated by column chromatography (silica gel/hexane-ether). White solid. mp 98 ºC (lit.[10] 99 ºC). IR: (KBr) 3578, 3033, 2880, 1452, 1050, 965, 706 cm^{-1}. ^{1}H NMR (400 MHz) δ 2.10 (d, *J* = 3.9 Hz, 1H), 4.98 – 5.03 (m, 1H), 5.52 (dd, *J* = 45.8, *J* = 5.56 Hz, 1H), 7.22 – 7.35 (m, 10H). ^{13}C NMR (100 MHz) δ 76.31 (d, *J* = 27.2 Hz), 96.21 (*J* = 177.8 Hz), 126.78 (d, *J* = 7.2 Hz), 126.98 (2C), 127.00 (2C), 128.19 (2C), 128.25 (2C), 128.79 (d, *J* = 1.7 Hz), 135.95 (d, *J* = 19.9 Hz), 138.82 (d, *J* = 3.1 Hz). ^{19}F NMR (376 MHz) δ -183.83 (dd, *J* = 45.8, *J* = 12.2 Hz, 1F). $[\alpha]_D^{22.1}$ = +19.7 (c = 1.00, MeOH).

(1R, 2S)-2-Fluoro-1,2-diphenylethyl 3-methylbenzoate

To a CH_2Cl_2 solution (3 ml) of 2-fluoro-1,2-diphenylethanol (66 mg, 0.3 mmol) in a 30 ml-Teflon FEP tube was added DFMBA (70 mg, 0.33 mmol) at 0 ºC, and the mixture was stirred at room temperature for 1 h. To the reaction mixture, 2 ml of water was added and the separated aqueous layer was extracted with ether three times. Organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/hexane-ether) to give 2-fluoro-1,3-diphenylethyl 3-methylbenzoate (87 mg, 0.26 mmol). $[\alpha]^{24}_D$ = +60.7 (c = 1.00, MeOH) {lit[1] $[\alpha]^{21}_D$ = +61.3 (c = 1.02, MeOH)}

*3.3.11. 3-Fluoro-1-propyl 4-methoxybenzoate (**8**)*

IR: (neat) ν 2970, 1710, 1607, 1511, 1257, 1103 cm^{-1}. ^{1}H NMR (400 MHz) δ 2.16 (dm, *J* = 25.7 Hz, 2H), 3.87 (s, 3H), 4.43 (t, *J* = 6.2 Hz, 2H), 4.62 (dt, *J* = 46.9, *J* =

5.9 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (100 MHz) δ 29.81 (d, *J* = 19.8 Hz), 55.26, 60.44 (d, *J* = 5.7 Hz), 80.61 (d, *J* = 165.2 Hz), 113.50 (2C), 122.37, 131.45 (2C), 163.31, 166.03. ^{19}F NMR (376 MHz) δ -222.57 (tt, *J* = 47.0, *J* = 25.7 Hz, 1F). HRMS (EI): calc. for $C_{11}H_{13}FO_3$: 212.0849 found: 212.0841.

*3.3.12. 3-Fluoro-2,2-dimethylpropyl 4-methoxybenzoate (**9**)*

IR: (neat) ν 2968, 1714, 1607, 1258 cm^{-1}. ^{1}H NMR (400 MHz) δ 1.05 (d, *J* = 1.8 Hz, 6H), 3.84 (s, 3H), 4.14 (d, *J* = 1.1 Hz, 2H), 4.27 (d, *J* = 47.9 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (100 MHz) δ 20.63 (d, *J* = 5.0 Hz, 2C), 35.87 (d, *J* = 17.4 Hz), 55.26, 68.56 (d, *J* = 4.1 Hz), 88.10, 113.54 (2C), 122.44, 131.42 (2C), 163.32, 165.92. ^{19}F NMR (376 MHz) δ -226.89 (t, *J* = 47.6 Hz, 1F). HRMS (EI): calc. for $C_{13}H_{17}FO_3$: 240.1162 found: 240.1160.

*3.4.3. N-(2-Fluoroethyl)-N-phenyl 4-methoxybenzamide (**10**)*

IR: (neat) ν 2959, 2839, 1642, 1606, 1254 cm^{-1}. ^{1}H NMR (400 MHz) δ 3.74 (s, 3H), 4.19 (dt, *J* = 25.6, *J* = 4.9 Hz, 2H), 4.75 (dt, *J* = 47.5, *J* = 4.9 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 2H), 7.09 – 7.29 (m, 7H). ^{13}C NMR (100 MHz) δ 51.58 (d, *J* = 21.4 Hz), 55.10, 81.43 (d, *J* = 169.0 Hz), 112.91 (2C), 126.48, 127.47 (2C), 127.58, 129.14 (2C), 130.90 (2C), 144.46, 160.67, 170.12. ^{19}F NMR (376 MHz) δ -222.81 – -222.43 (m, 1F). HRMS (EI): calc. for $C_{16}H_{16}FNO_2$: 273.1165 found: 273.1159.

*3.4.2. N-(2-Fluorooctyl)-N-phenyl 4-methoxybenzamide (**11**)*

White solid. mp 47 ºC. IR: (KBr) ν 2931, 2857, 1644, 1606, 1254 cm^{-1}. ^{1}H NMR (400 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.29 – 1.72 (m, 10H), 3.70 (s, 3H), 3.71 – 3.78 (m, 1H), 4.30 (ddd, *J* = 33.7, *J* = 14.4, *J* = 2.1 Hz, 1H), 4.95 (dm, *J* = 51.0 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 2H), 7.09 – 7.29 (m, 7H). ^{13}C NMR (100 MHz) δ 13.93, 22.40, 24.69 (d, *J* = 3.0 Hz), 28.92, 31.52, 32.85 (d, *J* = 19.9 Hz), 54.99, 55.48 (d, *J* = 21.4 Hz),

92.13 (d, *J* = 170.5 Hz), 112.83 (2C), 126.26, 127.42 (2C), 127.72, 128.97 (2C), 130.82 (2C), 144.80, 160.56, 170.09. ^{19}F NMR (376 MHz) δ -184.97 – -184.58 (m, 1F). HRMS (EI): calc. for $C_{22}H_{28}NO_2F$: 357.2104 found: 357.2103.

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