Practical synthesis of 4,4,4-trifluorocrotonaldehyde: A versatile precursor for the enantioselective formation of trifluoromethylated stereogenic centers via organocatalytic 1,4-additions

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General
All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere and stirred via magnetic stir-plates. Thin-layer chromatography analyses were performed using Merck pre-coated silica gel plates with F-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.

Instrumentation
$^1$H, $^{13}$C, and $^{19}$F NMR spectra were recorded on a JEOL JNM-ECX500 (500 MHz $^1$H, 126 MHz $^{13}$C, 470 MHz $^{19}$F). Chemical shift values ($\delta$) are reported in ppm (tetramethylsilane 0.00 ppm for $^1$H; trichlorofluoromethane 0.00 ppm for $^{19}$F; residual chloroform 77.0 ppm for $^{13}$C). Infrared spectra were recorded as thin films on sodium chloride plates using a JASCO FTIR-230 spectrometer. Optical rotations were measured on a JASCO P-1030 digital polarimeter. GC analysis was performed with a Shimadzu model 2014 instrument using nitrogen as a carrier gas. Analytical HPLC was performed on a JASCO PU1586 with a UV-1575 UV/Vis detector using a chiral column.

Materials
Commercial grade reagents and solvents were used without further purification unless otherwise noted. Anhydrous toluene, diethyl ether, dimethylformamide (DMF), dichloromethane, and pyridine were purchased from Aldrich (packaged in Sure/Seal bottle) and used without further purification.
Synthesis of 4,4,4-trifluorocrotonaldehyde (1)

\[
\text{F}_3\text{C} = \text{CHO} \quad 1
\]

A solution of ethyl 4,4,4-trifluorocrotonate (4) (20 mmol) in anhydrous ether (10 mL) was added to a suspension of lithium aluminum hydride (30 mmol) and aluminum trichloride (15 mmol) in anhydrous ether (15 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. Saturated NaHCO₃ was added to the mixture. The compound was extracted with ether, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was distilled under atmospheric pressure to give pure 3 in 61% yield. The spectral data were identical to those previously reported for this compound [N. Ishikawa, M. G. Koh, T. Kitazume, S. K. Choi, \textit{J. Fluorine Chem.} 1984, \textbf{24}, 419.].

Manganese dioxide (320 mmol) was added to a solution of 3 (40 mmol) in mesitylene (30 mL), and the mixture was stirred for 24 h at 50 °C. The reaction mixture was filtrated thorough Celite. The filtrate was distilled under atmospheric pressure to give 4,4,4-trifluorocrotonaldehyde (1) in 47% yield as a nearly pure form (observed boiling point: 38 °C).

\(^{1}\text{H} \text{NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 9.73 (d, } 1\text{H, } J = 5.2 \text{ Hz), 6.72-6.62 (m, } 2\text{H); } ^{13}\text{C NMR (126 MHz, CDCl}_3\text{): } \delta \text{ 190.7, 136.5 (q, } J = 35.5 \text{ Hz), 135.8 (q, } J = 5.8 \text{ Hz), 122.0 (q, } J = 270.3 \text{ Hz); } ^{19}\text{F NMR (470 MHz, CDCl}_3\text{): } \delta \text{ –66.2 (d, } J = 1.5 \text{ Hz); FTIR (neat) } \nu_{\text{max}} \text{ 3505, 2919, 1604, 1129, 836, 685, 468 cm}^{-1}.

**General procedure for the enantioselective conjugate Friedel-Crafts arylation (Table 1):**

Pyroles or indoles (0.3 mmol) and 1 (0.2 mmol) were added successively to a solution of diarylprolinol silyl ethter 2 (0.02 mmol) in anhydrous toluene (2 mL). The mixture was stirred for 10–16 h at ambient temperature. The reaction mixture was directly subjected to silica gel column chromatography to give corresponding product 5 or 6 in high purity.

\(4,4,4\text{-trifluoro-3-(1H-pyrrol-2-yl)butanal (5a) \quad 5a}\)

The reaction mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 92% yield of 5a. \(^{1}\text{H} \text{NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 9.78 (s, } 1\text{H), 8.35 (brs, NH), 6.80-6.71 (m, } 1\text{H), 6.24-6.11 (m, } 2\text{H), 4.15-4.03 (m, } 1\text{H), 3.07 (d, } 2\text{H, } J = 6.5 \text{ Hz); } ^{13}\text{C NMR (126 MHz, CDCl}_3\text{): } \delta \text{ 197.9, 126.0 (q, } J = 279.5 \text{ Hz), 123.6, 118.6, 108.7, 107.9, 42.9, 37.2 (q, } J
The enantiomeric excess of 5a was determined by HPLC after converted into 19a (see below).

4,4,4-trifluoro-3-(1H-pyrrol-2-yl)butan-1-ol (18a)

To a solution of sodium borohydride (0.2 mmol) in methanol (0.5 mL) was added a solution of 5a (0.1 mmol) in dichloromethane (0.5 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C. Saturated aqueous NH₄Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na₂SO₄ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give 81% yield of 18a. ¹H NMR (500 MHz, CDCl₃): δ 8.35 (brs, NH), 6.82-6.74 (m, 1H), 6.23-6.13 (m, 2H), 3.73 (ddd, 1H, J = 5.0, 5.4, 10.3 Hz), 3.70-3.60 (m, 1H), 3.50 (ddd, 1H, J = 4.2, 4.9, 9.9 Hz), 2.26-2.16 (m, 1H), 2.02-1.91 (m, 1H), 1.66 (brs, OH); ¹³C NMR (126 MHz, CDCl₃): δ 126.6 (q, J = 279.5 Hz), 123.8, 118.4, 108.6, 108.4, 59.3, 40.1 (d, J = 28.8 Hz), 31.1; ¹⁹F NMR (470 MHz, CDCl₃): δ -70.9 (d, J = 9.4 Hz); [α]²⁴D = -21.6 (c = 0.2, CHCl₃); FTIR (neat) ν_max 3432, 3132, 2963, 1762, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm⁻¹; Anal. Calcd (%) for C₈H₁₁F₃NO: C, 49.74; H, 5.22; N, 7.25. Found: C, 49.79; H, 5.31; N, 7.33.

4,4,4-trifluoro-3-(1H-pyrrol-2-yl)butyl 2-naphthoate (19a)

To a solution of 18a (0.08 mmol) in anhydrous dichloromethane (0.5 mL) were added triethylamine (0.16 mmol), DMAP (0.01 mmol), and 2-naphthoyl chloride (0.12 mmol) successively. The reaction mixture was stirred for 4 h at ambient temperature. Saturated NaHCO₃ was added to the mixture. The compound was extracted with dichloromethane, dried over Na₂SO₄, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane : CH₂Cl₂ = 1 : 1) to give 80% yield of 19a. ¹H NMR (500 MHz, CDCl₃): δ 8.55 (s, 1H), 8.32 (brs, NH), 8.03-7.94 (m, 2H), 7.89 (d, 2H, J = 8.6 Hz),
7.63-7.53 (m, 2H), 6.81-6.78 (m, 1H), 6.24-6.19 (m, 2H), 4.47-4.39 (m, 1H), 4.33-4.26 (m, 1H), 3.69-3.59 (m, 1H), 2.56-2.49 (m, 1H), 2.31-2.21 (m, 1H); $^1$H NMR (126 MHz, CDCl$_3$): $\delta$ 166.6, 135.6, 132.4, 131.1, 129.4, 128.4, 128.3, 127.8, 127.0, 126.8, 126.3 (q, $J = 279.9$ Hz), 125.1, 123.1, 118.7, 109.0, 108.9, 62.0, 40.8 (q, $J = 28.8$ Hz), 28.1; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –71.4 (d, $J = 8.4$ Hz); [$\alpha$]$^2$D –50.4 (c = 0.2, CHCl$_3$); FTIR (neat) $\nu_{\max}$ 3056, 2359, 1743, 1510, 1404, 1308, 1239, 1152, 1051, 1156, 784, 433 cm$^{-1}$; Anal. Calcd (%) for C$_{19}$H$_{16}$F$_3$NO$_2$: C, 65.70; H, 4.64; N, 4.03. Found: C, 65.96; H, 4.62; N, 4.11.

The enantiomeric ratio was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cm $\phi$ x 25 cm): major isomer 12.6 min and minor isomer 14.0 min.

