Convenient Asymmetric Synthesis of β -Trifluoromethyl - β -amino Acid, - β -amino Ketones and γ -amino Alcohols via Reformatsky and Mannich Type Reactions from 2-Trifluoromethyl-1,3-Oxazolidines

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General informations

Unless otherwise mentioned, all the reagents were purchased from commercial source. All glassware was dried in an oven at 150 °C prior to use. Ether and THF were distilled under nitrogen from sodium/benzophenone prior to use. CH₂Cl₂ was distilled under nitrogen from CaH₂ prior to use. Chemical shifts of ¹H NMR (250,13 MHz) were expressed in parts per million downfield from tetramethylsilane (δ = 0) in CDCl₃. Chemical shifts of ¹³C NMR (62,89 MHz) were expressed in parts per million downfield from CDCl₃ as internal standard (δ = 77.0). Chemical shifts of ¹⁹F NMR (235,36 MHz) were expressed in parts per million downfield from CFC1₃ as internal standard (δ = 0). Coupling constants are reported in hertz. Column chromatography was performed on 0,040-0,063 mm silicagel, employing mixture of petroleum ether and ethyl acetate as eluent. Silica TLC plates were visualized under UV light, by a 10% solution of phosphomolybdic acid in ethanol followed by heating. Gas chromatography (FID detection) was performed with a polydimethylsiloxane column (25 m X 3,2 mm X 0,52 μ m thickness of layer). Mass Spectrometry was carried out in the EI mode. High Resolution Mass Spectrometry was carried out by using electrospray method. Wavenumbers of infrared spectra (IR) are given in cm⁻¹. Optical rotations are reported as their specific rotations at 25 °C in g/100 mL. Melting points are uncorrected.

(4*R*)-2-Trifluoromethyl-4-phenyl-1,3-oxazolidines(1a,b). To a stirred solution of 4.73 g of trifluoroacetaldehyde methyl hemiacetal (36.2 mmol, 1.0 equiv) in 60 mL of toluene at room temperature, were added 4.96 g of (*R*)-phenylglycinol (36.2 mmol, 1.0 equiv) and 0.91 g of pyridinium *p*-toluenesulfonate (3.62 mmol, 0.1 equiv). The mixture was warmed to reflux with a Dean-Stark apparatus for 12 h, then cooled to 0°C with an ice-bath. The resulting mixture was filtered and toluene was evaporated. Purification by flash chromatography (19:1 petroleum ether /ethyl acetate) gave 7.15 g (91%) of an oil as a 2.5:1 mixture of diastereomers. An analytical sample of each diastereomer was isolated.

(2*S*,4*R*)-2-Trifluoromethyl-4-phenyl-1,3-oxazolidine (1a). Colorless oil; [α]_D²⁰ -43.0 (*c* 1.1, CHCl₃); IR (neat) 3364, 2896, 1458, 1291, 1152 cm⁻¹; ¹H NMR δ 2.61 (m, 1H), 3.70 (t, J_{AB} = 7.4, J = 7.4 Hz, 1H), 4.35 (t, J_{AB} = 7.4, J = 7.4 Hz, 1H), 4.47 (t, J = 7.4 Hz, 1H), 5.17 (q, J = 5.7 Hz, 1H), 7.2-7.4 (m, 5H); ¹³C NMR δ 60.8, 73.2, 87.9 (q, J = 34.5 Hz), 123.5 (q, J = 238.5 Hz), 126.8, 128.5, 129.1, 138.0; ¹⁹F NMR δ -81.7 (d, J = 5.7 Hz); MS (EI 70 eV) *m/z* 218 (*M*⁺+1), 200, 186 (100), 180, 167, 148, 139, 120. Anal. Calcd for C₁₀H₁₀F₃NO: C, 55.30; H, 4.64; N, 6.46. Found C, 55.67; H, 4.72; N, 6.11.

(2*R*,4*R*)-2-Trifluoromethyl-4-phenyl-1,3-oxazolidine (1b). Colorless oil; $[\alpha]_D^{20}$ -56.4 (*c* 1.2, CHCl₃); ¹H NMR δ 2.85 (m, 1H), 3.77 (dd, J_{AB} = 8.0, J = 6.9 Hz, 1H), 4.35 (dd, J_{AB} = 8.0, J = 6.9 Hz, 1H), 5.11 (quint, J = 5.0 Hz, 1H), 4.62 (t, J = 6.9 Hz, 1H), 7.2-7.4 (m, 5H); ¹³C NMR δ 61.1, 73.8, 87.0 (q, J = 34.5 Hz), 123.6 (q, J = 238.5 Hz), 126.7, 128.0, 128.6, 138.4; ¹⁹F NMR δ -82.0 (d, J = 5.0 Hz).

