Enantioselective Fluorination of $\alpha$-Branched Aldehydes and Subsequent Conversion to $\alpha$-Hydroxyacetals via Stereospecific C–F Bond Cleavage

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Supplementary Information

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**General methods:** All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere and stirred using magnetic stir-plates. Thin-layer chromatography analyses were performed using Merck pre-coated silica gel plates with 254 indicator. Visualization was accomplished by UV light (254 nm), potassium permanganate, phosphomolybdic acid, or anisaldehyde. Flash column chromatography was performed using silica gel 60 (mesh 230-400) supplied by Kanto Chemical Co., Inc. $^1$H, $^{13}$C, and $^{19}$F NMR spectra were recorded on a JEOL JNM-ECX400 (400 MHz $^1$H, 100 MHz $^{13}$C, 376 MHz $^{19}$F) or a JEOL JNM-ECX500 (500 MHz $^1$H, 126 MHz $^{13}$C, 470 MHz $^{19}$F). Chemical shift values (δ) are reported in ppm (tetramethylsilane δ 0.00 ppm, residual benzene δ 7.15 ppm or methanol δ 3.31 for $^1$H; hexafluorobenzene δ –162.20 ppm for $^{19}$F; residual chloroform δ 77.0 ppm, benzene δ 128.0 or methanol δ 49.0 ppm for $^{13}$C). Optical rotations were measured on a JASCO P-1030 digital polarimeter. GC analysis was performed with a Shimadzu model 2014 instrument. Analytical HPLC was performed on a JASCO PU1586 with a UV-1575 UV/Vis detector using a chiral column. DART mass (positive mode) analyses were performed on a LC-TOF JMS-T100LP. We confirmed that the optical purity of selected products 5a and 10a did not change even after chromatographic purification using silica gel and subsequent solvent evaporation.

**Materials:** Commercial grade reagents and solvents were used without further purification unless otherwise noted. Anhydrous $t$-butyl methyl ether (TBME), ethyl acetate, dimethylformamide (DMF), methanol and ethylene glycol were purchased from Aldrich. Anhydrous acetonitrile and acetone were purchased from Wako Pure Chemical Industries, Ltd. Anhydrous toluene, dichloromethane, tetrahydrofuran (THF), and benzene were purchased from Kanto Chemical Co. Inc. and used after purification by GLASS-Contour Solvent Dispensing System, but benzene was used without purification. Chiral primary amine catalysts 1c was synthesized from ($R$)-BINOL according to the reported procedure.

**Synthesis of chiral primary amine catalysts 1 (Scheme 2).**

![Synthesis of chiral primary amine catalysts 1](image-url)
A solution of \((R)-14\) (3 mmol), 3,5-di-\(t\)-Bu-phenylboronic acid (9 mmol, 3 equiv), \(\text{Pd(OAc)}_2\) (67.4 mg, 0.3 mmol, 10 mol%), \(\text{PPh}_3\) (173.1 mg, 0.66 mmol, 22 mol%), and \(\text{K}_3\text{PO}_4\cdot\text{nH}_2\text{O}\) (150 wt%) in dry THF (30 mL) was degassed by bubbling argon through this solution for 30 min. The solution was refluxed for 15 h under argon atmosphere. The resulting mixture was poured into saturated aq.\(\text{NH}_4\text{Cl}\), and the whole mixture was filtered to remove the catalyst, then extracted with ethyl acetate. The organic extracts were dried over \(\text{Na}_2\text{SO}_4\) and concentrated. The crude mixture was purified by silica gel column chromatography (hexane : \(\text{CH}_2\text{Cl}_2 = 5:1\)) to give 75% yield of \((R)-15\) (white solid). \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\)): \(\delta\) 8.14 (s, 2H), 7.99 (d, \(J = 7.9\) Hz, 2H), 7.58–7.36 (m, 12H), 1.40 (s, 36H); \(^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\)): \(\delta\) 150.9, 144.3, 135.5, 135.3, 132.9, 132.5, 128.3, 127.6, 127.4, 127.3, 125.5, 124.0, 122.2, 119.2, 116.0, 34.9, 31.3; \(^{19}\text{F} \text{NMR (376 MHz, CDCl}_3\)): \(\delta\) –75.8; \([\alpha]_D^{23} –194.3\) (c = 6.4, CHCl\(_3\)); HRMS (DART): Anal. For \(\text{C}_{40}\text{H}_{53}\text{F}_{6}\text{O}_{6}\text{S}_2\) +1 [M+H]\(^+\) Calcd.: 927.3188, Found: 927.3185.

To a solution of \((R)-15\) (1.46 mmol) and \(\text{NiCl}_2(\text{PPh}_3)_2\) (95.5 mg, 0.146 mmol, 10 mol%) in TBME (14.6 mL) was added 3M ethereal solution of MeMgl (2.92 mL, 8.76 mmol, 6 equiv) at 0 °C. The solution was refluxed for 16 h under argon atmosphere. This mixture was poured into ice-cooled 1M HCl, and the whole mixture was filtered to remove the catalyst. The filtrate was poured into saturated aq.\(\text{NaHCO}_3\), and extracted with dichloromethane. The organic extracts were dried over \(\text{Na}_2\text{SO}_4\) and concentrated. The crude mixture was purified by silica gel column chromatography (hexane : \(\text{CH}_2\text{Cl}_2 = 10:1\)) to give 91% yield of \((R)-16\) (white solid). \(^1\text{H} \text{NMR (500 MHz, CDCl}_3\)): \(\delta\) 7.94–7.87 (m, 4H), 7.48–7.45 (m, 2H), 7.41–7.38 (m, 2H), 7.36–7.34 (m, 4H), 7.25–7.18 (m, 4H), 2.03 (s, 6H), 1.40 (s, 36H); \(^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\)): \(\delta\) 150.2, 142.4, 141.4, 136.6, 132.9, 132.1, 132.0, 128.2, 127.9, 126.0, 125.8, 125.3, 123.9, 120.7, 35.0, 31.6, 18.4; \([\alpha]_D^{21} +51.5\) (c = 9.5, CHCl\(_3\)); HRMS (DART): Anal. For \(\text{C}_{50}\text{H}_{58}\) +1 [M+H]\(^+\) Calcd.: 659.4617, Found: 659.4616.
A solution of (R)-16 (3.24 mmol), N-bromosuccinimide (NBS) (1.27 g, 7.13 mmol, 2.2 equiv), and 2,2’-azobis(isobutyronitrile) (AIBN) (53.2 mg, 0.324 mmol, 10 mol%) in benzene (16.2 mL) was refluxed for 3 h. After being cooled to room temperature, the mixture was poured into water and extracted with ethyl acetate. The organic extracts were dried over Na₂SO₄ and concentrated. The crude mixture was purified by silica gel column chromatography (hexane : CH₂Cl₂ = 10:1) to give 97% yield of (R)-2b (white solid). ¹H NMR (400 MHz, CDCl₃): δ 7.98–7.88 (m, 4H), 7.50–7.46 (m, 8H), 7.29–7.18 (m, 4H), 4.29 (s, 4H), 1.40 (s, 36H); ¹³C NMR (100 MHz, CDCl₃): δ 150.3, 142.2, 139.6, 136.5, 133.2, 132.5, 131.8, 130.1, 127.8, 127.4, 127.1, 126.2, 124.0, 121.2, 35.0, 32.7, 31.6; [α]D²² +31.7 (c = 9.4, CHCl₃); HRMS (DART): Anal. For C₅₀H₅₇Br₂+1 [M+H]⁺ Calcd.: 815.2827, Found: 815.2827.

To a suspension of (R)-2a³ or (R)-2b (5.25 mmol), tetrabutylammonium hydrogen sulfate (356.5 mg, 1.05 mmol, 20 mol%) and K₂CO₃ (7.26 g, 52.5 mmol, 10 equiv) in CH₃CN (105 mL) was added ethyl isocyanoacetate (688 μL, 6.30 mmol, 1.2 equiv) at 0 °C. The solution was refluxed for 16 h under argon atmosphere. The resulting mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to afford (R)-17.

(R)-17a: The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to give 69% of (R)-17a (white solid). ¹H NMR (400 MHz, CDCl₃): δ 7.95 (s, 1H), 7.93 (dd, J = 22.9, 8.2 Hz, 2H), 7.82 (s, 1H), 7.51–7.20 (m, 16H), 3.88–3.80 (m, 1H), 3.77 (d, J = 13.7 Hz, 1H), 3.56–3.48 (m, 1H), 3.32 (d, J = 14.3 Hz, 1H), 3.09 (d, J = 14.3 Hz, 1H),
2.84 (d, J = 14.0 Hz, 1H); 0.90 (t, J = 7.3 Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 166.7, 159.8, 141.0, 140.6, 139.8, 136.0, 135.5, 131.2, 131.1, 130.6, 130.1, 130.1, 129.6, 129.4, 128.3, 128.2, 128.1, 127.2, 127.2, 127.1, 127.0, 126.2, 126.1, 126.1, 126.1, 126.1, 70.7, 62.6, 38.9, 34.8, 13.4; \([\alpha]\)\textsubscript{D}\textsuperscript{1)} +3.5 (c = 0.74, CHCl\textsubscript{3}); HRMS (DART): Anal. For C\textsubscript{30}H\textsubscript{30}N\textsubscript{1}O\textsubscript{2}\textsuperscript{+} [M+H]\textsuperscript{+} Calcd.: 544.2277, Found: 544.2280.

\(\text{(R)-17b}\): The crude mixture was purified by silica gel column chromatography (hexane : CH\textsubscript{2}Cl\textsubscript{2} = 3:1) to give 48% yield of \(\text{(R)-17b}\) (white solid). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.98–7.92 (m, 3H), 7.65–7.14 (m, 12H), 4.00 (d, J = 14.0 Hz, 1H), 3.76–3.68 (m, 1H), 3.37–3.27 (m, 2H), 3.06 (d, J = 14.3 Hz, 1H), 2.91 (d, J = 14.0 Hz, 1H), 1.37 (s, 36H), 0.82 (t, J = 7.0 Hz, 3H); \(\text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3): \(\delta\) 166.8, 160.2, 150.5, 142.2, 140.7, 139.8, 139.6, 136.3, 135.6, 133.0, 132.6, 131.1, 131.0, 130.5, 129.8, 129.5, 129.5, 128.1, 127.3, 127.1, 126.1, 126.0, 125.9, 125.8, 124.7, 121.2, 120.9, 70.6, 62.1, 39.0, 34.9, 34.6, 31.5; \([\alpha]\)\textsubscript{D}\textsuperscript{23} +13.0 (c = 6.5, CHCl\textsubscript{3}); HRMS (DART): Anal. For C\textsubscript{55}H\textsubscript{62}N\textsubscript{1}O\textsubscript{2}\textsuperscript{+} [M+H]\textsuperscript{+} Calcd.: 768.4781, Found: 768.4781.