4,4,4-trifluoro-3-(1-methyl-1H-pyrrol-2-yl)butanal (5b)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 96% yield of 5b. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.69 (brs, 1H), 6.61-6.57 (m, 1H), 6.14-6.04 (m, 2H), 4.20-4.02 (m, 1H), 3.69 (s, 3H), 3.25-3.03 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 197.2, 126.5, 126.0 (q, $J = 279.5$ Hz), 108.1, 107.2, 43.7, 35.0 (q, $J = 30.0$ Hz), 34.0, 30.6; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –70.9 (d, $J = 9.4$ Hz); [$\alpha$]$^2$D –19.3 (c = 0.2, CHCl$_3$); FTIR (neat) $\nu_{\max}$ 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm$^{-1}$; Anal. Calcd (%) for C$_9$H$_{10}$F$_3$NO: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.83; H, 4.95; N, 6.65.

The enantiomeric excess of 5b was determined by HPLC after converted into 19b (see below).

4,4,4-trifluoro-3-(1-methyl-1H-pyrrol-2-yl)butan-1-ol (18b)

The compound was synthesized according to a procedure similar to that employed for the synthesis of 18a. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 81% yield of 18b. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.62-6.58 (m, 1H), 6.15-6.11 (m, 2H), 3.79-3.67 (m, 2H), 3.61 (s, 3H), 3.46 (ddd, 1H, $J = 3.8$, 3.8, 10.3 Hz), 2.30-2.20 (m, 1H), 2.06-1.97 (m, 1H), 2.06 (brs, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 126.6 (q, $J = 279.5$ Hz), 125.3, 122.9, 108.0, 107.2, 59.1, 37.3 (q, $J = 27.6$ Hz), 33.9, 31.6; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –71.2 (d, $J = 8.0$ Hz); [$\alpha$]$^2$D –20.5 (c = 0.2, CHCl$_3$); FTIR
The compound was synthesized according to a procedure similar to that employed for the synthesis of 19a. The crude mixture was purified by silica gel column chromatography (hexane : CH₂Cl₂ = 1 : 1) to give 80% yield of 19b. ¹H NMR (500 MHz, CDCl₃): δ 8.54 (s, 1H), 8.00 (dd, 1H, J = 1.6, 8.6 Hz), 7.97 (d, 1H, J = 7.64 Hz), 7.89 (d, 2H, J = 8.41 Hz), 7.64-7.59 (m, 1H), 7.59-7.54 (m, 1H), 6.60 (dd, 1H, J = 1.9, 2.7 Hz), 6.23 (dd, 1H, J = 1.5, 3.4 Hz), 6.18 (dd, 1H, J = 2.7, 3.4 Hz), 4.48 (ddd, 1H, J = 5.4, 5.4, 10.7 Hz), 4.25 (ddd, 1H, J = 4.6, 9.6, 11.1 Hz), 3.72-3.62 (m, 1H), 3.56 (s, 3H), 2.61-2.52 (m, 1H), 2.37-2.27 (m, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 166.4, 135.6, 132.4, 131.1, 129.3, 128.4, 128.3, 127.8, 126.8, 126.2 (q, J = 280.8 Hz), 125.0, 123.3, 108.4, 107.5, 62.1, 38.3 (q, J = 28.8 Hz), 33.8, 28.5; ¹⁹F NMR (470 MHz, CDCl₃): δ -71.4 (d, J = 8.4 Hz); [α]₂⁴D -50.4 (c = 0.2, CHCl₃); FTIR (neat) νₘₐₓ 3056, 2359, 1743, 1510, 1404, 1308, 1239, 1152, 1051, 1156, 784, 433 cm⁻¹; Anal. Calcd (%) for C₁₉H₁₁F₃NO: C, 65.70; H, 4.64; N, 4.03. Found: C, 65.96; H, 4.62; N, 4.11.

The enantiomeric ratio of 19b was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cm x 25 cm): major isomer 12.0 min, minor isomer 11.2 min (97% ee).

4,4,4-trifluoro-3-(1-benzyl-1H-pyrrol-2-yl)butanal (5c)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 85% yield of 5c. ¹H NMR (500 MHz, CDCl₃): δ 9.37 (s, 1H), 7.39-7.24 (m, 3H), 7.07-7.03 (m, 2H), 6.71-6.67 (m, 1H), 6.22-6.16 (m, 2H), 5.19 (ddd, 2H, J = 16.4, 36.8 Hz), 4.01-3.91 (m, 1H), 3.03-2.90 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 197.5, 137.4, 128.8, 127.8, 126.7, 125.8 (q, J = 275.9 Hz), 124.7, 123.3, 109.3, 107.9, 50.7, 43.5, 35.1 (q, J = 30.0 Hz); ¹⁹F NMR (470 MHz, CDCl₃): δ -71.0 (d, J = 8.9 Hz); [α]₂⁴D +8.8 (c = 0.2, CHCl₃); FTIR (neat) νₘₐₓ 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm⁻¹; Anal. Calcd (%)
for C₁₅H₁₄F₃NO: C, 64.05; H, 5.02; N, 4.98. Found: C, 64.22; H, 5.06; N, 5.31.

The enantiomeric excess of 5c was determined by HPLC after converted into 18c (see below).

4,4,4-trifluoro-3-(1-benzyl-1H-pyrrol-2-yl)butan-1-ol (18c)

The compound was synthesized according to a procedure similar to that employed for the synthesis of 18a. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give 85% yield of 18c. ¹H NMR (500 MHz, CDCl₃): δ 7.40-7.25 (m, 3H), 7.09-7.00 (m, 2H), 6.82-6.76 (m, 1H), 6.29-6.17 (m, 2H), 5.17 (d, 1H, J = 16.4 Hz), 5.11 (d, 1H, J = 16.4 Hz), 3.54-3.43 (m, 2H), 3.18-3.08 (m, 1H), 2.14-2.03 (m, 1H), 1.95-1.85 (m, 1H), 0.53 (brs, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 197.5, 137.4, 128.8, 127.8, 126.7, 125.8 (q, J = 275.9 Hz), 124.7, 123.3, 109.3, 107.9, 50.7, 43.5, 35.1 (q, J = 30.0 Hz); ¹⁹F NMR (470 MHz, CDCl₃): δ –71.0 (d, J = 8.9 Hz); [α]²⁰D +3.4 (c = 0.2, CHCl₃); FTIR (neat) ν max 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm⁻¹; Anal. Caled (%) for C₁₅H₁₆F₃NO: C, 63.60; H, 5.69; N, 4.94. Found: C, 63.57; H, 5.48; N, 5.06.

The enantiomeric ratio of 18c was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmϕ x 25 cm): major isomer 18.9 min, minor isomer 13.7 min (99% ee).

4,4,4-trifluoro-3-(4-methyl-1H-pyrrol-2-yl)butanal (5d)

This compound was obtained together with 2,3-disubstituted form 5d’ which was inseparable by silica gel column chromatography. The isolation and determination of enantiomeric ratio were performed after converted into 19d (see below).

4,4,4-trifluoro-3-(3-methyl-1H-pyrrol-2-yl)butyl 2-naphthoate (19d)
The compound was synthesized according to procedures similar to those employed for the synthesis of 18a and 19a. The crude mixture was purified by silica gel column chromatography (hexane : CH₂Cl₂ = 1 : 2) to give 81% yield of 19d. ¹H NMR (500 MHz, CDCl₃): δ 8.55 (s, 1H), 8.06 (brs, NH), 8.01 (d, 1H, J = 8.8 Hz), 7.96 (d, 1H, J = 8.0 Hz), 7.89 (d, 2H, J = 8.4 Hz), 7.61 (dd, 1H, J = 7.3, 7.3 Hz), 7.56 (dd, 1H, J = 7.3, 7.3 Hz), 6.74-6.71 (m, 1H), 6.04-6.01 (m, 1H), 4.40 (ddd, 1H, J = 5.4, 5.4, 11.1 Hz), 4.10 (ddd, 1H, J = 5.4, 9.6, 9.6 Hz), 3.85-3.69 (m, 1H), 2.60-2.45 (m, 1H), 2.26-2.11 (m, 1H), 2.05 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 166.4, 135.6, 132.4, 131.1, 129.3, 128.4, 128.2, 127.8, 127.0 (q, J = 280.7 Hz), 126.7, 126.6, 125.0, 119.2, 118.7, 118.0, 110.3, 61.8, 38.3 (q, J = 28.8 Hz), 27.7, 10.9; ¹⁹F NMR (470 MHz, CDCl₃): δ –70.5 (d, J = 9.4 Hz); [α]²⁴D –35.4 (c = 0.2, CHCl₃); FTIR (neat) νmax 3056, 2359, 1743, 1510, 1404, 1308, 1329, 1152, 1051, 1156, 784, 433 cm⁻¹; Anal. Calcd (%) for C₂₀H₁₈F₃NO₂: C, 66.48; H, 5.02; N, 3.88. Found: C, 66.67; H, 5.31; N, 3.85.