Reformatsky-type reaction:

4-Trifluoromethyl-1-((1*R*)-2-hydroxy-1-phenylethyl)-azetidin-2-one (2a,b). To a refluxing suspension of zinc dust (920 mg, 15.0 mmol) in dry THF (10 mL) under argon was added dropwise a solution of oxazolidine **1a,b** (650 mg, 3.0 mmol) and ethyl bromoacetate (1.2 mL, 10.5 mmol) in THF (1.5 mL). After 3 h, the reaction mixture was cooled to room temperature and quenched by addition to a saturated NH₄Cl solution. The aqueous layer was extracted four times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was then purified by flash chromatography (7:3 petroleum ether/ethyl acetate) to give 160 mg (17%) of **2a** and 225 mg (25%) of a 55:45 mixture of **2a** and **2b**.

(4*R*)-4-Trifluoromethyl-1-((1*R*)-2-hydroxy-1-phenylethyl)-azetidin-2-one (2a). yellow solid; mp 82-86°C; $[\alpha]_D^{20}$ +68.0 (*c* 0.6, CHCl₃); IR (neat) 3439, 3032, 2945, 1750, 1138 cm⁻¹; ¹H NMR δ 2.87 (m, 1H), 3.02 (dd, J = 15.1, 2.4 Hz, 1H), 3.19 (dd, J = 15.1, 5.5 Hz, 1H), 3.8-4.0 (m, 2H), 4.2 (m, 1H), 4.58 (dd, J = 8.9, 4.6 Hz, 1H), 7.2-7.4 (m, 5H); ¹³C NMR δ 37.3, 52.4 (q, J = 35.4 Hz), 63.3, 63.5, 123.9 (q, J_{CF} = 280.0 Hz, CF₃), 127.3, 128.1, 128.6, 135.8, 166.7; ¹⁹F NMR δ -75.6 (d, J = 5.4); MS (EI 70 eV) m/z 259 (M⁺), 241, 224, 228 (100), 186, 104, 77. Anal. Calcd for C₁₂H₁₂F₃NO₂: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.93; H, 4.83; N, 5.36.

(4*S*)-4-Trifluoromethyl-1-((1*R*)-2-hydroxy-1-phenylethyl)-azetidin-2-one (2b). ¹H NMR δ 2.90 (dd, J = 15.2, 2.3 Hz, 1H), 3.08 (dd, J = 15.2, 5.5 Hz, 1H), 3.63 (ddq, $J_{HH} = J_{HF}$ = 5.5, J = 2.3 Hz, 1H), 3.80 (dd, J = 8.6, 3.9 Hz, 1H), 4.04 (dd, J = 8.9, 7.9 Hz, 1H), 4.31 (dd, J = 7.9, 3.1 Hz, 1H), 7.2-7.5 (m, 5H); ¹³C NMR δ 36.9, 49.1 (q, J = 34.9 Hz), 64.3, 64.5, 124.1 (q, J = 279.4 Hz), 126.3, 128.5, 128.9, 135.0, 166.5; ¹⁹F NMR δ -75.2 (d, J = 5.5 Hz).

β -amino esters and β -amino acid:

(3*R*) Ethyl 4,4,4-trifluoro-3-((1*R*)-2-hydroxy-1-phenylethylamino)-butanoate (3a).

Ethanolysis of azetidinone 2a. A solution of **2a** (260 mg, 0.85 mmol) in EtOH/HCl_g (5 mL) was stirred under argon 48 h at room temperature. A saturated NaHCO₃ solution was

added to the crude mixture and the aqueous layer was extracted four times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated. Purification of the residue by flash chromatography (17:3 petroleum ether/ ethyl acetate) gave pure **3a** (245 mg, 80%) as a yellow oil.

Mannich-type reactions. To a solution of oxazolidines **1a,b** (62:38 mixture, 860 mg, 4 mmol) in propionitrile (10 mL) under argon was added the ketene silyl acetal (70:30 mixture of *O*- and *C*-silylated compound, 1.61 g, 12 mmol) and BF₃·Et₂O (1.45 mL, 12 mmol). The reaction mixture was refluxed for 1.5 h. After being cooled to room temperature, the mixture was poured into a saturated NaHCO₃ solution. The aqueous layer was extracted four times with CH₂Cl₂. The combined organic layer were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (17:3 petroleum ether/ ethyl acetate) to give pure **3a** (750 mg, 61%) and **3b** (142 mg, 12%).