To a solution of \(\text{(R)-17}\) (2.3 mmol) in ethanol (230 mL) was added conc. HCl (6.1 mL) at 0 °C. The solution was stirred at room temperature for 1 h under argon atmosphere. The resulting mixture was poured into ice-cooled saturated aq. NaHCO\textsubscript{3} and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The residue was purified by column chromatography on silica gel to afford \(\text{(R)}-\text{1}\).

\(\text{(R)-1a}\): The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to afford 79% of \(\text{(R)-1a}\) (white solid). \(^1\)H NMR (500 MHz, CD\textsubscript{6}D\textsubscript{6}): \(\delta\) 7.81 (d, J = 23.7 Hz, 2H), 7.74 (dd, J = 16.8, 8.0 Hz, 2H), 7.60 (dd, J = 8.4, 3.1 Hz, 2H), 7.39–7.09 (m, 12H), 7.05–6.99 (m, 2H), 3.66–3.60 (m, 1H), 3.46 (d, J = 13.8 Hz, 1H), 3.40–3.34 (m, 2H), 3.12 (d, J = 13.8 Hz, 1H), 2.51 (d, J = 13.4 Hz, 1H), 0.98 (s, 2H), 0.58 (t, J = 6.9 Hz, 3H); \(\text{\textsuperscript{13}C NMR (125 MHz, CD}_6D}_6): \(\delta\) 174.4, 142.5, 142.1, 142.0, 140.7, 136.2, 135.9, 134.0, 133.9, 133.0, 132.9, 132.0, 131.9, 130.7, 130.6, 129.5, 129.3, 128.7, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.1, 126.9, 126.2, 126.0, 125.9, 68.8, 60.6, 40.0, 36.6; \([\alpha]\)\textsubscript{D}\textsuperscript{28} –16.8 (c = 0.9, CHCl\textsubscript{3}); HRMS (DART): Anal. For C\textsubscript{30}H\textsubscript{32}N\textsubscript{1}O\textsubscript{2}\textsuperscript{+} [M+H]\textsuperscript{+} Calcd.: 534.2433, Found: 534.2431.
(R)-1b: The crude mixture was purified by silica gel column chromatography (hexane : CH$_2$Cl$_2$ = 1:1) to give 86% yield of (R)-1b (white solid). $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 8.02 (s, 2H), 7.76 (dd, $J$ = 8.4, 8.0 Hz, 2H), 7.63–7.51 (m, 8H), 7.24–7.18 (m, 2H), 7.01–6.94 (m, 2H), 3.83 (d, $J$ = 13.4 Hz, 1H), 3.60–3.54 (m, 1H), 3.49 (d, $J$ = 13.7 Hz, 1H), 3.36–3.28 (m, 1H), 3.24 (d, $J$ = 13.7 Hz, 1H), 2.69 (d, $J$ = 13.4 Hz, 1H), 1.31 (s, 36H), 0.55 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 174.2, 150.5, 143.0, 142.0, 141.6, 141.4, 136.5, 136.1, 134.3, 134.0, 133.2, 132.9, 132.0, 129.9, 129.1, 128.6, 126.2, 126.1, 125.9, 125.5, 125.4, 120.9, 120.6, 68.8, 60.4, 40.3, 36.6, 35.0, 31.6, 13.7; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1; 0.5 mL/min; using a CHIRALPAK IB-3 column (0.46 cmφ × 25 cm)): 8.7 min (minor) and 9.4 min (major); $[\alpha]_D^{27}$ –14.1 (c = 1.1, CHCl$_3$); HRMS (DART): Anal. For C$_{54}$H$_{64}$N$_1$O$_2$ (+[M+H])$^+$ Calcd.: 758.4937, Found: 758.4935.

Highly enantioselective fluorination of $\alpha$-branched aldehydes 3 (Table 2).

![Reaction Scheme]

General procedure for fluorination of $\alpha$-branched aldehydes: All of aldehydes were purified before the reactions by flash column chromatography on silica gel or Kugelrohr distillation. To a solution of catalyst 1b (20 mg, 0.026 mmol, 10 mol%) in toluene (0.54 mL) was added 3,5-dinitrobenzoic acid (5.5 mg, 0.026 mmol, 10 mol%), aldehydes 3 (0.39 mmol, 1.5 equiv), and N-fluorobenzenesulfonylimide (NFSI) (0.26 mmol, 82 mg, 1 equiv) at 0 °C. The reaction mixture was stirred at room temperature or at 0 °C, then poured into MeOH/CH$_2$Cl$_2$ (1 : 4, 1.3 mL) at 0 °C. To this solution, NaBH$_4$ (1.6 mmol, 6 equiv) was added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aq. NH$_4$Cl, and the mixture was extracted with Et$_2$O. The organic layer was dried over Na$_2$SO$_4$, concentrated, and chromatographed on silica gel to give 5.

(S)-2-fluoro-2-phenylpropan-1-ol [(S)-5a, 95% ee]

![Structure Image]

The reaction was carried out at 0 °C and stirred for 48 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3:1) to give 86% yield of (S)-5a (white solid). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40–7.27 (m, 5H), 3.88–3.69 (m, 2H), 2.50 (s,
1H), 1.69 (d, J = 23.2 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 141.5 (d, J = 21.1 Hz), 128.4, 127.8, 124.4 (d, J = 9.6 Hz), 97.8 (d, J = 172.5 Hz), 69.5 (d, J = 24.9 Hz), 23.1 (d, J = 24.0 Hz); 19F NMR (376 MHz, CDCl3): δ –157.6 (m); [α]D –15.8 (c = 0.87, CHCl3); HRMS (DART): Anal. For C9H11FO1: [M + NH4]+ Calcd.: 172.1138, Found: 172.1135. 

The enantiopurity was determined after conversion into the corresponding benzoate (S)-18a. The absolute configuration of the major enantiomer was determined to be S by comparing the specific rotation with that in the literature.4

**General procedure for benzylation of 5:** A flame-dried flask under argon was charged with 5 (0.30 mmol) and CH2Cl2 (1.0 mL). Triethylamine (0.60 mmol), benzylo chloride (0.45 mmol), and 4-dimethylaminopyridine (0.03 mmol) were added to this solution, and the mixture was stirred for 1 h at 0 °C. The mixture was diluted by saturated aq.NaHCO3, and extracted with CH2Cl2. The organic layer was dried over Na2SO4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford 18.

**((S)-2-fluoro-2-phenylpropyl benzoate [(S)-18a, 95% ee]**

![Chemical Structure](image)

The crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate (S)-18a in 85% yield (white solid). 1H NMR (400 MHz, CDCl3): δ 8.01 (dd, J = 8.2, 1.2 Hz, 2H), 7.58–7.54 (m, 1H), 7.46–7.38 (m, 6H), 7.36–7.32 (m, 1H), 4.63–4.50 (m, 2H), 1.81 (d, J = 22.3 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 166.1, 141.1 (d, J = 22.0 Hz), 133.1, 129.7, 128.4, 128.0, 128.0, 124.5, 124.4, 95.6 (d, J = 176.4 Hz), 69.7 (d, J = 24.9 Hz), 23.6 (d, J = 24.9 Hz); 19F NMR (376 MHz, CDCl3): δ –153.8 (m); [α]D20 +12.1 (c = 1.6, CHCl3); HRMS (DART): Anal. For C16H15FO2: [M + NH4]+ Calcd.: 276.1400, Found: 276.1400. The enantiopurity was determined by HPLC (hexane : 2-propanol = 99 : 1; 0.5 mL/min; using a CHIRALPAK ID column (0.46 cmφ × 25 cm): 16.7 min (major) and 19.0 min (minor).

**2-(4-bromophenyl)-2-fluoropropan-1-ol (5b, 92% ee)**

![Chemical Structure](image)

The reaction was stirred for 20 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 98% yield of 5b (white solid). 1H NMR
(400 MHz, CDCl$_3$): $\delta$ 7.52 (d, $J = 8.9$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 3.87–3.70 (m, 2H), 1.83 (t, $J = 6.6$ Hz, 1H), 1.68 (d, $J = 22.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.6 (d, $J = 22.0$ Hz), 131.6, 126.3 (d, $J = 9.6$ Hz), 121.9, 97.5 (d, $J = 172.5$ Hz), 69.3 (d, $J = 24.9$ Hz), 23.1 (d, $J = 24.9$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –157.8 (m); $[\alpha]_D^{20}$+18.4 (c = 0.31, CHCl$_3$); HRMS (DART): Anal. For C$_9$H$_{10}$BrF$_3$O$_7$$^+$$^+$ [M+NH$_4$]$^+$ Calcd.: 250.0243, Found: 250.0245. The enantiopurity was determined after conversion into the corresponding benzoate 18b.

2-[(4-bromophenyl)-2-fluoropropyl] benzoate (18b, 92% ee)

According to the general procedure, 5b was converted into 18b, the crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate 18b in 93 % yield (white solid). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.99 (d, $J = 7.3$ Hz, 2H), 7.58–7.51 (m, 3H), 7.45–7.41 (m, 2H), 7.32 (d, $J = 8.5$ Hz, 2H), 4.63–4.48 (m, 2H), 1.79 (d, $J = 22.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.9, 140.2 (d, $J = 22.0$ Hz), 133.3, 131.6, 129.7, 129.5, 128.4, 126.3 (d, $J = 9.6$ Hz), 122.2, 95.3 (d, $J = 176.4$ Hz), 69.3 (d, $J = 25.9$ Hz), 23.6 (d, $J = 24.0$ Hz); $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –153.9 (m); $[\alpha]_D^{20}$+19.0 (c = 1.6, CHCl$_3$); HRMS (DART): Anal. For C$_{16}$H$_{16}$BrF$_3$O$_{11}$$^+$$^+$ [M+NH$_4$]$^+$ Calcd.: 354.0505, Found: 354.0503. The enantiopurity was determined by HPLC (hexane : 2-propanol = 99 : 1; 0.5 mL/min; using a CHIRALPAK ID column (0.46 cm$\phi$ x 25 cm)): 17.8 min (major) and 21.2 min (minor).