The enantiomeric ratio of 19d was determined by HPLC (hexane : 2-propanol = 50 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cm φ x 25 cm): major isomer 21.7 min, minor isomer 19.4 min (80% ee).

4,4,4-trifluoro-3-(1H-indol-2-yl)butanal (6a)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 98% yield of 6a. ¹H NMR (500 MHz, CDCl₃): δ 9.63 (s, 1H), 8.25 (brs, NH), 7.67 (d, 1H, J = 7.6 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.25-7.20 (m, 1H), 7.20-7.15 (m, 1H), 7.11 (d, 1H, J = 2.7 Hz), 4.34 (qdd, 1H, J = 5.7, 8.8, 8.8 Hz), 3.18-3.07 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 198.3, 136.0, 126.8 (q, J = 279.5 Hz), 126.3, 123.7, 122.7, 120.2, 118.9, 111.5, 108.6, 42.9, 35.6 (q, J = 30.0 Hz); ¹⁹F NMR (470 MHz, CDCl₃): δ –71.0 (d, J = 9.4 Hz); [α]²⁴D –24.3 (c = 0.2, CHCl₃); FTIR (neat) νmax 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm⁻¹; Anal. Calcd (%) for C₁₂H₁₀F₃NO: C, 59.75; H, 4.18; N, 5.81. Found: C, 59.86; H,
The enantiomeric excess of 6a was determined by HPLC after converted into 20a (see below).

**4,4,4-trifluoro-3-(1H-indol-2-yl)butan-1-ol (20a)**

The compound was synthesized according to a procedure similar to that employed for the synthesis of 18a. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 92% yield of 20a. $^1$H NMR (500 MHz, CDCl$_3$): \(\delta\) 8.22 (brs, NH), 7.67 (d, 1H, \(J = 8.0\) Hz), 7.40 (d, 1H, \(J = 1.2, 6.9, 8.1\) Hz), 7.20 (d, 1H, \(J = 2.3\) Hz), 7.17 (dd, 1H, \(J = 1.2, 6.9, 8.1\) Hz), 3.91 (ddd, 1H, \(J = 3.8, 9.6, 9.9\) Hz), 3.71 (ddd, 1H, \(J = 5.4, 5.4, 10.3\) Hz), 3.50 (ddd, 1H, \(J = 5.0, 9.6, 9.6\) Hz), 2.40 - 2.31 (m, 1H), 2.16 (ddddd, 1H, \(J = 4.6, 4.6, 11.1, 13.8\) Hz), 1.48 (brs, OH); $^{13}$C NMR (126 MHz, CDCl$_3$): \(\delta\) 136.1, 127.5 (q, \(J = 279.5\) Hz), 127.0, 123.4, 122.5, 120.1, 119.1, 111.4, 109.2, 59.6, 38.0 (q, \(J = 28.8\) Hz), 31.7; $^{19}$F NMR (470 MHz, CDCl$_3$): \(\delta\) –70.7 (d, \(J = 9.9\) Hz); \([\alpha]_D^{24}\) –8.4 (c = 0.3, CHCl$_3$); FTIR (neat) \(\nu_{max}\) 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm$^{-1}$; Anal. Calcd (%) for C$_{12}$H$_{12}$F$_3$NO: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.05; H, 4.82; N, 5.94.

The enantiomeric ratio of 20a was determined by HPLC (hexane : 2-propanol = 10 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cm$\phi$ x 25 cm): major isomer 13.4 min, minor isomer 12.1 min (90% ee).

**4,4,4-trifluoro-3-(1-methyl-1H-indol-2-yl)butanal (6b)**

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 83% yield of 6b. $^1$H NMR (500 MHz, CDCl$_3$): \(\delta\) 9.66 (s, 1H), 7.66 (d, 1H, \(J = 8.0\) Hz), 7.32 (d, 1H, \(J = 8.0\) Hz), 7.27 (dd, 1H, \(J = 1.2, 6.9, 8.0\) Hz), 7.20 (d, 1H, \(J = 2.3\) Hz), 7.18 (ddd, 1H, \(J = 1.2, 6.9, 8.0\) Hz), 4.34 (qdd, 1H, \(J = 6.1, 9.2, 9.2\) Hz), 3.77 (s, 3H), 3.18 - 3.08 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): \(\delta\) 198.2, 136.9, 128.2, 126.8, 126.8 (q, \(J = 283.1\) Hz), 122.2, 119.8, 119.0, 109.6, 106.9, 43.0, 35.6 (q, \(J = 30.0\) Hz), 32.9; $^{19}$F NMR (470 MHz, CDCl$_3$): \(\delta\) –71.0 (d, \(J = 9.4\) Hz); \([\alpha]_D^{24}\) –37.3 (c = 0.1, CHCl$_3$); FTIR (neat) \(\nu_{max}\) 3397, 2850, 1464, 1324,
The enantiomeric excess of 6b was determined by HPLC after converted into 20b (see below).

4,4,4-trifluoro-3-(1-methyl-1H-indol-2-yl)butan-1-ol (20b)

The compound was synthesized according to a procedure similar to that employed for the synthesis of 18a. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 97% yield of 20b. \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 7.64 (d, 1H, \(J = 8.0\) Hz), 7.33 (d, 1H, \(J = 8.4\) Hz), 7.26 (ddd, 1H, \(J = 1.2, 6.9, 8.1\) Hz), 7.15 (ddd, 1H, \(J = 1.2, 6.9, 8.1\) Hz), 3.93-3.82 (m, 1H), 3.79 (s, 3H), 3.69 (ddd, 1H, \(J = 5.4, 5.4, 10.3\) Hz), 3.48 (ddd, 1H, \(J = 5.0, 9.6, 10.3\) Hz), 2.38-2.29 (m, 1H), 2.18-2.08 (m, 1H), 1.44 (brs, OH); \(^{13}\)C NMR (126 MHz, CDCl₃): \(\delta\) 136.8, 128.0, 127.6, 127.5 (q, \(J = 28.8\) Hz), 122.0, 119.9, 119.1, 109.5, 107.3, 59.6, 37.9 (q, \(J = 28.8\) Hz), 32.9, 31.8; \(^{19}\)F NMR (470 MHz, CDCl₃): \(\delta\) –70.8 (d, \(J = 9.9\) Hz); \([\alpha]_D^{24}\) –27.2 (c = 0.2, CHCl₃); FTIR (neat) \(\nu_{max}\) 1672, 1370, 1335, 1310, 1256, 1105, 956, 748, 735 cm\(^{-1}\); Anal. Calcd (%) for C₁₃H₁₄F₃NO: C, 60.70; H, 5.49; N, 5.44. Found: C, 61.01; H, 5.70; N, 5.72.

The enantiomeric ratio of 20b was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cm \(\times\) 25 cm): major isomer 29.1 min, minor isomer 21.1 min (97% ee).

4,4,4-trifluoro-3-(5-methoxy-1H-indol-2-yl)butanal (6c)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 71% yield of 6c. \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 9.67 (s, 1H), 8.21 (brs, NH), 7.26 (d, 1H, \(J = 8.8\) Hz), 7.13 (d, 1H, \(J = 2.7\) Hz), 7.09 (d, 1H, \(J = 2.3\) Hz), 6.89 (dd, 1H, \(J = 2.3, 8.8\) Hz), 4.31 (qdd, 1H, \(J = 5.4, 5.4, 9.2\) Hz), 3.88 (s, 3H), 3.19-3.07 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl₃): \(\delta\) 154.3, 131.1, 127.5, 127.5, 124.0, 112.7, 112.1, 108.8, 100.8, 59.6, 55.8, 37.9 (d, \(J = 28.8\) Hz), 25.3; \(^{19}\)F NMR (470 MHz, CDCl₃): \(\delta\) –71.1 (d, \(J = 8.9\) Hz);
[α]$_{D}^{24}$−35.4 (c = 0.1, CHCl$_3$); FTIR (neat) $\nu_{\text{max}}$ 3397, 2850, 1464, 1324, 1320, 1315, 1212, 935, 907, 765, 698 cm$^{-1}$; Anal. Calcd (%) for C$_{13}$H$_{12}$F$_3$NO$_2$: C, 57.57; H, 4.46; N, 5.16. Found: C, 57.55; H, 4.46; N, 5.44.