(3R) Ethyl 4,4,4-trifluoro-3-((1R)-2-hydroxy-1-phenylethylamino)-butanoate (3a). Pale yellow oil; $[\alpha]_D^{20}$ -15.9 (*c* 0.96, CHCl₃); IR (neat) 3345, 3064, 2984, 2938, 2875, 1735 cm⁻¹; ¹H NMR δ 1.27 (t, *J* = 7.3 Hz, 3H), 2.53 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.73 (dd, *J* = 16.2, 4.4 Hz, 1H), 3.57 (dd, *J* = 11.0, 8.2 Hz, 1H), 3.70 (m, 1H), 3.72 (dd, *J* = 11.0, 3.4 Hz, 1H), 4.00 (dd, *J* = 8.2, 3.4 Hz, 1H), 4.18 (q, *J* = 7.3 Hz, 2H), 7.2-7.4 (m, 5H); ¹³C NMR δ 13.9, 34.5, 54.7 (q, *J* = 28.5 Hz), 61.3, 62.3, 67.1, 125.9 (q, *J* = 283.5 Hz), 127.3, 127.8, 128.5, 140.0, 170.9; ¹⁹F NMR δ -75.5 (d, *J* = 8.1 Hz); MS (EI 70 eV) *m/z* 306 (M⁺), 274, 259, 201, 186, 104 (100). Anal. Calcd for C₁₄H₁₈F₃NO₂: C, 55.08; H, 5.94; N, 4.59. Found: C, 55.19; H, 5.89; N, 4.4.

(3S) Ethyl 4,4,4-trifluoro-3-((1R)-2-hydroxy-1-phenylethylamino)-butanoate (3b). Pale yellow oil; $[\alpha]_D^{20}$ -22.0 (*c* 0.72, CHCl₃); ¹H NMR δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.40 (dd, *J* = 14.9, 9.2 Hz, 1H), 2.60 (dd, *J* = 14.9, 4.2 Hz, 1H), 3.52 (dq, *J* = 9.2, 8.1, 4.2 Hz, 1H), 3.54 (dd, *J* = 11.4, 10.3 Hz, 1H), 3.68 (dd, *J* = 11.4, 3.8 Hz, 1H), 4.10 (dd, *J* = 10.3, 3.8 Hz, 1H), 4.11 (q, *J* = 7.3 Hz, 2H), 7.2-7.4 (m, 5H); ¹³C NMR δ 13.9, 35.7, 53.9 (q, *J* = 28.5 Hz), 61.0, 62.7, 67.4, 125.6 (q, *J* = 285.5 Hz), 127.6, 128.0, 128.5, 139.1, 169.9; ¹⁹F NMR δ -74.1 (d, *J* = 8.1 Hz).

(R)-N-(2-Hydroxy-1-phenylethyl)-4,4,4-trifluorobut-2-enamide (4). To a solution of oxazolidines **1a,b** (62:38 mixture, 430 mg, 2 mmol) in propionitrile (10 mL) under argon was added the ketene silyl acetal (70:30 mixture of *O*- and *C*-silylated compound, 805 mg, 6 mmol) and TiCl₄ (0.66 mL, 6.0 mmol). After 24 h reflux, the reaction mixture was poured into a saturated aqueous solution of NaHCO₃ (10mL). The aqueous layer was extracted with diethyl ether (4x10mL) and the combined organic extracts were dried over Na₂SO₄, filtered,

and concentrated under reduced pressure. Purification by flash chromatography (9:1 petroleum ether/ ethyl acetate) gave **4** (434 mg, 48%) as a viscous oil. IR (neat) 3348, 3066, 2986, 2930, 1745, 1710, 1478, 1377, 1246 cm^{-1} ; ^1H NMR δ 3.87 (dd, $J_{AB} = 11.5$, $J = 5.8$ Hz, 1H), 3.91 (dd, $J_{AB} = 11.5$, $J = 5.2$ Hz, 1H), 5.41 (ddd, $J = 7.8$, 5.8, 5.2 Hz, 1H), 6.54 (dq, $J = 15.4$, 1.7 Hz, 1H), 6.78 (dq, $J = 15.4$, $J = 6.0$ Hz, 1H), 7.2-7.5 (m, 5H); ^{13}C NMR δ 47.1, 54.0, 122.1 (q, $J = 269.6$ Hz), 126.6, 128.5, 129.0, 129.5 (q, $J = 36.4$ Hz), 130.0 (q, $J = 5.9$ Hz), 137.5, 162.0; ^{19}F NMR δ -75.4 (d, $J = 7.6$ Hz); MS (EI 70 eV) m/z 452 ($\text{M}^+ + 1$), 382, 352, 298, 286, 242, 180, 91 (100), 57.