2-fluoro-2-(4-fluorophenyl)propan-1-ol [5c, 90% ee]

The reaction was carried out at 0 °C and stirred for 48 h. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1–1:1) to give 76% yield of 5c (white solid; including ca. 3% of an inseparable by-product). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.34–7.32 (m, 2H), 7.08–7.04 (m, 2H), 3.85–3.69 (m, 2H), 1.94 (bs, 1H), 1.68 (d, $J = 22.6$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 162.3 (d, $J = 247.1$ Hz), 137.3 (dd, $J = 22.2$, 3.0 Hz), 126.3 (t, $J = 8.4$ Hz), 115.3 (d, $J = 21.6$ Hz), 97.6 (d, $J = 171.5$ Hz), 69.5 (d, $J = 26.4$ Hz), 23.2 (d, $J = 25.2$ Hz); $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –115.2 (s), –156.3 (m); $[\alpha]_D^{20}$+10.9 (c = 0.80, CHCl$_3$); HRMS (DART): Anal. For C$_{16}$H$_{16}$F$_2$O$_{11}$$^+$$^+$ [M+NH$_4$]$^+$ Calcd.: 190.1044, Found: 190.1044. The enantiopurity was determined by HPLC (hexane : 2-propanol = 20 : 1; 1.0
mL/min; using a CHIRALPAK AD-H column (0.46 cmφ × 25 cm)): 11.5 min (minor) and 12.8 min (major).

2-fluoro-2-(p-tolyl)propan-1-ol [5d, 93% ee]

The reaction was carried out at 0 °C and stirred for 48 h. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1–1:1) to give 88% yield of 5d (white solid). 1H NMR (500 MHz, CDCl₃): δ 7.25 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 3.86–3.68 (m, 2H), 2.35 (s, 3H), 1.92 (t, J = 6.1 Hz, 1H), 1.68 (d, J = 22.6 Hz, 3H); 13C NMR (126 MHz, CDCl₃): δ 138.5 (d, J = 21.6 Hz), 137.6, 129.1, 124.4 (d, J = 8.4 Hz), 97.8 (d, J = 171.5 Hz), 69.6 (d, J = 25.2 Hz), 23.1 (d, J = 24.0 Hz), 21.0; 19F NMR (470 MHz, CDCl₃): δ –157.0 (m); [α]D²³ +14.4 (c = 1.25, CHCl₃); HRMS (DART): Anal. For C₁₀H₁₃F₁O₁⁺ [M+H]⁺ Calcd.: 169.1029, Found: 169.1029. The enantiopurity was determined by HPLC (hexane : 2-propanol = 20 : 1; 1.0 mL/min; using a CHIRALPAK AD-H column (0.46 cmφ × 25 cm)): 12.2 min (major) and 14.7 min (minor).

2-fluoro-2-(4-nitropheno)propan-1-ol (5e, 88% ee)

The reaction was stirred for 48 h at 0 °C. The crude mixture was purified by silica gel chromatography (hexane : diethyl ether = 1 : 1–1 : 2) to give 88% yield of 5e (white solid; including small amount of inseparable by-product). 1H NMR (500 MHz, CDCl₃): δ 8.25 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 3.91–3.80 (m, 2H), 2.16 (s, 1H), 1.72 (d, J = 22.6 Hz, 3H); 13C NMR (126 MHz, CDCl₃): δ 148.9 (d, J = 21.6 Hz), 147.4, 125.6 (d, J = 9.6 Hz), 123.6, 97.5 (d, J = 173.9 Hz), 69.0 (d, J = 25.2 Hz), 23.2 (d, J = 24.0 Hz); 19F NMR (470 MHz, CDCl₃): δ –158.0 (m); [α]D²⁸ +19.0 (c = 1.1, CHCl₃); HRMS (DART): Anal. For C₁₉H₁₉FNO₃⁺ [M+NH₄⁺]⁺ Calcd.: 217.0988, Found: 217.0989. The enantiopurity was determined by HPLC (hexane : 2-propanol = 9 : 1; 1 mL/min; using a CHIRALCEL OD-H column (0.46 cmφ × 25 cm)): 9.3 min (minor) and 10.4 min (major).
2-(3-bromophenyl)-2-fluoropropan-1-ol (5g, 93% ee)

\[
\text{Br} \quad \text{F} \quad \text{OH}
\]

The reaction was stirred for 48 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 77% yield of 5g (colorless oil). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.53 (s, 1H), 7.48–7.41 (m, 1H), 7.32–7.20 (m, 2H), 3.87–3.70 (m, 2H), 1.92 (bs, 1H), 1.67 (d, \(J = 22.6\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 143.8 (d, \(J = 22.0\) Hz), 130.9, 130.0, 127.7 (d, \(J = 10.5\) Hz), 123.1 (d, \(J = 8.6\) Hz), 127.2, 97.3 (d, \(J = 174.4\) Hz), 69.3 (d, \(J = 24.9\) Hz), 23.2 (d, \(J = 24.0\) Hz); F NMR (376 MHz, CDCl\(_3\)): \(\delta -157.8\) (m); \([\alpha]_D^{20}\) +12.3 (c = 0.32, CHCl\(_3\)); HRMS (DART): Anal. For C\(_9\)H\(_8\)BrF \(^{+}\) [M+NH\(_3\)] \(^+\) Calcd.: 250.0243, Found: 250.0243. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1 mL/min; using a CHIRALPAK ID-3 column (0.46 cm\(\phi\) \(\times\) 25 cm)): 12.8 min (major) and 27.2 min (minor).

2-fluoro-2-(naphthalen-2-yl)propan-1-ol (5h, 92% ee)

\[
\text{F} \quad \text{OH}
\]

The reaction was stirred for 21 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 98% yield of 5h (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.86–7.82 (m, 4H), 7.52–7.47 (m, 2H), 7.42 (d, \(J = 8.8\) Hz, 1H), 3.97–3.78 (m, 2H), 2.01 (bs, 1H), 1.77 (d, \(J = 22.6\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 138.8 (d, \(J = 21.1\) Hz), 132.9, 132.7, 128.3, 128.2, 127.6, 126.4, 126.3, 123.5 (d, \(J = 10.5\) Hz), 122.4 (d, \(J = 8.6\) Hz), 98.0 (d, \(J = 172.5\) Hz), 69.4 (d, \(J = 25.9\) Hz), 23.2 (d, \(J = 24.9\) Hz); F NMR (376 MHz, CDCl\(_3\)): \(\delta -157.2\) (m); \([\alpha]_D^{20}\) +16.4 (c = 1.4, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{14}\)H\(_{13}\)F\(_2\)O\(_4\) \(^{+}\) [M+NH\(_3\)] \(^+\) Calcd.: 222.1294, Found: 222.1294. The enantiopurity was determined by HPLC (hexane : 2-propanol = 99 : 1; 2 mL/min; using a CHIRALPAK ID column (0.46 cm\(\phi\) \(\times\) 25 cm)): 15.2 min (major) and 25.0 min (minor).

2-fluoro-2-(5,6,7,8-tetrahydronaphthalen-2-yl)propan-1-ol (5i, 92% ee)

\[
\text{F} \quad \text{OH}
\]

The reaction was stirred for 20 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 95% yield of 5i (white solid). \(^1\)H NMR
(400 MHz, CDCl$_3$): $\delta$ 7.10–7.05 (m, 3H), 3.88–3.69 (m, 2H), 2.91–2.76 (m, 4H), 1.82–1.79 (m, 5H), 1.67 (d, $J$ = 22.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.6 (d, $J$ = 21.1 Hz), 137.2, 136.9, 129.2, 125.2 (d, $J$ = 9.6 Hz), 121.5 (d, $J$ = 8.6 Hz), 97.8 (d, $J$ = 171.6 Hz), 69.6 (d, $J$ = 24.9 Hz), 29.5, 29.0, 23.3, 23.1; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ –157.2 (m); [α]$^D_{20}$ +17.3 (c = 0.63, CHCl$_3$); HRMS (DART): Anal. For C$_{13}$H$_{17}$F$_2$O$_7$ $^{[M+NH_4]^+}$ Calcd.: 226.1607, Found: 226.1608. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1 mL/min; using a CHIRALPAK IC-3 column (0.46 cm × 25 cm)): 18.1 min (major) and 21.3 min (minor).

2-fluoro-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propan-1-ol (5j, 92% ee)

The reaction was stirred for 24 h at 0 °C. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 98% yield of 5j (white solid). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.56–7.53 (m, 2H), 7.48–7.41 (m, 3H), 7.39–7.36 (m, 1H), 7.22–7.16 (m, 2H), 3.92–3.76 (m, 2H), 1.97–1.94 (m, 1H), 1.72 (d, $J$ = 22.6 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 159.6 (d, $J$ = 248.3 Hz), 143.0 (dd, $J$ = 22.8, 7.2 Hz), 135.2, 130.8 (d, $J$ = 3.6 Hz), 128.9 (d, $J$ = 3.6 Hz), 128.5, 127.8, 120.4 (dd, $J$ = 9.6, 3.6 Hz), 112.8 (d, $J$ = 10.8 Hz), 112.6 (d, $J$ = 9.6 Hz), 97.3 (d, $J$ = 172.7 Hz), 69.3 (d, $J$ = 25.2 Hz), 23.2 (d, $J$ = 25.2 Hz); $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –117.7 (m), –157.3 (m); [α]$^D_{21}$ +20.5 (c = 1.1, CHCl$_3$); HRMS (DART): Anal. For C$_{13}$H$_{17}$F$_2$O$_7$ $^{[M+NH_4]^+}$ Calcd.: 266.1357, Found: 266.1354. The enantiopurity was determined after conversion into the corresponding benzoate 18j.