The enantiomeric excess of 6c was determined by HPLC after converted into 20c (see below).

**4,4,4-trifluoro-3-(5-methoxy-1H-indol-2-yl)butan-1-ol (20c)**

The compound was synthesized according to a procedure similar to that employed for the synthesis of 18a. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give 94% yield of 20c. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.19 (brs, NH), 7.26 (d, 1H, $J$ = 8.8 Hz), 7.13 (d, 1H, $J$ = 2.7 Hz), 7.08 (d, 1H, $J$ = 2.3 Hz), 7.15 (dd, 1H, $J$ = 2.7, 8.8 Hz), 4.02 (qdd, 1H, $J$ = 6.1, 6.1, 12.2 Hz), 3.85 (s, 3H), 3.70 (ddd, 1H, $J$ = 5.0, 5.4, 10.3 Hz), 3.49 (ddd, 1H, $J$ = 5.0, 9.6, 10.3 Hz), 2.37-2.29 (m, 1H), 2.17-2.08 (m, 1H), 1.53 (brs, OH); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 154.3, 131.1, 127.5, 127.5 (q, $J$ = 280.7 Hz), 124.0, 112.1, 108.8, 100.8, 59.6, 55.8, 37.9 (d, $J$ = 28.8 Hz), 25.3; $^{19}$F NMR (470 MHz, CDCl$_3$): δ −70.7 (d, $J$ = 9.9 Hz); [α]$_{D}^{24}$−10.8 (c = 0.2, CHCl$_3$); FTIR (neat) $\nu_{\text{max}}$ 1672, 1370, 1335, 1310, 1302, 1256, 1105, 956, 748, 735 cm$^{-1}$; Anal. Calcd (%) for C$_{13}$H$_{14}$F$_3$NO$_2$: C, 57.14; H, 5.16; N, 5.13. Found: C, 57.11; H, 5.15; N, 5.38.

The enantiomeric ratio of 20c was determined by HPLC (hexane : 2-propanol = 10 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cm\(\phi\) x 25 cm): major isomer 8.2 min, minor isomer 10.2 min (93% ee).

**Experimental procedure and characterization of the products for Scheme 3:**

Aromatic compounds (0.3 mmol) and 1 (0.2 mmol) were added successively to a solution of diarylprolinol silyl ether 2 (0.06 mmol) in anhydrous toluene (2 mL). The mixture was stirred for 12–14 h at ambient temperature. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 0.5 h at 0 °C. Saturated aqueous NH$_4$Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the corresponding adducts in high purity.
3-((dimethylamino)-2-methoxyphenyl)-4,4,4-trifluorobutan-1-ol (7)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 74% yield (99% ee). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.16 (d, 1H, $J = 8.4$ Hz), 6.35 (dd, 1H, $J = 8.8$, 2.3 Hz), 6.25 (d, 1H, $J = 2.7$ Hz), 4.12–4.01 (m, 1H), 3.85 (s, 3H), 3.64–3.55 (m, 1H), 3.43–3.34 (m, 1H), 2.97 (s, 6H), 2.30–2.20 (m, 1H), 1.96–1.85 (m, 1H), 1.78 (brs, OH); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 158.6, 151.4, 128.6, 127.6 (q, $J = 279.5$ Hz), 110.1, 105.2, 95.7, 59.7, 55.8, 40.4, 36.5 (q, $J = 26.4$ Hz), 31.9; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –69.7 (d, $J = 9.9$ Hz); [a]$^2\beta$ $\Delta$ $-20.4$ (c = 0.95, CHCl$_3$); FTIR (neat) $\nu_{\max}$ 3386, 2946, 1616, 1571, 1521, 1453, 1361, 1246, 1123, 1039, 813 cm$^{-1}$; Anal. Calcd (%) for C$_{13}$H$_{18}$F$_3$NO$_2$: C, 56.31; H, 6.54; N, 5.05. Found: C, 56.19; H, 6.67; N, 5.11.

The enantiomeric excess was determined by HPLC (hexane : 2-propanol = 10 : 1, 0.5 mL/min) using a CHIRALPAK IC column (0.46 cm $\phi$ x 25 cm): major isomer 12.9 min and minor isomer 11.9 min.

4,4,4-trifluoro-3-(5-methoxyfuran-2-yl)butan-1-ol (8)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 47% yield (70% ee). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.20 (d, 1H, $J = 3.4$ Hz), 5.11 (d, 1H, $J = 3.4$ Hz), 3.83 (s, 3H), 3.79–3.70 (m, 1H), 3.65–3.48 (m, 2H), 2.18–2.10 (m, 1H), 2.10–2.02 (m, 1H), 1.61 (brs, OH); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 161.5, 137.3, 125.8 (q, $J = 279.5$ Hz), 111.1, 80.0, 59.2, 57.7, 40.2 (q, $J = 28.8$ Hz), 29.7; $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ –70.4 (d, $J = 9.9$ Hz); [a]$^{25\beta}$ $\Delta$ +43.1 (c = 0.45, CHCl$_3$); FTIR (neat) $\nu_{\max}$ 3328, 2925, 1500, 1321, 1264, 1175, 1132, 1064, 916, 835, 737 cm$^{-1}$; Anal. Calcd (%) for C$_9$H$_{14}$F$_3$O$_2$: C, 48.22; H, 4.95. Found: C, 48.24; H, 4.97. The enantiomeric excess was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cm $\phi$ x 25 cm): major isomer 16.7 min and minor isomer 15.1 min.
General procedure for the enantioselective Michael addition with alkylthiols (Table 2, Entries 1–6):

Alkylthiols (0.2 mmol) and 1 (0.3 mmol) were added successively to a solution of diarylprolinol silyl ether 2 (0.02 mmol) and benzoic acid (0.02 mmol) in anhydrous toluene (0.5 mL). The mixture was stirred for 5 h at ambient temperature. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 0.5 h at 0 °C. Saturated aqueous NH₄Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give corresponding thioethers 9 in high purity.

4,4,4-trifluoro-3-(phenylthio)butan-1-ol (9a)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 97% yield of 9a. ¹H NMR (500 MHz, CDCl₃): δ 7.60-7.47 (m, 2H), 7.40-7.27 (m, 3H), 4.11-3.98 (m, 1H), 3.98-3.89 (m, 1H), 3.74-3.64 (m, 1H), 2.25-2.12 (m, 1H), 1.85-1.69 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): δ 133.1, 133.1, 129.2, 128.3, 126.8 (q, J = 278.0 Hz), 58.7, 49.1 (q, J = 29.7 Hz), 31.0; ¹⁹F NMR (470 MHz, CDCl₃): δ –71.1 (d, J = 8.3 Hz); [α]²²D –40.7 (c = 0.3, CHCl₃); FTIR (neat) νmax 1983, 1822, 1737, 1366, 1280, 1161, 853, 714 cm⁻¹; Anal. Calcd (%) for C₁₀H₁₁F₃OS: C, 50.84; H, 4.69. Found: C, 50.86; H, 4.70.

The enantiomeric ratio of 9a was determined by HPLC (hexane : 2-propanol = 99 : 1, 0.5 mL/min) using a CHIRALPAK IC column (0.46 cm φ x 25 cm): major isomer 20.7 min, minor isomer 21.6 min (94% ee).