(3R)-3-Amino-4,4,4-trifluorobutanoic acid (5). To a solution of **3a** (305 mg, 1 mmol) in a 2:1 mixture of MeOH/ CH_2Cl_2 (10 mL) was added at 0°C $\text{Pb}(\text{OAc})_4$ (620 mg, 1.4 mmol). After 20 min of stirring at 0°C, the reaction mixture was poured in a buffer aqueous solution pH=7 (10 mL) at room temperature, then filtered on Celite. The aqueous layer was extracted with dichloromethane (4x10 mL) and the combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. HCl 6N (5 mL) was then added and then warmed to reflux. The reaction mixture was extracted with diethyl ether (3x5 mL) and the combined aqueous extracts were concentrated under reduced pressure to afford (*R*)-3-amino-4,4,4-trifluorobutanoic acid hydrochloride. The hydrochloride was dissolved in propylene oxide (10 mL) and stirred for 1 h at room temperature. The crude mixture was concentrated under reduced pressure and pure **5** (126 mg, 80%) was obtained after recrystallization in methanol. $[\alpha]_{\text{D}}^{25} +26.6$ (c 0.5, 6N HCl) ($[\alpha]_{\text{D}}^{25} \text{Diit} -27.1$ (c 1.4, 6N HCl) for *S* enantiomer¹); ^1H NMR δ (D_2O) 2.48 (dd, $J_{AB} = 16.0$, $J = 4.4$ Hz, 1H), 2.69 (dd, $J_{AB} = 16.0$, $J = 3.9$ Hz, 1H), 4.05 (ddq, $J = 8.7$, 4.4, 3.9 Hz, 1H); ^{13}C NMR δ (D_2O) 37.2, 53.2 (q, $J = 31.5$ Hz), 121.5 (q, $J = 280.1$ Hz), 170.4; ^{19}F NMR δ (D_2O) -73.5 (d, $J = 8.7$ Hz).

β -amino ketones.

(3R)-6,6,6-Trifluoro-5-((1R)-2-hydroxy-1-phenylethylamino)-2,2-dimethylhexan-3-one (7a). According to the general procedure, **7a** was obtained from **1a,b** (62:38 mixture, 1.0 g, 4.6 mmol) and *t*-butyl methyl ketone trimethylsilyl enol ether (1.6 g, 6.9 mmol) as a yellow solid (1.3 g, 88%) after purification by flash chromatography (17:3 petroleum ether/ ethyl acetate). Mp 58-60°C; $[\alpha]_{\text{D}}^{25} -16.4$ (c 0.64, CHCl_3); IR (KBr) 3495, 3384, 3031, 2964, 2904, 1701, 1430, 1272, 1142 cm^{-1} ; ^1H NMR δ 1.18 (s, 9H); 2.73 (d, $J_{AB} = 18.0$ Hz, 1H), 2.83 (d,

(1) Soloshonok, V. A.; Kirilenko, A. G.; Fokina, N. A.; Shishkina, I. P.; Galushko, S. V.; Kukhar, V. P.; Svedas, V. K.; Kozlova, E. V. *Tetrahedron: Asymmetry* **1994**, 5, 1119-1126.

$J_{AB} = 18.0$ Hz, 1H), 3.58 (dd, $J_{AB} = 10.9$, $J = 7.6$ Hz, 1H), 3.78 (dd, $J_{AB} = 10.9$, $J = 3.5$ Hz, 1H), 3.86 (q, $J = 7.3$ Hz, 1H), 4.03 (dd, $J = 7.6$, 3.5 Hz, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR δ 26.1, 36.9, 44.5, 53.7 (q, $J = 30.0$ Hz), 67.1, 62.3, 126.6 (q, $J = 283.3$ Hz), 127.3, 127.8, 128.6, 140.5, 213.3; ^{19}F NMR δ -75.0 (d, $J = 7.3$ Hz); MS (EI 70 eV) m/z 318 ($\text{M}^+ + 1$), 286, 200, 104, 69, 57 (100). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{F}_3\text{NO}_2$: C, 60.56; H, 6.99; N, 4.41. Found: C, 60.64; H, 7.11; N, 4.43.