2-fluoro-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propyl benzoate (18j, 92% ee)

According to the general procedure, 5j was converted into 18j, the crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate 18j in 97 % yield (white solid). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.03 (d, $J$ = 7.3 Hz, 2H), 7.59–7.54 (m, 3H), 7.50–7.42 (m, 5H), 7.40–7.37 (m, 1H), 7.30–7.26 (m, 2H), 4.66–4.53 (m, 2H), 1.83 (d, $J$ = 22.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.0, 159.6 (d, $J$ = 248.2 Hz), 142.6 (dd, $J$ = 23.0, 7.7 Hz), 135.1, 133.3, 130.8 (d, $J$ = 3.8 Hz), 129.7, 129.5, 129.0 (d, $J$ = 2.9 Hz), 128.7 (d, $J$ = 13.3 Hz), 128.5 (d, $J$ = 3.8 Hz), 127.9, 120.5 (dd, $J$ = 8.6, 2.9 Hz), 112.9 (d, $J$ = 10.5 Hz), 112.7 (d, $J$ = 9.6 Hz), 95.1 (d, $J$ = 177.3 Hz), 69.4 (d, $J$ = 24.9 Hz), 23.6
(d, \( J = 24.9 \) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –117.6 (m), –153.3 (m); [\( \alpha \)]\(_D\)^20 +23.8 (c = 0.74, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{22}\)H\(_{18}\)F\(_2\)O\(_2\)^{+1} [M+NH\(_4\)]\(^{+}\) Calcd.: 370.1619, Found: 370.1618. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 0.5 mL/min; using a CHIRALPAK IB-3 column (0.46 cm\( \times \) 25 cm)): 18.2 min (minor) and 21.7 min (major).

1-fluoro-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (4k, 95% ee)

After completion of fluorination (stirred for 2 h at room temperature), the reaction mixture was added saturated aq.NaHCO\(_3\) at 0 °C. The mixture was extracted with Et\(_2\)O, and the organic later was dried over Na\(_2\)SO\(_4\), concentrated and purified by silica gel column chromatography (pentane : diethyl ether = 10 : 1) to afford 90% yield of 4k (colorless oil; including small amount of impurities). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 9.80 (d, \( J = 6.1 \) Hz, 1H), 7.34–7.20 (m, 4H), 2.92–2.74 (m, 2H), 2.28–2.09 (m, 2H), 2.05–1.90 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 197.9 (d, \( J = 38.3 \) Hz), 138.9 (d, \( J = 3.8 \) Hz), 130.3 (d, \( J = 21.1 \) Hz), 129.7 (d, \( J = 3.8 \) Hz), 129.6, 128.6 (d, \( J = 3.8 \) Hz), 126.7 (d, \( J = 1.9 \) Hz), 95.5 (d, \( J = 181.2 \) Hz), 29.5 (d, \( J = 3.8 \) Hz), 28.9, 18.5 (d, \( J = 2.9 \) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –142.4 (t, \( J = 23.1 \) Hz); [\( \alpha \)]\(_D\)^22 –18.5 (c = 0.49, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{11}\)H\(_{15}\)F\(_1\)N\(_1\)O\(_1\)^{+1} [M+NH\(_4\)]\(^{+}\) Calcd.: 196.1138, Found 196.1131; The enantiopurity was determined by GC (100–150 °C, 5 °C/min; using a \( \beta \)-DEX 120 column): 21.5 min (minor) and 21.8 min (major).

2-fluoro-2-phenylbutan-1-ol (5l, 84% ee)

The reaction was stirred for 12 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 93% yield of 5l (colorless oil). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.40–7.29 (m, 5H), 3.90–3.78 (m, 2H), 2.21–2.09 (m, 1H), 1.98–1.80 (m, 2H), 0.81 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 139.7 (d, \( J = 21.1 \) Hz), 128.3, 127.6, 124.8 (d, \( J = 9.6 \) Hz), 100.3 (d, \( J = 175.4 \) Hz), 68.7 (d, \( J = 24.0 \) Hz), 28.8 (d, \( J = 23.0 \) Hz), 7.1 (d, \( J = 5.8 \) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –170.6 (m); [\( \alpha \)]\(_D\)^23 +2.90 (c = 1.8, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{10}\)H\(_{13}\)F\(_1\)O\(_1\)^{+1} [M+NH\(_4\)]\(^{+}\) Calcd.: 186.1294, Found: 186.1294. The enantiopurity was determined after conversion into the corresponding benzoate 18l.
2-fluoro-2-phenylbutyl benzoate (18l, 84% ee)

According to the general procedure, 51 was converted into 18l. The crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate 18l in 92 % yield (white solid). 1H NMR (500 MHz, CDCl3): δ 7.97 (d, J = 8.2 Hz, 2H), 7.57–7.53 (m, 1H), 7.43–7.37 (m, 6H), 7.35–7.30 (m, 1H), 4.68–4.53 (m, 2H), 2.30–2.18 (m, 1H), 2.11–1.94 (m, 1H), 0.86 (t, J = 7.5 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 166.1, 139.4 (d, J = 22.0 Hz), 133.1, 129.7, 129.7, 128.4, 127.7, 124.9, 124.8, 98.1 (d, J = 179.2 Hz), 69.1 (d, J = 24.9 Hz), 29.3 (d, J = 24.0 Hz), 7.1 (d, J = 4.8Hz); 19F NMR (376 MHz, CDCl3): δ −167.6 (m); [α]D20 = +8.90 (c = 0.61, CHCl3); HRMS (DART): Anal. For C17H17F2O2·[M+NH4]⁺ Calcd.: 290.1556, Found: 290.1558. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 0.5 mL/min; using a CHIRALCEL OJ-H column (0.46 cmφ × 25 cm)): 22.5 min (minor) and 25.8 min (major).

2-fluoro-2,3-diphenylpropan-1-ol (5m, 84% ee)

The reaction was stirred for 12 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 99% yield of 5m (white solid). 1H NMR (400 MHz, CDCl3): δ 7.34–7.16 (m, 8H), 7.01–6.99 (m, 2H), 3.99–3.84 (m, 2H), 3.35 (dd, J = 17.7, 14.0 Hz, 1H), 3.22 (dd, J = 26.1, 14.2 Hz, 1H), 1.86 (t, J = 6.6 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 139.6 (d, J = 21.1 Hz), 134.9 (d, J = 3.8 Hz), 130.5, 128.2, 127.9, 127.7, 126.6, 124.9, 124.8, 99.3 (d, J = 177.3 Hz), 67.5 (d, J = 24.0 Hz), 43.1 (d, J = 23.0 Hz); 19F NMR (376 MHz, CDCl3): δ −165.5 (m); [α]D20 = −35.1 (c = 1.1, CHCl3); HRMS (DART): Anal. For C15H15F2O·[M+NH4]⁺ Calcd.: 248.1451, Found: 248.1453. The enantiopurity was determined after conversion into the corresponding benzoate 18m.

2-fluoro-2,3-diphenylpropyl benzoate (18m, 84% ee)

According to the general procedure, 5m was converted into 18m. The crude mixture was purified by flash column chromatography on silica gel (hexane : ethylacetate = 20:1) to afford the desired benzoate 18m in 95 % yield (white solid). 1H NMR (400 MHz, CDCl3): δ 7.95 (d, J = 8.2 Hz, 2H), 7.56–7.52 (m, 1H), 7.42–7.39 (m, 2H), 7.35–7.26 (m, 5H), 7.22–7.16 (m, 3H), 7.06–7.04 (m, 2H), 4.72–4.59 (m, 2H), 3.44 (dd, J = 19.7, 14.2 Hz, 1H), 3.33 (dd, J = 25.2, 14.2 Hz, 1H).
2-((1,1'-biphenyl)-4-yl)-2-fluoro-3-phenylpropan-1-ol (5n, 89% ee)

The reaction was stirred for 20 h at 0 °C using 20 mol% of 1b. The crude mixture was purified by silica gel column chromatography (hexane : ethyl ether = 2:1) to give 91% yield of 5n (89% ee) with a trace amount of impurity. Subsequent recrystallization from dichloromethane/hexane gave pure product with 93% ee (white solid). \^1H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.56–7.50 (m, 4H), 7.42–7.38 (m, 2H), 7.33–7.29 (m, 1H), 7.26 (d, \(J = 10.4\) Hz, 2H), 7.17–7.16 (m, 3H), 7.03–7.01 (m, 2H), 3.95–3.83 (m, 2H), 3.35 (dd, \(J = 18.0, 14.0\) Hz, 1H), 3.22 (dd, \(J = 25.8, 14.2\) Hz), 2.15 (bs, 1H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 140.3 (d, \(J = 4.7\) Hz), 138.7 (d, \(J = 21.9\) Hz), 134.9 (d, \(J = 2.9\) Hz), 130.5, 128.7, 127.9, 127.4, 127.0., 126.8, 126.6, 125.4, 125.3, 99.2 (d, \(J = 176.4\) Hz), 67.3 (d, \(J = 23.8\) Hz), 43.0 (d, \(J = 23.9\) Hz); \(^{19}\)F NMR (376 MHz, CDCl\textsubscript{3}): \(\delta\) –164.9 (m); \([\alpha]\)\textsubscript{D}\textsuperscript{20} +51.9 (c = 2.0, CHCl\textsubscript{3}); HRMS (DART): Anal. For C\textsubscript{26}H\textsubscript{18}F\textsubscript{2}O\textsubscript{3} [M+NH\textsubscript{4}]\textsuperscript{+} Calcd.: 342.1764, Found: 342.1761. The enantiopurity was determined by HPLC (hexane : 2-propanol = 30: 1; 1 mL/min; using a CHIRALPAK ID-3 column (0.46 cm\textsubscript{φ} × 25 cm)): 21.1 min (minor) and 24.6 min (major).