4,4,4-trifluoro-3-(benzylthio)butan-1-ol (9b)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 98% yield of 9b. ¹H NMR (500 MHz, CDCl₃): δ 7.40-7.27 (m, 5H), 3.83 (s, 2H), 3.60 (dd, 2H, J = 4.0, 7.6 Hz), 3.07 (qdd, 1H, J = 3.4, 8.5, 11.6 Hz), 2.07-1.95 (m, 2H), 1.53 (dddd, 1H, J = 4.0, 4.0, 11.6, 15.3 Hz), 1.25 (brs, OH); ¹³C NMR (126 MHz, CDCl₃): δ 137.2, 129.1, 127.6, 127.4 (q, J = 278.0 Hz), 58.6, 42.8 (q, J = 28.8 Hz), 30.4; ¹⁹F NMR (470 MHz, CDCl₃): δ –71.3 (d, J = 8.0 Hz); [α]²⁴D –147.7 (c = 0.2, CHCl₃); FTIR (neat) νmax 1764, 1735, 1456, 1394, 1326, 1281, 1212, 1121, 1025, 959, 864, 716 cm⁻¹; Anal. Calcd (%) for...
C_{10}H_{17}F_{3}OS: C, 52.79; H, 5.24. Found: C, 52.62; H, 5.24.

The enantiomeric ratio of 9b was determined by HPLC (hexane : 2-propanol = 50 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmφ x 25 cm): major isomer 8.1 min, minor isomer 10.1 min (95% ee).

4,4,4-trifluoro-3-(cyclohexylthio)butan-1-ol (9c)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 99% yield of 9c. \(^1\)H NMR (500 MHz, CDCl\(_3\))\(\delta\) 3.98-3.82 (m, 2H), 3.37 (qdd, 1H, \(J = 3.1, 8.5, 11.6\) Hz), 2.91-2.80 (m, 1H), 2.19-2.04 (m, 2H), 2.01-1.90 (m, 1H), 1.84-1.71 (m, 2H), 1.71-1.58 (m, 3H), 1.41-1.19 (m, 5H); \(^1\)C NMR (126 MHz, CDCl\(_3\))\(\delta\) 127.2 (q, \(J = 278.0\) Hz), 59.1, 44.8, 42.9 (q, \(J = 29.7\) Hz), 33.8, 33.2, 31.3, 26.0, 25.8, 25.6; \(^1\)F NMR (470 MHz, CDCl\(_3\))\(\delta\) –71.8 (d, \(J = 8.0\) Hz); [\(\alpha\)]\(^24\)_D –17.2 (c = 0.2, CHCl\(_3\)); FTIR (neat) \(\nu\)\(_{max}\) 1738, 1735, 1439, 1333, 1292, 1203, 1022, 959, 932, 794, 723 cm\(^{-1}\); Anal. Calcd (%) for C\(_{10}\)H\(_{17}\)F\(_3\)OS: C, 49.57; H, 7.07. Found: C, 49.33; H, 7.02.

The enantiomeric excess of 9c was determined by HPLC after converted into corresponding benzoate 21c (see below).

4,4,4-trifluoro-3-(cyclohexylthio)butyl benzoate (21c)

To a solution of 9c (0.1 mmol) in anhydrous dichloromethane (2 mL) were added triethylamine (0.3 mmol), DMAP (0.01 mmol), and benzoyl chloride (0.2 mmol) successively. The mixture was stirred for 6 h at ambient temperature. Saturated NaHCO\(_3\) was added to the mixture. The compound was extracted with dichloromethane, dried over Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : CH\(_2\)Cl\(_2\) = 2 : 1) to give 76% yield of 21c. \(^1\)H NMR (500 MHz, CDCl\(_3\))\(\delta\) 8.07-8.00 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.43 (m, 2H), 4.63-4.53 (m, 2H), 3.38-3.25 (m, 1H), 2.90-2.77 (m, 1H), 2.49-2.36 (m, 1H), 2.02-1.89 (m, 2H), 1.89-1.78 (m, 1H), 1.78-1.64 (m, 2H), 1.64-1.51 (m, 1H), 1.40-1.15 (m, 5H); \(^1\)C NMR (126 MHz, CDCl\(_3\))\(\delta\) 166.2, 133.1, 129.8, 129.5, 128.4, 127.0 (q, \(J = 278.3\) Hz), 61.3, 44.7, 43.0 (q, \(J = 28.8\) Hz), 33.5, 33.1, 28.2, 25.8, 25.6, 25.5; \(^1\)F NMR (470 MHz, CDCl\(_3\))\(\delta\) –71.8 (d, \(J = 8.0\) Hz); [\(\alpha\)]\(^24\)_D –58.1 (c = 0.2, CHCl\(_3\)); FTIR (neat)
υ\text{max} 2057, 1742, 1504, 1315, 1251, 1172, 1023, 960, 784, 740, 698 cm\textsuperscript{-1}; Anal. Calcd (%) for C\textsubscript{10}H\textsubscript{17}F\textsubscript{3}OS: C, 58.94; H, 6.11. Found: C, 58.99; H, 6.12.

The enantiomeric ratio of 21c was determined by HPLC (hexane : 2-propanol = 400 : 1, 0.2 mL/min) using a CHIRALPAK AS–H column (0.46 cm φ x 25 cm): major isomer 27.7 min, minor isomer 33.7 min (96% ee)

4,4,4-trifluoro-(butylthio)butan-1-ol (9d)

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give 93% yield of 9d. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 3.97-3.82 (m, 2H), 3.30 (qdd, 1H, J = 3.4, 8.5, 11.6 Hz), 2.75-2.62 (m, 2H), 2.19-2.08 (m, 1H), 1.76 (brs, OH), 1.73-1.58 (m, 3H), 1.49-1.35 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): δ 127.3 (q, J = 279.5 Hz), 59.1, 44.7 (q, J = 28.8 Hz), 32.3, 31.3, 30.8, 21.8, 13.6; \textsuperscript{19}F NMR (470 MHz, CDCl\textsubscript{3}): δ –71.6 (d, J = 8.0 Hz); [α]\textsubscript{24}\text{D} –31.3 (c = 0.2, CHCl\textsubscript{3}); FTIR (neat) υ\text{max} 1735, 1411, 1392, 1305, 1147, 1011, 912, 781, 714 cm\textsuperscript{-1}; Anal. Calcd (%) for C\textsubscript{8}H\textsubscript{15}F\textsubscript{3}OS: C, 44.43; H, 6.99. Found: C, 44.07; H, 6.81.

The enantiomeric excess of 9d was determined by HPLC after converted into corresponding benzoate 21d (see below).

4,4,4-trifluoro-(butylthio)butyl benzoate (21d)

The compound was synthesized according to a procedure similar to that employed for the synthesis of 21c. The crude product was purified by silica gel column chromatography (hexane : CH\textsubscript{2}Cl\textsubscript{2} = 2 : 1) to give 92% yield of 21d. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 8.09-7.99 (m, 2H), 7.62-7.54 (m, 1H), 7.50-7.42 (m, 2H), 4.64-4.52 (m, 2H), 3.24 (qdd, 1H, J = 3.4, 8.2, 11.6 Hz), 2.74-2.60 (m, 2H), 2.47-2.35 (m, 1H), 1.87 (dddd, 1H, J = 4.3, 4.6, 11.3, 15.6 Hz), 1.71-1.48 (m, 2H), 1.45-1.29 (m, 2H), 0.85 (t, 3H, J = 7.3 Hz); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): δ 166.2, 133.1, 129.8, 129.5, 128.4, 127.1 (q, J = 278.0 Hz), 61.2, 44.8 (q, J = 29.7 Hz), 32.3, 31.3, 27.8, 21.7, 13.5; \textsuperscript{19}F NMR (470 MHz, CDCl\textsubscript{3}): δ –71.7 (d, J = 8.3 Hz); [α]\textsubscript{24}\text{D} –29.5 (c = 0.9, CHCl\textsubscript{3}); FTIR (neat) υ\text{max} 2850, 1772, 1474, 1384, 1335, 1264, 1052, 1023, 960, 746, 678 cm\textsuperscript{-1}; Anal. Calcd (%) for C\textsubscript{15}H\textsubscript{19}F\textsubscript{3}O\textsubscript{2}S: C, 56.24; H, 5.98. Found: C, 56.30; H, 6.02.

The enantiomeric ratio of 21d was determined by HPLC (hexane : 2-propanol = 400 : 1, 0.3 mL/min) using a CHIRALPAK AS–H column (0.46 cm φ x 25 cm): major isomer 17.7 min,
minor isomer 19.7 min (93% ee).