2-cyclohexyl-2-fluoropropan-1-ol [5o, 83% ee]

The reaction was carried out at 0 °C and stirred for 48 h with 30 mol% catalyst 1b in the absence of 3,5-(NO\textsubscript{2})\textsubscript{2}C\textsubscript{6}H\textsubscript{4}CO\textsubscript{2}H. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 24% yield of 5o (colorless oil, mixture of 5o and 2-cyclohexylpropan-1-ol). \(^{1}\)H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 3.69 (dd, \(J = 21.4, 12.2\) Hz, 1H), 3.57 (dd, \(J = 23.0, 11.8\) Hz, 1H), 1.84–1.62 (m, 7H), 1.28–1.20 (m, 1H), 1.24 (d, 3H), 1.18–1.07 (m, 2H), 1.02–0.94 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\textsubscript{3}): \(\delta\) 99.8 (d, \(J = 167.9\) Hz),
66.8 (d, \(J = 24.0\) Hz), 42.9 (d, \(J = 21.6\) Hz), 27.6 (d, \(J = 7.2\) Hz), 26.4–26.3 (3C), 17.6 (d, \(J = 25.2\) Hz); \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \(\delta -158.1\); HRMS (DART): Anal. For C\(_9\)H\(_{17}\)FO\(_1\)^{+1} [M+NH\(_4^+\)] Calcd.: 178.1605, Found: 178.1607. The enantiopurity was determined by GC (100 °C–130 °C, 8 °C/min, then 60 min at 130 °C) using a β-DEX 120 column: 20.0 (major) and 22.4 (minor).

2-fluoro-3-(4-isoproplyphenyl)-2-methylpropan-1-ol (5p, 14% ee)

The reaction was stirred for 24 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : diethyl ether = 2:1) to give 59% yield of 5p (colorless oil). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.16\) (s, 4H), 3.58 (dd, \(J = 19.5, 5.5\) Hz, 2H), 3.01–2.82 (m, 3H), 1.88 (m, 1H), 1.30–1.23 (m, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 147.3, 133.2\) (d, \(J = 5.8\) Hz), 130.3, 126.3, 97.4 (d, \(J = 169.7\) Hz), 67.5 (d, \(J = 24.0\) Hz), 41.9 (d, \(J = 23.0\) Hz), 33.7, 24.0, 20.9 (d, \(J = 24.0\) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta -154.7\) (m); HRMS (DART): Anal. For C\(_{13}\)H\(_{19}\)FO\(_1\)^{+1} [M+NH\(_4^+\)] Calcd.: 210.1420, Found: 210.1419. The enantiopurity was determined after conversion into the corresponding benzoate 18p.

2-fluoro-3-(4-isoproplyphenyl)-2-methylpropyl benzoate (18p, 14% ee)

According to the general procedure, 5p was converted into 18p. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to afford 91% of 18p (colorless oil). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 8.09\) (d, \(J = 8.2\) Hz, 2H), 7.59 (t, \(J = 7.9\) Hz, 1H), 7.47 (t, \(J = 7.6\) Hz, 2H), 7.16 (s, 4H), 4.35 (dd, \(J = 37.0, 11.9\) Hz, 1H), 4.30 (dd, \(J = 37.2, 11.9\) Hz, 1H), 3.06 (d, \(J = 19.5\) Hz, 2H), 2.88 (sept, \(J = 7.0\) Hz, 1H), 1.41 (d, \(J = 21.5\) Hz, 3H), 1.24 (d, \(J = 7.0\) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 166.1, 147.5, 133.2, 132.6\) (d, \(J = 4.8\) Hz), 130.2, 129.8, 129.7, 128.5, 126.4, 95.0 (d, \(J = 175.1\) Hz), 68.1 (d, \(J = 25.2\) Hz), 42.8 (d, \(J = 22.8\) Hz), 33.7, 24.0, 21.7 (d, \(J = 24.0\) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta -151.6\); HRMS (DART): Anal. For C\(_{20}\)H\(_{24}\)FO\(_2\)^{+1} [M+H^+] Calcd.: 315.1760, Found: 315.1763; The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 0.5 mL/min; using a CHIRALCEL OJ-H column (0.46 cm\(\phi\) × 25 cm)): 26.5 min (minor) and 27.9 min (major).
Derivatization of α-fluoroaldehydes (Scheme 3),

Horner–Wadsworth–Emmons reaction of α-fluoroaldehydes.

To a solution of catalyst 1b (20 mg, 0.026 mmol, 10 mol%) in toluene (0.54 mL) was added 3,5-dinitrobenzoic acid (5.5 mg, 0.026 mmol, 10 mol%), aldehydes 3 (0.39 mmol, 1.5 equiv), and NFSI (0.26 mmol, 82 mg, 1 equiv) at 0 ºC. The mixture was stirred for 24 h at 0 ºC, then poured into aq. NaHCO₃, and extracted by Et₂O. The organic layer was dried over Na₂SO₄ and concentrated under the reduced pressure gave 4 as the crude product. To a solution of \((\text{EtO})₂\text{P(O)CH₂CO₂Et}\) (1.35 mmol) in THF (0.7 mL) was added NaH (60%, 1.35 mmol) at 0 ºC. After the mixture was stirred for 0.5 h at 0 ºC, a solution of 4 in THF (1.0 mL) was added to the mixture, then stirred for another 1 h. The mixture was quenched with saturated aq. NH₄Cl and extracted with Et₂O. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. The crude mixture was purified by flash column chromatography on silica gel to afford 8.

**ethyl \((E)\)-4-(4-bromophenyl)-4-fluoropent-2-enoate (8b, 92% ee)**

![Chemical structure](image)

The crude mixture was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 30 : 1) to afford 80% yield of 8b (colorless oil). \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 7.51 (d, \(J = 8.0\) Hz, 2H), 7.26 (d, \(J = 8.4\) Hz, 2H), 7.05 (dd, \(J = 18.7, 15.7\) Hz, 1H), 6.09 (d, \(J = 15.7\) Hz, 1H), 4.20 (q, \(J = 7.13\) Hz, 2H), 1.80 (d, \(J = 21.8\) Hz, 3H), 1.29, (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃): \(\delta\) 166.0, 148.0 (d, \(J = 22.8\) Hz), 140.5 (d, \(J = 22.8\) Hz), 131.7, 126.4 (d, \(J = 8.4\) Hz), 122.3, 119.8 (d, \(J = 10.8\) Hz), 94.8 (d, \(J = 176.3\) Hz), 60.8, 26.5 (d, \(J = 25.2\) Hz), 14.2; \(^{19}\)F NMR (470 MHz, CDCl₃): \(\delta\) -146.2 (m); \([\alpha]_D^{29}\) +17.1 (c = 1.2, CHCl₃); HRMS (DART): Anal. For C₁₅H₁₈BrF₁N₁O₂⁺ [M+NH₄]⁺ Calcd.: 318.0505, Found: 318.0504.
ethyl \((E)-4\text{-fluoro-4-(naphthalen-2-yl)pent-2-enoate (8h, 92\% ee)}\)

The crude mixture was purified by flash column chromatography on silica gel (hexane : ethyl acetate = 30 : 1) to afford 80\% yield of 8h (white solid). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.85–7.81 (m, 4H), 7.51–7.46 (m, 3H), 7.20 (dd, \(J = 18.7, 15.7\) Hz, 1H), 6.16 (dd, \(J = 15.6, 0.8\) Hz, 1H), 4.20 (q, \(J = 7.3\) Hz, 2H), 1.92 (d, \(J = 22.2\) Hz, 3H), 1.27 (t, \(J = 6.9\) Hz, 3H); \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 166.2, 148.7 (d, \(J = 24.0\) Hz), 138.7 (d, \(J = 22.8\) Hz), 132.9 (d, \(J = 10.8\) Hz), 128.5, 128.3, 127.6, 126.5, 123.4 (d, \(J = 9.6\) Hz), 122.6 (d, \(J = 6.0\) Hz), 119.6 (d, \(J = 10.8\) Hz), 95.3 (d, \(J = 175.1\) Hz), 60.7, 26.5 (d, \(J = 25.2\) Hz), 14.1; \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \(\delta\) –145.5 (m); \([\alpha]_D^{29} +24.5\) (c = 1.1, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{17}\)H\(_{21}\)F\(_{1}\)N\(_1\)O\(_1\) [M+NH\(_4\)]\(^+\) Calcd.: 290.1556, Found: 290.1554.

**Synthesis of fluorinated analogue of flurbiprofen**

2-fluoro-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoic acid (9, 92\% ee)

A solution of 5j (0.106 mmol) in acetone (1.06 mL) was added to 2.5 M aq.H\(_2\)CrO\(_4\) (3 mmol, 128 \(\mu\)L) at 0 °C. After the mixture was stirred for 4 h at room temperature, 2-propanol was added to this mixture. The mixture was filtered, extracted by CH\(_2\)Cl\(_2\), and the organic layer was washed by 1.2N HCl twice and brine, dried over Na\(_2\)SO\(_4\) and concentrated. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1 – 1 : 4) to afford 69\% yield of 9 (white solid; including small amount of impurities). \(^1\)H NMR (500 MHz, CD\(_3\)OD): \(\delta\) 7.54–7.49 (m, 3H), 7.45–7.40 (m, 3H), 7.39–7.34 (m, 2H), 1.93 (d, \(J = 22.2\) Hz, 3H); \(^1\)C NMR (126 MHz, CD\(_3\)OD): \(\delta\) 173.7 (d, \(J = 27.6\) Hz), 160.8 (d, \(J = 247.1\) Hz), 142.7 (d, \(J = 7.2\) Hz), 142.5 (d, \(J = 7.2\) Hz), 136.4, 132.0 (d, \(J = 2.4\) Hz), 130.5 (d, \(J = 13.2\) Hz), 130.0 (d, \(J = 2.4\) Hz), 129.0, 122.1 (d, \(J = 3.6\) Hz), 122.0 (d, \(J = 3.6\) Hz), 113.9 (d, \(J = 9.2\) Hz), 113.7 (d, \(J = 9.2\) Hz), 95.1 (d, \(J = 184.7\) Hz), 25.0 (d, 24.0 Hz); \(^{19}\)F NMR (470 MHz, CD\(_3\)OD): \(\delta\) –116.1, –147.9 (q, \(J = 22.0\) Hz); \([\alpha]_D^{27} +28.6\) (c = 0.84, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{15}\)H\(_{16}\)F\(_2\)N\(_2\)O\(_2\) [M+NH\(_4\)]\(^+\) Calcd.: 280.1149, Found 280.1143.
Synthesis of-hydroxyacetals 10 (Table 3).

\[
\text{Ar}^1\text{CHO} \quad \xrightarrow{\text{3.5-(NO}_2\text{)}_2\text{C}_6\text{H}_5\text{CO}_2\text{H}} \quad \text{MeOH} \quad \text{NaOMe} \quad \text{ethyl} \quad \text{glycol} \quad 10 \quad 12
\]

**General procedure:** Enantioselective fluorination of 3 was carried out according to the procedure described in page S6. After completion of the reaction, MeOH (2.64 mL)/NaOMe (1.32 mmol, 5 equiv.) or ethylene glycol (2.64 mL)/NaH (1.32 mmol, 5 equiv) were added at 0 °C. The mixture was stirred at room temperature, then diluted by adding sat.NaHCO\(_3\) aq., and extracted with Et\(_2\)O. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give \(\alpha\)-hydroxylacetals 10–12.