**ethyl 2-(1,1,1-trifluoro-4-hydroxybutan-2-ylthio)acetate (9e)**

The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give 93% yield of 9e. $^1$H NMR (500 MHz, CDCl$_3$): δ 4.27-4.18 (m, 2H), 4.05 (ddd, 1H, $J$ = 3.4, 11.0, 11.0 Hz), 3.85-3.77 (m, 2H), 3.65-3.52 (m, 1H), 3.58 (d, 1H, $J$ = 16.8 Hz), 3.31 (d, 1H, $J$ = 16.8 Hz), 2.33 (brs, OH), 2.24-2.14 (m, 1H), 1.55 (dddd, 1H, $J$ = 3.1, 3.4, 12.2, 14.7 Hz), 1.31 (t, 3H, $J$ = 7.0 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 127.2 (q, $J$ = 278.0 Hz), 59.1, 42.9 (q, $J$ = 29.7 Hz), 33.8, 26.0, 25.6; $^{19}$F NMR (470 MHz, CDCl$_3$): δ −71.6 (d, $J$ = 8.0 Hz); [$\alpha$]$_{22}^D$ = −20.4 (c = 0.2, CHCl$_3$); FTIR (neat) $\nu_{\text{max}}$ 1715, 1355, 1321, 1312, 1301, 1181, 931, 912, 773, 711 cm$^{-1}$; Anal. Calcd (%) for C$_8$H$_{13}$F$_3$O$_3$S: C, 39.02; H, 5.32. Found: C, 39.33; H, 5.12.

The enantiomeric excess of 9e was determined by HPLC after converted into corresponding benzoate 21e (see below).

**3-((ethoxycarbonyl)methylthio)-4,4,4-trifluorobutyl benzoate (21e)**

The compound was synthesized according to a procedure similar to that employed for the synthesis of 21c. The crude mixture was purified by silica gel column chromatography (hexane : CH$_2$Cl$_2$ = 2 : 1) to give 80% yield of 21e. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.10-8.01 (m, 2H), 7.63-7.54 (m, 1H), 7.50-7.42 (m, 2H), 4.63-4.50 (m, 2H), 4.16-4.07 (m, 2H), 3.64 (qdd, 1H, $J$ = 3.4, 8.2, 11.6 Hz), 3.48 (d, 1H, $J$ = 15.3 Hz), 3.28 (d, 1H, $J$ = 15.3 Hz), 2.47-2.36 (m, 1H), 1.90 (ddddd, 1H, $J$ = 4.6, 4.6, 11.0, 15.6 Hz), 1.23 (t, 3H, $J$ = 7.3 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 166.2, 133.1, 129.8, 129.5, 128.4, 127.1 (q, $J$ = 278.0 Hz), 61.2, 44.8 (q, $J$ = 29.7 Hz), 32.3, 30.8, 21.7, 13.5; $^{19}$F NMR (470 MHz, CDCl$_3$): δ −71.8 (d, $J$ = 8.0 Hz); [$\alpha$]$_{24}^D$ = −45.0 (c = 0.2, CHCl$_3$); FTIR (neat) $\nu_{\text{max}}$ 2822, 1832, 1829, 1474, 1371, 1321, 1184, 1062, 9540, 752, 669 cm$^{-1}$; Anal. Calcd (%) for C$_{15}$H$_{17}$F$_3$O$_4$S: C, 51.42; H, 4.89. Found: C, 51.41; H, 4.89.

The enantiomeric ratio of 21e was determined by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cm$\phi$ x 25 cm): major isomer 8.2 min, minor isomer 10.2 min (92% ee).

**The enantioselective aza-Michael reaction with triazoles (Table 2, Entries 7 and 8)**

Triazoles (0.2 mmol) and 1 (0.3 mmol) were added successively to a solution of diarylprolinol
silyl ether 2 (0.04 mmol) and benzoic acid (0.04 mmol) in anhydrous toluene (5 mL) at −20 °C. The mixture was stirred for 40 h at −20 °C. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 1 h at ambient temperature. Saturated aqueous NH₄Cl solution was added to the reaction mixture. The compound was then extracted with dichloromethane, dried over Na₂SO₄ and concentrated under reduced pressure.

4,4,4-trifluoro-3-(1H-1,2,4-triazol-1-yl)butan-1-ol (10a)

The crude product was purified by silica gel column chromatography (CH₂Cl₂ : MeOH = 20 : 1) to give 77% yield of 10a. ¹H NMR (500 MHz, CDCl₃): δ 8.22 (s, 1H), 8.04 (s, 1H), 5.24-5.13 (m, 1H), 3.87-3.78 (m, 1H), 3.31-3.21 (m, 1H), 2.52 (ddddd, 1H, J = 3.4, 3.4, 11.5, 14.5 Hz), 2.42-2.32 (m, 1H), 1.96 (brs, OH); ¹³C NMR (126 MHz, CDCl₃): δ 152.4, 144.8, 123.6 (q, J = 280.7 Hz), 57.5 (q, J = 32.4 Hz), 56.4, 29.7; ¹⁹F NMR (470 MHz, CDCl₃): δ −74.7 (d, J = 7.0 Hz); [α]₂⁰D −31.5 (c = 0.2, CHCl₃); FTIR (neat) υ max 3349, 2895, 1512, 1439, 1273, 1199, 1135, 1065, 1008, 856, 680 cm⁻¹; Anal. Calcd (%) for C₆H₈F₃N₃O: C, 36.93; H, 4.13; N, 21.53. Found: C, 36.91; H, 4.13; N, 21.72.

The enantiomeric excess of 10a was determined by HPLC after converted into corresponding 2-naphthoate 22a (see below).

4,4,4-trifluoro-3-(1H-1,2,4-triazol-1-yl)butyl 2-naphthoate (22a)

The compound was synthesized according to a procedure similar to that employed for the synthesis of 19a. The crude mixture was purified by silica gel column chromatography (CH₂Cl₂ acetone = 50 : 1) to give 96% yield of 22a. ¹H NMR (500 MHz, CDCl₃): δ 8.51 (s, 1H), 8.28 (s, 1H), 8.06 (s, 1H), 8.01-7.94 (m, 2H), 7.93-7.88 (m, 2H), 7.66-7.55 (m, 2H), 5.12-5.03 (m, 1H), 4.55-4.48 (m, 1H), 4.22-4.14 (m, 1H), 2.90 (ddddd, 1H, J = 4.6, 4.6, 11.1, 15.3 Hz), 2.72-2.62 (m, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 166.3, 152.8, 144.7, 135.7, 132.4, 131.2, 129.4, 128.6, 128.4, 127.8, 126.9, 126.4, 124.9, 123.2 (q, J = 281.9 Hz), 59.9, 58.5 (q, J = 32.4 Hz), 27.1; ¹⁹F NMR (470 MHz, CDCl₃): δ −75.0 (d, J = 7.0 Hz); [α]₂⁰D −69.6 (c = 0.2, CHCl₃); FTIR (neat)
υ_{max} 3123, 1715, 1633, 1511, 1466, 1384, 1278, 1195, 1136, 1098, 1005, 864, 679 cm^{-1}; Anal. Calcd (%) for C_{17}H_{14}F_{3}N_{3}O_{2}: C, 58.45; H, 4.04; N, 12.03. Found: C, 58.47; H, 4.33; N, 11.85.

The enantiomeric ratio was determined by HPLC (hexane : 2-propanol = 10 : 1, 1.0 mL/min) using a CHIRALPAK AS-H column (0.46 cmφ x 25 cm): major isomer 14.2 min, minor isomer 11.2 min (86% ee).

4,4,4-trifluoro-3-(1H-1,2,3-triazol-1-yl)butan-1-ol (10b)

The crude mixture was purified by silica gel column chromatography (dichloromethane : methanol = 15 : 1) to give 76% yield. ¹H NMR (500 MHz, CD_{3}OD): δ 8.21 (s, 1H), 7.83 (s, 1H), 5.70–5.60 (m, 1H), 3.67–3.59 (m, 1H), 3.21–3.12 (m, 1H), 2.61–2.51 (m, 1H), 2.42–2.32 (m, 1H); ¹³C NMR (126 MHz, CDCl_{3}): δ 134.3, 123.8, 123.6 (q, J = 281.9 Hz), 58.5 (q, J = 32.4 Hz), 56.5, 30.5; ¹⁹F NMR (470 MHz, CDCl_{3}): δ −74.8 (d, J = 7.5 Hz); [α]^{24}_{D} −24.7 (c = 0.71, CHCl_{3}); FTIR (neat) υ_{max} 3393, 3123, 2959, 2893, 1650, 1452, 1389, 1267, 1195, 1132, 1065, 919, 853, 762, 700 cm^{-1}; Anal. Calcd (%) for C_{6}H_{8}F_{3}N_{3}O: C, 36.93; H, 4.13; N, 21.53. Found: C, 36.9; H, 4.20; N, 21.77.