\((R)\)-1,1-dimethoxy-2-phenylpropan-2-ol [(\(R\))-10a, 94% ee]

\[
\begin{align*}
\text{CH(O Me)}_2 & \quad \text{OH} \\
& \quad \text{Ar}
\end{align*}
\]

The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 66% yield of (\(R\))-10a (pale yellow oil). \(^1\)H NMR (400 MHz, \(\text{C}_6\text{D}_6\)); \(\delta 7.70–7.67\) (m, 2H), 7.26–7.22 (m, 2H), 7.14–7.10 (m, 1H), 3.98 (s, 1H), 3.04 (s, 3H), 2.95 (s, 3H), 2.50 (s, 1H), 1.59 (s, 3H); \(^{13}\)C NMR (100 MHz, \(\text{C}_6\text{D}_6\)); \(\delta 145.1, 128.0, 127.1, 126.6, 111.1, 76.1, 57.4, 57.3, 23.8\); \([\alpha]_D^{25}\) \(-7.6\) (c = 1.00, CHCl\(_3\)); HRMS (DART): Anal. For \(\text{C}_{11}\text{H}_{20}\text{N}_1\text{O}_3\) \([\text{M}+\text{NH}_4]^+\) Calcd.: 214.1443, Found: 214.1441; The enantiopurity was determined after conversion into methyl ether (\(R\))-19a.

**Methylation of 10.**

**General procedure:** To a suspension of NaH (0.408 mmol, 2 equiv.) in DMF (1.0 mL), \(\alpha\)-hydroxyacetal 10 (0.204 mmol) was added, and the mixture was stirred at 0 °C for 30 min. MeI (0.408 mmol, 2 equiv.) was added to the mixture, and stirred for 60 min at 0 °C. The reaction was quenched by adding sat. NH\(_4\)Cl aq. and extracted with Et\(_2\)O. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to afford 19.

S18
(R)-(1,1,2-trimethoxypropan-2-yl)benzene [(R)-19a, 94% ee]

According to the general procedure, reaction was carried out with 0.204 mmol of (R)-10a. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 15 : 1) to afford 83% yield of (R)-19a (colorless oil). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.44–7.42 (m, 2H), 7.38–7.34 (m, 2H), 7.30–7.26 (m, 1H), 4.13 (s, 1H), 3.48 (s, 3H), 3.10 (s, 3H), 3.08 (s, 3H), 1.56 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 141.2, 127.9, 127.5, 127.2, 111.0, 81.7, 58.2, 57.3, 50.2, 15.5; $[\alpha]_D^{23}$ = 53.2 (c = 1.00, CHCl$_3$); HRMS (DART): Anal. For C$_{12}$H$_{22}$N$_1$O$_3$+1 [M+NH$_4$]$^+$ Calcd.: 228.1600, Found: 228.1600; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IC-3 column (0.46 cm φ x 25 cm): 10.6 min (major) and 12.9 min (minor).

2-(4-bromophenyl)-1,1-dimethoxypropan-2-ol (10b, 92% ee)

The reaction was stirred for 12 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 70% yield of 10b (pale yellow oil). $^1$H NMR (500 MHz, CD$_6$D$_6$): δ 7.34 (s, 4H), 3.81 (s, 1H), 2.99 (s, 3H), 2.89 (s, 3H), 2.38 (s, 1H), 1.47 (s, 3H); $^{13}$C NMR (100 MHz, CD$_6$D$_6$): δ 144.0, 131.1, 128.5, 121.3, 110.7, 75.7, 57.4, 57.3, 23.7; $[\alpha]_D^{21}$ = 3.2 (c = 1.02, CHCl$_3$); HRMS (DART): Anal. For C$_{11}$H$_{19}$BrN$_1$O$_3$+1 [M+NH$_4$]$^+$ Calcd.: 292.0548, Found: 292.0548; The enantiopurity was determined after conversion into 19b.

1-bromo-4-(1,1,2-trimethoxypropan-2-yl)benzene (19b, 92% ee)

According to the general procedure, reaction was carried out with 0.145 mmol of 10b. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 15 : 1) to give 76% yield of 19b (colorless oil). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.49–7.47 (m, 2H), 7.31–7.28 (m, 2H), 4.08 (s, 1H), 3.48 (s, 3H), 3.16 (s, 3H), 3.09 (s, 3H), 1.56 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 140.4, 131.0, 129.4, 121.4, 110.6, 81.6, 58.2, 57.6, 50.2, 15.9; $[\alpha]_D^{23}$ = 41.0 (c = 1.01, CHCl$_3$); HRMS (DART): Anal. For C$_{12}$H$_{23}$N$_1$O$_3$+1 [M+NH$_4$]$^+$ Calcd.: 306.0705,
Found: 306.0705; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IC-3 column (0.46 cmφ x 25 cm): 7.7 min (major) and 9.0 min (minor).

2-(4-fluorophenyl)-1,1-dimethoxypropan-2-ol [10c, 93% ee]

\[
\text{F} \quad \begin{array}{c}
\text{CH(O\text{Me})}_2 \\
\text{OH}
\end{array}
\]

The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1–2 : 1) to give 64% yield of 10c (colorless oil). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.50–7.46 (m, 2H), 6.90–6.86 (m, 2H), 3.85 (s, 1H), 3.03 (s, 3H), 2.91 (s, 3H), 2.42 (s, 1H), 1.52 (s, 3H); \(^13\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 162.4 (d, \(J\) = 244.7 Hz), 140.6, 128.4 (d, \(J\) = 7.2 Hz), 114.6 (d, \(J\) = 21.6 Hz), 111.0, 75.7, 57.5, 57.3, 23.7; \(^19\)F NMR (470 MHz, CDCl\(_3\)): \(\delta\) –115.8; \([\alpha]_D^{25}\) –7.6 (c = 0.33, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{11}\)H\(_{15}\)FO\(_3\)^+ \([\text{M+NH}_4]^+\) Calcd.: 232.1347, Found: 232.1349.

The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ x 25 cm)): 12.2 min (minor) and 14.2 min (major).

1,1-dimethoxy-2-(p-tolyl)propan-2-ol [10d, 93% ee]

\[
\text{CH(O\text{Me})}_2 \\
\text{OH}
\]

The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1–2 : 1) to give 50% yield of 10d (colorless oil). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.62 (d, \(J\) = 8.4 Hz, 2H), 7.08 (\(J\) = 8.0 Hz, 2H), 4.01 (s, 1H), 3.06 (s, 3H), 2.98 (s, 3H), 2.50 (s, 1H), 2.14 (s, 3H), 1.65 (s, 3H); \(^13\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 142.2, 136.3, 128.7, 126.6, 111.2, 75.9, 57.4, 57.2, 23.8, 21.0; \([\alpha]_D^{25}\) –8.5 (c = 0.90, CHCl\(_3\)); HRMS (DART): Anal. For C\(_{12}\)H\(_{18}\)O\(_3\)^+ \([\text{M+NH}_4]^+\) Calcd.: 228.1597, Found: 228.1600. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ x 25 cm)): 17.0 min (minor) and 19.8 min (major).

1,1-dimethoxy-2-(naphthalen-2-yl)propan-2-ol (10h, 92% ee)

\[
\text{CH(O\text{Me})}_2 \\
\text{OH}
\]

The reaction was stirred for 12 h. The crude mixture was purified by silica gel column
chromatography (hexane : ethyl acetate = 4 : 1) to give 82% yield of 10h (pale yellow oil). 1H NMR (400 MHz, CDCl3): δ 8.25 (s, 1H), 7.81–7.65 (m, 4H), 7.28–7.25 (m, 2H), 4.08 (s, 1H), 3.06 (s, 3H), 2.94 (s, 3H), 2.64 (s, 1H), 1.72 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 142.6, 133.7, 133.1, 128.6, 127.8, 126.1, 125.9, 125.4, 125.2, 111.0, 76.2, 57.4, 57.2, 23.9; [α]D23 –1.0 (c = 1.00, CHCl3); HRMS (DART): Anal. For C15H22N1O3+1 [M+NH4+]: Calcd.: 264.1600, Found: 264.1603; The enantiopurity was determined after conversion into 19h.

2-(1,1,2-trimethoxypropan-2-yl)naphthalene (19h, 92% ee)

According to the general procedure, reaction was carried out with 0.162 mmol of 10h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 10 : 1) to give 84% yield of 19h (white solid). 1H NMR (400 MHz, CDCl3): δ 7.88–7.86 (m, 4H), 7.62–7.59 (m, 1H), 7.50–7.46 (m, 2H), 4.25 (s, 1H), 3.52 (s, 3H), 3.13 (s, 3H), 3.07 (s, 3H), 1.71 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 139.0, 133.0, 132.6, 128.2, 127.44, 127.40, 126.8, 125.9, 125.8, 125.5, 110.9, 81.9, 58.2, 57.5, 50.3, 15.7; [α]D23 –55.2 (c = 1.00, CHCl3); HRMS (DART): Anal. For C16H24N1O3+1 [M+NH4+]: Calcd.: 278.1756, Found: 278.1757; The enantiopurity was determined by HPLC (hexane : 2-propanol = 300 : 1, 1.0 mL/min, 254 nm) using a CHIRALPAK IC-3 column (0.46 cm x 25 cm): 14.1 min (major) and 17.6 min (minor).

1,1-dimethoxy-2-(5,6,7,8-tetrahydronaphthalen-2-yl)propan-2-ol [10i, 91% ee]

The reaction was stirred for 12 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1–2 : 1) to give 57% yield of 10i (colorless oil). 1H NMR (500 MHz, CDCl3): δ 7.51 (s, 1H), 7.46 (dd, J = 7.8, 1.7 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.09 (s, 1H), 3.10 (s, 3H), 3.03 (s, 3H), 2.68–2.66 (m, 2H), 2.61–2.59 (m, 2H), 2.58 (s, 1H), 1.68 (s, 3H), 1.60–1.54 (m, 4H); 13C NMR (126 MHz, CDCl3): δ 142.3, 136.3, 135.5, 128.8, 127.1, 123.9, 111.1, 76.0, 57.3, 57.2, 26.9, 26.3, 24.0, 23.7, 23.6; [α]D25 –4.2 (c = 0.98, CHCl3); HRMS (DART): Anal. For C13H22O3+1 [M+H]+: Calcd.: 251.1650, Found: 251.1647. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1.0 mL/min; using a CHIRALPAK IC-3 column (0.46 cm x 25 cm)): 25.3 min (minor) and 32.7 min (major).
2-(2-fluoro-[1,1'-biphenyl]-4-yl)-1,1-dimethoxypropan-2-ol [10j, 90% ee]

The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1 : 2 : 1) to give 71% yield of 10j (colorless oil). 

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.61 (dd, $J = 12.6, 1.9$ Hz, 1H), 7.55–7.52 (m, 2H), 7.44 (dd, $J = 8.0, 1.9$ Hz, 1H), 7.30 (t, $J = 8.4$ Hz, 1H), 7.21–7.18 (m, 2H), 7.12–7.09 (m, 1H), 3.95 (s, 1H), 3.06 (s, 3H), 2.98 (s, 3H), 2.54 (s, 1H), 1.56 (s, 3H); 

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 160.0 (d, $J = 245.9$ Hz), 147.0 (d, $J = 7.2$ Hz), 136.2, 130.3 (d, $J = 3.6$ Hz), 129.4 (d, $J = 2.4$ Hz), 128.7, 128.3, 127.9, 122.6 (d, $J = 3.6$ Hz), 114.7 (d, $J = 25.2$ Hz), 110.7, 75.8, 57.5, 57.4, 23.9; 

$^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –117.8 ($J = 14.7$ Hz); 

[α]$_D^{24}$ –3.5 (c = 1.65, CHCl$_3$); 

HRMS (DART): Anal. For C$_{17}$H$_{19}$FO$_3$ [M+NH$_4$]$^+$ Calcd.: 308.1664, Found: 308.1662. 

The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cmφ × 25 cm)): 16.7 min (major) and 18.0 min (minor).

1-(dimethoxymethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (10k, 94% ee)

The reaction was carried out with 10 equiv. of NaOMe and stirred for 8 h at room temperature. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 55% yield of 10k (pale yellow oil). 

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.70–7.68 (m, 1H), 7.16–7.13 (m, 1H), 7.10–7.06 (m, 1H), 6.97–6.95 (m, 1H), 4.30 (s, 1H), 3.19 (s, 3H), 2.91 (s, 3H), 2.60–2.56 (m, 2H), 2.46–2.37 (m, 2H), 1.94–1.85 (m, 2H), 1.78–1.69 (m, 1H); 

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 139.1, 138.9, 129.0, 127.9, 127.3, 126.0, 73.8, 57.6, 57.4, 32.5, 30.4, 19.8; 

[α]$_D^{21}$ –3.7 (c = 1.00, CHCl$_3$); 

HRMS (DART): Anal. For C$_{13}$H$_{22}$N$_2$O$_3$ [M+NH$_4$]$^+$ Calcd.: 240.1600, Found: 240.1597; The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IE-3 column (0.46 cmφ × 25 cm): 41.1 min (major) and 36.6 min (minor).

1,1-dimethoxy-2-phenylbutan-2-ol (10l, 82% ee)
The reaction was stirred for 24 h under reflux condition. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 6 : 1) to give 71% yield of 10l (colorless oil). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 7.67–7.65 (m, 2H), 7.27–7.23 (m, 2H), 7.14–7.10 (m, 1H), 4.02 (s, 1H), 2.41 (s, 6H), 2.09–1.97 (m, 2H), 0.869 (t, 3H, $J = 7.6$ Hz); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 142.9, 128.0, 127.0, 126.8, 110.9, 78.7, 57.20, 57.15, 28.9, 7.4; [a]$_D$$^{21}$$^{+}$12.2 (c = 0.99, CHCl$_3$); HRMS (DART): Anal. For C$_{12}$H$_{22}$N$_1$O$_3$+1 [M+NH$_4$]$^+$ Calcd.: 228.1600, Found: 228.1590. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IC-3 column (0.46 cm φ x 25 cm): major isomer 12.3 min and minor isomer 11.4 min.

1,1-diethoxy-2-phenylpropan-2-ol [11, 79% ee]

![1,1-diethoxy-2-phenylpropan-2-ol](image)

Fluorination was carried out at room temperature and stirred for 1.5 h. The reaction was stirred for 17 h in ethanol under reflux condition. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 15 : 1–10 : 1) to give 43% yield of 11 (yellow oil, including ca. 10% of an inseparable by-product). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.75–7.72 (m, 2H), 7.26–7.23 (m, 2H), 7.15–7.11 (m, 1H), 4.19 (s, 1H), 3.47 (qd, $J = 9.4, 7.1$ Hz, 1H), 3.36 (qd, $J = 9.2, 6.9$ Hz, 1H), 3.13 (qd, $J = 9.4, 7.1$ Hz, 1H), 2.95 (qd, $J = 9.2, 6.9$ Hz, 1H), 2.68 (s, 1H), 1.68 (s, 3H), 0.94 (t, $J = 6.9$ Hz, 3H), 0.92 (t, $J = 5.4$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 145.2, 127.9, 127.0, 126.7, 108.7, 75.9, 65.7, 65.4, 23.6, 15.4, 15.3; [a]$_D$$^{25}$$^{–}$9.9 (c = 1.20, CHCl$_3$); HRMS (DART): Anal. For C$_{13}$H$_{20}$O$_3$+1 [M+NH$_4$]$^+$ Calcd.: 242.1759, Found: 242.1756. The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cm φ x 25 cm)): 6.5 min (minor) and 7.1 min (major).

1-(1,3-dioxolan-2-yl)-1-phenylethan-1-ol (12a, 94% ee)

![1-(1,3-dioxolan-2-yl)-1-phenylethan-1-ol](image)

According to the typical procedure, reaction was carried out using ethyleneglycole and NaH instead of MeOH and NaOMe and stirred for 5 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 63% yield of 12a (colorless oil). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 7.64–7.62 (m, 2H), 7.24–7.20 (m, 2H), 7.13–7.08 (m, 1H), 4.90 (s, 1H), 3.30–3.18 (m, 4H), 2.49 (bs, 1H), 1.55 (s, 3H); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ 144.5, 128.1,
127.1, 126.3, 107.9, 75.0, 65.6, 65.3, 24.7; \([\alpha]_D^{24} = 3.4\) (c = 1.00, CHCl₃); HRMS (DART): Anal. For C₁₁H₁₈N₁O₃⁺ [M+NH₄⁺] Calcd.: 212.1287, Found: 212.1284; The enantiopurity was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min, 220 nm) using a CHIRALPAK IB-3 column (0.46 cm φ x 25 cm): 20.3 min (major) and 22.3 min (minor).

1-(1,3-dioxolan-2-yl)-1-(2-fluoro-[1,1'-biphenyl]-4-yl)ethan-1-ol [12j, 90% ee]

The reaction was stirred for 10 h. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1–1 : 1) to give 76% yield of 12j (colorless oil). \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 7.55–7.51 (m, 3H), 7.37 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.28 (t, \(J = 8.0\) Hz, 1H), 7.21–7.17 (m, 2H), 7.12–7.09 (m, 1H), 4.82 (s, 1H), 3.32–3.18 (m, 4H), 2.32 (s, 1H), 1.49 (s, 3H); \(^1^3\)C NMR (126 MHz, CDCl₃): \(\delta\) 160.1 (d, \(J = 245.9\) Hz), 146.4 (d, \(J = 8.4\) Hz), 136.2, 130.4 (d, \(J = 3.6\) Hz), 129.4 (d, \(J = 2.4\) Hz), 128.7, 128.3, 127.8, 122.3 (d, \(J = 3.6\) Hz), 114.5 (d, \(J = 25.2\) Hz), 107.5, 74.7, 65.6, 65.4, 24.6; \(^1^9\)F NMR (470 MHz, CDCl₃): \(\delta\) –117.7 (J = 22.0 Hz); \([\alpha]_D^{24} = 4.8\) (c = 1.97, CHCl₃); HRMS (DART): Anal. For C₁₇H₁₇F₃O₃⁺ [M+H⁺] Calcd.: 289.1242, Found: 289.1249. The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1; 1.0 mL/min; using a CHIRALPAK IA-3 column (0.46 cm φ x 25 cm)): 28.1 min (minor) and 31.6 min (major).
**1H NMR measurement of hemiacetal derived from 4.**

After fluorination of 3a, NaHCO₃ aq. was added to the mixture, and extracted with Et₂O. The organic layer was dried over Na₂CO₃ and concentrated to give the crude mixture of 4a. **1H NMR measurement of 4a in CD₃OD clearly showed the generation of hemiacetal as a diastereomeric mixture (dr = 6 : 4).**

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**Synthesis of α-hydroxyester (Scheme 4)**