The enantiomeric excess of 10b was determined by HPLC after converted into corresponding 2-naphthoate 22b (see below).

4,4,4-trifluoro-3-(1H-1,2,3-triazol-1-yl)butyl 2-benzoate (22b)

The compound was synthesized according to a procedure similar to that employed for the synthesis of 21c. The crude mixture was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 86% yield (84% ee). ¹H NMR (500 MHz, CD_{3}OD): δ 7.99–7.94 (m, 2H), 7.81 (s, 1H), 7.74 (s, 1H), 7.62–7.57 (m, 1H), 7.49–7.43 (m, 2H), 5.49–5.34 (m, 1H), 4.51–4.44 (m, 1H), 4.12–4.03 (m, 1H), 2.83–2.74 (m, 1H), 2.74–2.65 (m, 1H); ¹³C NMR (126 MHz, CDCl_{3}): δ 166.1, 133.6, 133.5, 129.6, 129.2, 128.5, 123.5, 123.3 (q, J = 281.9 Hz), 59.5, 59.2 (q, J = 32.4 Hz), 27.7; ¹⁹F NMR (470 MHz, CDCl_{3}): δ −74.4 (d, J = 7.0 Hz). The enantiomeric excess was determined by HPLC (hexane : dichloromethane = 1 : 1, 1.0 mL/min) using a CHIRALPAK IE column (0.46 cmφ x 25 cm): major isomer 17.5 min and minor isomer 18.8 min.
The enantioselective oxa-Michael reaction with aldoxime (Table 2, Entry 9): benzoaldehyde O-(1,1,1-trifluoro-4-hydroxybutan-2-yl) oxime (11)

Benzaldehyde oxime (0.6 mmol) and 1 (0.2 mmol) were added to a solution of diarylprolinol silyl ether 2 (0.02 mmol) and benzoic acid (0.02 mmol) in toluene (0.5 mL). The mixture was stirred for 12 h at ambient temperature. To the mixture were added methanol (2 mL) and sodium borohydride (0.8 mmol) successively, and the mixture was stirred for 1 h at 0 °C. Saturated aqueous NH₄Cl solution was added to the reaction mixture. The compound was then extracted with ethyl acetate, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 73% yield of 11. 

**¹H NMR (500 MHz, CDCl₃):** δ 8.17 (s, 1H), 7.62-7.52 (m, 2H), 7.45-7.34 (m, 3H), 4.87-4.78 (m, 1H), 3.91-3.81 (m, 2H), 2.17-1.88 (m, 2H), 1.77 (brs, 1H, OH); 

**¹³C NMR (126 MHz, CDCl₃):** δ 150.5, 131.0, 130.5, 128.8, 127.3, 124.6 (q, J = 238.1 Hz), 77.9 (q, J = 30.0 Hz), 57.8, 30.6; 

**¹⁹F NMR (470 MHz, CDCl₃):** δ -77.2 (d, J = 30.0 Hz); [α]²⁵D +14.3 (c = 0.3, CHCl₃); FTIR (neat) v max 3368, 2963, 1277, 1172, 931, 763, 695, 453 cm⁻¹; Anal. Calcd (%) for C₁₁H₁₂F₃NO₂: C, 53.34; H, 4.89; N, 5.67. Found: C, 53.46; H, 4.97; N, 5.81.

The enantiomeric ratio of 11 was determined by HPLC (hexane : 2-propanol = 50 : 1, 0.5 mL/min) using a CHIRALPAK ID column (0.46 cm φ x 25 cm): major isomer 18.8 min and minor isomer 13.5 min (95% ee).

### Asymmetric synthesis of befloxatone (Scheme 4):

(R)-4,4,4-trifluorobutane-1,3-diol (12)

To a suspension of 20% Pd(OH)₂/C (10 mg) in methanol (0.4 mL) was added a solution of 1 (0.15 mmol) in methanol (0.6 mL). The mixture was stirred for 3 h at ambient temperature under a hydrogen atmosphere. After the reaction mixture was filtered, the filtrate was concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (CH₂Cl₂ : MeOH = 5 : 1) to give 91% yield of 12. 

**¹H NMR (500 MHz, CDCl₃):** δ 4.87-4.78 (m, 1H), 3.91-3.81 (m, 2H), 2.17-1.88 (m, 2H); 

**¹³C NMR (126 MHz,
CDCl₃): δ 124.9 (q, J = 281.9 Hz), 69.4 (q, J = 34.8 Hz), 59.8, 31.1; ³⁹F NMR (470 MHz, CDCl₃): δ -80.4 (d, J = 7.0 Hz); [α]D²⁺ = +7.4 (c = 0.2, CHCl₃); FTIR (neat) vₘₐₓ 3378, 2930, 1706, 1275, 1129, 413 cm⁻¹; Anal. Calcd (%) for C₁₁H₁₂F₃NO₂: C, 33.34; H, 4.90. Found: C, 33.49; H, 5.02.

The absolute configuration of 12 was determined to be R by comparing the optical rotation with a reported value. [T. Yamazaki, N. Okamura, T. Kitazume, Tetrahedron: Asymmetry 1990, 1, 521]

4,4,4-trifluoro-3-hydroxybutyl 4-methylbenzenesulfonate (13)

Tosyl chloride (0.33 mmol) was added to a solution of diol 12 (0.3 mmol) in pyridine (4.5 mmol). The mixture was stirred for 24 h at ambient temperature. Saturated NaHCO₃ was added to the mixture. The compound was extracted with dichloromethane, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give 53% yield of 13.¹H NMR (500 MHz, CDCl₃): δ 7.83 (d, 2H, J = 7.6 Hz), 7.37 (d, 2H, J = 8.0 Hz), 5.17-5.04 (m, 1H), 3.88-3.77 (m, 2H), 2.47 (s, 3H), 2.15-2.02 (m, 1H), 1.97-1.86 (m, 1H); ¹³C NMR (126 MHz, CDCl₃): δ 125.3 (q, J = 282.7 Hz), 71.1, 69.2 (q, J = 34.8 Hz), 59.8, 31.3, 29.7; [α]D²⁻ = +24.7 (c = 0.3, CHCl₃); FTIR (neat) vₘₐₓ 3282, 1782, 1387, 1257, 1232, 1041, 1033, 417, 369 cm⁻¹; Anal. Calcd (%) for C₁₁H₁₁F₃O₄S: C, 44.29; H, 4.39. Found: C, 44.22; H, 4.07.

methyl 4-(benzylxylo)phenylcarbamate (14)

To a solution of 4-benzylxyloaniline hydrochloride (4 mmol) and triethylamine (4.4 mmol) in anhydrous dichloromethane (5 mL) was added methyl chloroformate (6 mmol). The mixture was stirred at ambient temperature for 8 h. Saturated NaHCO₃ was added to the mixture. The compound was extracted with dichloromethane, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was used in the next step without further purification (90% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.49-7.18 (m, 7H), 6.98-6.87 (m, 2H), 6.48 (brs, NH), 5.04 (s, 2H), 3.76 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 155.1, 154.3, 137.0, 131.1, 128.5, 127.9, 127.4, 120.5, 115.2, 70.2, 52.2; FTIR (neat) vₘₐₓ 3320, 1706, 1597, 1453, 1416, 1298, 1239, 1074, 733 cm⁻¹; Anal. Calcd (%) for C₁₅H₁₂NO₃: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.04; H,
5.88; N, 5.43.

3-(4-(benzyloxy)phenyl)-5-(methoxymethyl)oxazolidin-2-one (16)

To a solution of 14 (3 mmol) and K₂CO₃ (6 mmol) in anhydrous DMF (6 mL) was added (5)-4-methoxymethyl-1,3-dioxolane-2-one (15) (3 mmol). The mixture was stirred for 3 h at 155 °C. After the mixture was diluted with water, the compound was extracted with dichloromethane. The organic layer was washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (CH₂Cl₂ : MeOH = 10 : 1) to give 83% yield of 16. ¹H NMR (500 MHz, CDCl₃): δ 7.47-7.28 (m, 7H), 6.99-6.95 (m, 2H), 5.05 (s, 2H), 4.77-4.70 (m, 1H), 4.02 (d, 1H, J = 8.8, 8.8 Hz), 3.88 (dd, 1H, J = 6.5, 8.8 Hz), 3.64 (d, 2H, J = 4.2 Hz), 3.44 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 155.4, 136.8, 131.6, 128.6, 128.0, 127.4, 120.0, 115.2, 72.6, 71.1, 70.2, 59.6, 47.5; [α]²⁰D −16.4 (c = 0.2, CHCl₃); FTIR (neat) ν_max 1745, 1510, 1229, 1132, 754 cm⁻¹; Anal. Calcd (%) for C₁₁H₁₃NO₄: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.76; H, 5.97; N, 4.22.

3-(4-hydroxyphenyl)-5-(methoxymethyl)oxazolidin-2-one (17)

A mixture of 16 (0.16 mmol) and 5% Pd/C (34 mg) dissolved in EtOH–CH₂Cl₂ (1:1) (1.6 mL) was stirred for 12 h at ambient temperature under hydrogen atmosphere. After the reaction mixture was filtered, the filtrate was concentrated at reduced pressure. The crude mixture was purified by silica gel column chromatography (CH₂Cl₂ : MeOH = 20 : 1) to give 92% yield of 17. ¹H NMR (500 MHz, CDCl₃): δ 7.31 (d, 2H, J = 8.0 Hz), 6.82 (d, 2H, J = 8.4 Hz), 4.81-4.69 (m, 1H), 4.01 (dd, 1H, J = 8.8, 8.8 Hz), 3.87 (dd, 1H, J = 6.5, 8.4 Hz), 3.64 (d, 2H, J = 4.2 Hz), 3.44 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): δ 155.4, 153.3, 130.6, 120.9, 115.9, 72.6, 71.4, 59.6, 47.9; [α]²⁵D −40.0 (c = 0.3, CHCl₃); FTIR (neat) ν_max 3248, 1717, 1515, 1427, 1236, 1134, 756 cm⁻¹; Anal. Calcd (%) for C₁₁H₁₃NO₄: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.22; H, 5.97; N, 6.21.

befloxacitone
A mixture of 17 (0.1 mmol), 13 (0.15 mmol), and K$_2$CO$_3$ (0.2 mmol) dissolved in anhydrous DMF (0.5 mL) was stirred for 6 h at 85 °C. After the mixture was diluted with water, the compound was extracted with dichloromethane. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give 84% yield of befloxatone as a diastereomeric mixture (dr = 98 : 2). $^1$H NMR (500 MHz, CD$_3$OD): $\delta$ 7.34-7.29 (m, 2H), 6.81-6.76 (m, 2H), 4.81-4.75 (m, 1H), 4.12-4.04 (m, 1H), 4.07 (dd, 1H, $J = 8.8, 9.2$ Hz), 3.84 (dd, 1H, $J = 6.5, 8.6$ Hz), 3.75-3.69 (m, 2H), 3.66 (dd, 1H, $J = 3.4, 11.1$ Hz), 3.59 (dd, 1H, $J = 4.6, 11.1$ Hz), 3.42 (s, 3H), 1.89-1.80 (m, 1H), 1.73-1.64 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 155.6, 153.2, 130.3, 124.9 (q, $J = 281.9$ Hz), 121.1, 115.8, 72.4, 71.5, 68.9 (q, $J = 31.2$ Hz), 59.5, 47.8, 31.0, 29.6; [$\alpha$]$^{26}_D +17.6$ (c = 0.2, CHCl$_3$); FTIR (neat) $\nu_{max}$ 3368, 2933, 1726, 1516, 1131, 756, 416 cm$^{-1}$; Anal. Calcd (%) for C$_{15}$H$_{18}$F$_3$NO$_5$: C, 51.58; H, 5.19; N, 4.01. Found: C, 51.66; H, 5.43; N, 4.33.

The diastereomeric ratio of befloxatone was confirmed by HPLC (hexane : 2-propanol = 100 : 1, 1.0 mL/min) using a CHIRALPAK ID column (0.46 cmφ x 25 cm): major isomer 18.9 min, minor isomer 13.5 min (96% de)
$\text{F}_3\text{C} = \text{CHO}$

$^1\text{H} \text{NMR}$

$^{13}\text{C} \text{NMR}$
$^{1}H$ NMR

$^{13}C$ NMR

HPLC racemic

HPLC optically active
$\text{Me-}^\text{N}$

$F_3\text{C-CHO}$

$5b$

$^1H$ NMR

$^13C$ NMR
$^{1}H$ NMR

$^{13}C$ NMR
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$\text{Ph} - \text{N} - \text{C} - \text{CHO} \quad 5c$

$^1\text{H NMR}$

$^13\text{C NMR}$
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$\text{Ph} \quad \text{N} \quad \text{F}_3\text{C} \quad \text{OH} \quad 18c$

$^1\text{H NMR}$

$^13\text{C NMR}$

HPLC racemic

HPLC optically active
$^{1}H$ NMR

$^{13}C$ NMR

HPLC racemic

HPLC optically active
$^1$H NMR

$^{13}$C NMR
$^{1}H$ NMR

$^{13}C$ NMR
$^1$H NMR

$^{13}$C NMR

HPLC \textit{racemic} \hspace{1cm} \textbf{HPLC optically active}
$^1$H NMR

$^{13}$C NMR
$\text{HNMR}$

$\text{C NMR}$

$\text{HPLC racemic}$

$\text{HPLC optically active}$
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$^1$H NMR

$^{13}$C NMR

HPLC racemic

HPLC optically active
$\text{OMe}$

$\text{F}_3\text{C}$

$\text{OH}$

$^1\text{H NMR}$

$\text{C NMR}$

HPLC $\text{racemic}$

HPLC $\text{optically active}$

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S41

$\text{F}_3\text{C} \quad \text{SPh} \quad \text{OH} \quad 9a$

$^1\text{H}$ NMR

$^{13}\text{C}$ NMR

HPLC racemic

HPLC optically active
$\text{Ph-S}$

$\text{F}_3\text{C-CH(OH) \quad 9b}$

$^1\text{H} \text{ NMR}$

$^13\text{C} \text{ NMR}$

$\text{HPLC racemic}$

$\text{HPLC optically active}$
**1H NMR**

![1H NMR spectrum](image)

**13C NMR**

![13C NMR spectrum](image)
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$\begin{align*}
\text{H NMR} \\
\text{13C NMR} \\
\text{HPLC racemic} & \quad \text{HPLC optically active}
\end{align*}$
$^{1}H$ NMR

$^{13}C$ NMR
$^1$H NMR

$^{13}$C NMR

HPLC racemic

HPLC optically active
$\text{EtO}_2\text{C} \rightleftharpoons \text{S} \quad \text{F}_3\text{C} \rightleftharpoons \text{OH} \quad 9e$

$^1\text{H} \text{ NMR}$

$^{13}\text{C} \text{ NMR}$
**H NMR**

![H NMR spectrum](image1)

**13C NMR**

![13C NMR spectrum](image2)

**HPLC racemic**

![HPLC racemic spectrum](image3)

**HPLC optically active**

![HPLC optically active spectrum](image4)
1H NMR

13C NMR
$^1$H NMR

$^{13}$C NMR

HPLC *racemic* 

HPLC *optically active*
1H NMR

13C NMR

HPLC racemic

HPLC optically active
Electronic Supplementary Material (ESI) for Chemical Communications

H NMR

\[ \text{F}_3\text{C} - \text{OH} \]

\[ ^1\text{H} \text{ NMR} \]

\[ ^{13}\text{C} \text{ NMR} \]

HPLC racemic

HPLC optically active

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$\text{OH}$
$\text{F}_3\text{C}$
$\text{OH}$

$^{1}H$ NMR

$^{13}C$ NMR
\[
\begin{align*}
\text{OH} \\
\text{F}_3\text{C} \text{OTs} \\
\end{align*}
\]

\[\text{1}^\text{H} \text{ NMR}\]

\[\text{1}^{13} \text{C} \text{ NMR}\]

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$^{1}H$ NMR

$^{13}C$ NMR
$^1$H NMR

$^{13}$C NMR
$^{1}H$ NMR

$^{13}C$ NMR
HPLC diastereomixture
(major : minor = 1 : 1)          (major : minor = 98 : 2)