**methyl (R)-2-hydroxy-2-phenylpropanoate [(R)-13, 91% ee]**

The reaction was carried out according to the reported procedure. To a solution of α-hydroxyacetal (R)-10a (0.335 mmol, 91% ee) in acetone (4.8 mL) was added 3N HCl (2.1 mL) at 0 °C. The mixture was stirred for 1 d at 30 °C. After being quenched with K₂CO₃ aq., acetone was removed under reduced pressure. The mixture was extracted with ethyl acetate, and the organic layer was dried over Na₂SO₄, and concentrated. The residue was dissolved in MeOH (11.2 mL) and cooled to 0 °C. To this solution were added KOH (0.872 mmol, 2.6 equiv.) and I₂ (0.436 mmol, 1.3 equiv.) successively. The mixture was stirred for 1 h and quenched by adding 1.2N HCl. Sat. Na₂S₂O₃ aq. was added until the mixture turned colorless. MeOH was removed under reduced pressure and the mixture was extracted with ethyl acetate. The organic layer was
dried over Na₂SO₄ and concentrated. The residue was purified silica gel column chromatography (hexane : MTBE = 9 : 1–2 : 1) to give 60% yield of (R)-13 (colorless oil). ¹H NMR (400 MHz, CDCl₃): δ 7.56–7.54 (m, 2H), 7.38–7.34 (m, 2H), 7.31–7.28 (m, 1H), 3.78 (s, 3H), 3.75 (s, 1H), 1.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 176.1, 142.6, 128.3, 127.8, 125.1, 75.7, 53.2, 26.6; [α]D₂¹ −51.9 (c = 0.98, CHCl₃); HRMS (DART): Anal. For C₁₀H₁₆N₁O₃⁺1 [M+NH₄⁺] Calcd.: 198.1130, Found: 198.1130; The enantiopurity was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK AD-3 column (0.46 cm φ x 25 cm): major isomer 10.2 min and minor isomer 8.9 min. The absolute configuration of the major enantiomer was determined to be R by comparing the specific rotation with that in the literature.⁶

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NMR spectra and HPLC traces

$^1$H NMR spectrum [(R)-15]

$^{13}$C NMR spectrum [(R)-15]

$^{19}$F NMR spectrum [(R)-15]
$^1$H NMR spectrum [(R)-16]

$^{13}$C NMR spectrum [(R)-16]
$^1$H NMR spectrum [(R)-2b]

$^{13}$C NMR spectrum [(R)-2b]
$^1$H NMR spectrum [(R)-17a]

$^{13}$C NMR spectrum [(R)-17a]
$^1$H NMR spectrum [(R)-17b]

$^{13}$C NMR spectrum [(R)-17b]
\textsuperscript{1}H NMR spectrum [(\textit{R})-1\textit{a}]

\textsuperscript{13}C NMR spectrum [(\textit{R})-1\textit{a}]
$^1$H NMR spectrum [(R)-1b]

$^{13}$C NMR spectrum [(R)-1b]

HPLC optically active [(R)-1b]  
HPLC racemic (1b)
$^1$H NMR spectrum [(S)-5a]

$^{13}$C NMR spectrum [(S)-5a]

$^{19}$F NMR spectrum [(S)-5a]
$^1$H NMR spectrum [(S)-18a]

$^{13}$C NMR spectrum [(S)-18a]

$^{19}$F NMR spectrum [(S)-18a]
**HPLC optically active [(S)-18a]**

**HPLC racemic (18a)**

**$^1$H NMR spectrum (5b)**

**$^{13}$C NMR spectrum (5b)**
\[^{19}\text{F} \text{NMR spectrum (5b)}\]

\[^{1}\text{H} \text{NMR spectrum (18b)}\]

\[^{13}\text{C} \text{NMR spectrum (18b)}\]
$^{19}$F NMR spectrum (18b)

HPLC optically active (18b)  HPLC racemic (18b)

$^1$H NMR spectrum (5c)
$^{13}$C NMR spectrum (5c)

$^{19}$F NMR spectrum (5c)

HPLC optically active (5c)

HPLC racemic (5c)
$^1$H NMR spectrum (5d)

$^{13}$C NMR spectrum (5d)

$^{19}$F NMR spectrum (5d)
**HPLC optically active (5d)**

**HPLC racemic (5d)**

**$^1$H NMR spectrum (5e)**

**$^{13}$C NMR spectrum (5e)**
**19F NMR spectrum (5e)**

**HPLC optically active (5e)**

**HPLC racemic (5e)**

**1H NMR spectrum (5g)**
$^{13}$C NMR spectrum (5g)

$^{19}$F NMR spectrum (5g)

HPLC optically active (5g)  HPLC racemic (5g)
$^1$H NMR spectrum (5h)

$^{13}$C NMR spectrum (5h)

$^{19}$F NMR spectrum (5h)
HPLC optically active (5h)  HPLC racemic (5h)

$^1$H NMR spectrum (5i)

$^{13}$C NMR spectrum (5i)
$^{19}$F NMR spectrum (5i)

HPLC optically active (5i)  HPLC racemic (5i)

$^1$H NMR spectrum (5j)
$^{13}$C NMR spectrum (5j)

$^{19}$F NMR spectrum (5j)

$^1$H NMR spectrum (18j)
**13C NMR spectrum (18j)**

![13C NMR spectrum](image)

**19F NMR spectrum (18j)**

![19F NMR spectrum](image)

**HPLC optically active (18j)**

![HPLC optically active](image)

**HPLC racemic (18j)**

![HPLC racemic](image)
$^1\text{H}$ NMR spectrum (4k)

$^{13}\text{C}$ NMR spectrum (4k)

$^{19}\text{F}$ NMR spectrum (4k)
GC optically active (4k)  

GC racemic (4k)  

\(^1\)H NMR spectrum (5l)  

\(^{13}\)C NMR spectrum (5l)
$^{19}$F NMR spectrum (51)

$^{1}$H NMR spectrum (181)

$^{13}$C NMR spectrum (181)
$^{19}$F NMR spectrum (18I)

HPLC optically active (18I)  HPLC racemic (18I)

$^1$H NMR spectrum (5m)
$^{13}$C NMR spectrum (5m)

$^{19}$F NMR spectrum (5m)

$^1$H NMR spectrum (18m)
$^{13}$C NMR spectrum (18m)

$^{19}$F NMR spectrum (18m)

HPLC optically active (18m)  
HPLC racemic (18m)
$^1$H NMR spectrum (5n)

$^{13}$C NMR spectrum (5n)

$^{19}$F NMR spectrum (5n)
HPLC optically active (5n)  
HPLC racemic (5n)  

$^{1}$H NMR spectrum (5o)  

$^{13}$C NMR spectrum (5o)
\[ ^{19}F \text{ NMR spectrum (5o)} \]

\[ \text{GC optically active (5o)} \quad \text{GC racemic (5o)} \]

\[ ^1H \text{ NMR spectrum (5p)} \]
$^{13}$C NMR spectrum (5p)

$^{19}$F NMR spectrum (5p)

$^{1}$H NMR spectrum (18p)
$^{13}$C NMR spectrum (18p)

$^{19}$F NMR spectrum (18p)

HPLC optically active (18p)  HPLC racemic (18p)
$^1$H NMR spectrum (8b)

$^{13}$C NMR spectrum (8b)

$^{19}$F NMR spectrum (8b)
$^1$H NMR spectrum (8h)

$^{13}$C NMR spectrum (8h)

$^{19}$F NMR spectrum (8h)
1H NMR spectrum (9)

13C NMR spectrum (9)

19F NMR spectrum (9)
$^1$H NMR spectrum [(R)-10a]

$^{13}$C NMR spectrum [(R)-10a]

$^1$H NMR spectrum [(R)-19a]
$^{13}$C NMR spectrum [(R)-19a]

HPLC optically active [(R)-19a]  

HPLC racemic (19a)

$^1$H NMR spectrum (10b)
$^{13}$C NMR spectrum (10b)

$^{1}$H NMR spectrum (19b)

$^{13}$C NMR spectrum (19b)
HPLC optically active (19b)  
HPLC racemic (19b)

$^1$H NMR spectrum (10c)

$^{13}$C NMR spectrum (10c)
$^{19}$F NMR spectrum (10c)

HPLC optically active (10c)  HPLC racemic (10c)

$^1$H NMR spectrum (10d)
\( ^{13}\)C NMR spectrum (10d)

\begin{center}
\begin{figure}
\includegraphics[width=\textwidth]{13C_NMR_spectrum.png}
\end{figure}
\end{center}

HPLC optically active (10d)

\begin{center}
\begin{figure}
\includegraphics[width=\textwidth]{HPLC_optically_active.png}
\end{figure}
\end{center}

HPLC racemic (10d)

\begin{center}
\begin{figure}
\includegraphics[width=\textwidth]{HPLC_racemic.png}
\end{figure}
\end{center}

\( ^{1}\)H NMR spectrum (10h)

\begin{center}
\begin{figure}
\includegraphics[width=\textwidth]{1H_NMR_spectrum.png}
\end{figure}
\end{center}
$^{13}$C NMR spectrum (10h)

$^1$H NMR spectrum (19h)

$^{13}$C NMR spectrum (19h)
HPLC optically active (19h)  

HPLC racemic (19h)  

$^{1}$H NMR spectrum (10i)  

$^{13}$C NMR spectrum (10i)
HPLC optically active (10i)  HPLC racemic (10i)

**1H NMR spectrum (10j)**

**13C NMR spectrum (10j)**
$^{19}$F NMR spectrum (10j)

HPLC optically active (10j)

HPLC racemic (10j)

$^1$H NMR spectrum (10k)
$^{13}\text{C} \text{ NMR spectrum (10k)}$

$^{1}\text{H} \text{ NMR spectrum (10l)}$

$\text{HPLC optically active (10k)}$  $\text{HPLC racemic (10k)}$
$^{13}$C NMR spectrum (10I)

HPLC optically active (10I)  

HPLC racemic (10I)

$^1$H NMR spectrum (11)
$^{13}$C NMR spectrum (11)

HPLC optically active (11)  
HPLC racemic (11)

$^1$H NMR spectrum (12a)
$^{13}$C NMR spectrum (12a)

HPLC optically active (12a)  HPLC racemic (12a)

$^1$H NMR spectrum (12j)
$^1$H NMR spectrum [(R)-13]

$^{13}$C NMR spectrum [(R)-13]

HPLC optically active [(R)-13]

HPLC racemic [(R)-13]