2-(2,2,2-Trifluoro-1-((1*R*)-2-hydroxy-1-phenylethylamino)-ethyl)-cyclohexanone (8a) and (8'a). According to the general procedure, a mixture of **8a** and **8'a** was obtained from **1a,b** (62:38 mixture, 500 mg, 2.3 mmol) and cyclohexanone trimethylsilyl enol ether (1.2 g, 6.9 mmol). After flash column chromatography (4:1 petroleum ether/ ethyl acetate), the major diastereomer **8a** (235 mg, 32%) and the minor diastereomer **8'a** (200 mg, 28%) were obtained in pure form. **8a**. yellow oil; $[\alpha]_{\text{D}}^{25}$ -16.5 (c 1.04, CHCl_3); IR (neat) 3372, 3063, 2943, 2863, 1708, 1450, 1426, 1149, 1039 cm^{-1} ; ^1H NMR δ 1.6-1.8 (m, 3H), 1.9-2.4 (m, 4H), 2.5-2.7 (m, 2H), 3.57 (dd, $J_{AB} = 11.1$, $J = 7.6$ Hz, 1H), 3.73 (dd, $J_{AB} = 11.1$, $J = 4.4$ Hz, 1H), 4.02 (dd, $J = 7.6$, 4.4 Hz, 1H), 4.06 (qd, $J = 7.6$, 1.5 Hz, 1H), 7.2-7.5 (m, 5H); ^{13}C NMR δ 24.5, 26.7, 26.8, 41.8, 49.8, 53.8 (q, $J = 26.6$ Hz), 62.3, 66.9, 127.3, 127.5, 128.9, 129.1 (q, $J = 284.6$ Hz), 140.6, 210.2; ^{19}F NMR δ -71.7 (d, $J = 7.6$ Hz). **8'a**. yellow oil; IR (neat) 3378, 3033, 2942, 2868, 1692, 1451, 1261, 1165 cm^{-1} ; ^1H NMR δ 1.5-1.8 (m, 4H), 1.8-2.1 (m, 2H), 2.1-2.4 (m, 2H), 2.44 (d, $J = 12.2$ Hz, 1H), 2.70 (m, 1H), 3.52 (dd, $J_{AB} = 10.7$, $J = 8.0$ Hz, 1H), 3.68 (dd, $J_{AB} = 10.7$, $J = 3.8$ Hz, 1H), 3.70 (qd, $J = 7.6$, 5.0 Hz, 1H), 3.95 (dd, $J = 8.0$, 3.8 Hz, 1H), 7.1-7.5 (m, 5H); ^{13}C NMR δ 24.8, 27.0, 29.5, 41.9, 50.8, 56.3 (q, $J = 27.6$ Hz), 62.2, 66.9, 126.1 (q, $J = 284.5$ Hz), 127.3, 127.6, 128.3, 140.0, 210.3; ^{19}F NMR δ -69.5 (d, $J = 7.6$ Hz).

Removal of the (*R*)-phenylglycinol side chain of β -amino ketones with $\text{Pb}(\text{OAc})_4$.

(*R*)-5-Amino-6,6,6-trifluoro-2,2-dimethylhexan-3-one hydrochloride (10a). Following the same procedure as for **9a**, **10a** (219 mg, 94%) was obtained from **7a** (318 mg, 1.0 mmol) as a solid. $[\alpha]_{\text{D}}^{25}$ +24.6 (c 0.82, HCl 1N); IR (KBr) 2969, 2879, 1715, 1371, 1199 cm^{-1} ; ^1H NMR δ (D_2O) 0.64 (s, 9H); 2.74 (dd, $J_{AB} = 19.4$, $J = 8.9$ Hz, 1H), 2.84 (dd, $J_{AB} = 19.4$, $J = 3.4$ Hz, 1H), 4.01 (dq, $J = 8.9$, 7.7, 3.4 Hz, 1H); ^{13}C NMR δ (D_2O) 27.7, 35.9, 46.4, 51.1 (q, $J = 32.7$ Hz), 125.8 (q, $J = 280.1$ Hz), 217.1; ^{19}F NMR δ (D_2O) -72.1 (d, $J = 7.7$ Hz).

(*R*)-5-Amino-6,6,6-trifluoro-2,2-dimethylhexan-3-one (12a). Following the same procedure as for **11a**, **12a** (89 mg, 48%) was obtained from **10a** (219 mg, 0.94 mmol) after

purification by flash chromatography (17:3 petroleum ether/ ethyl acetate) followed by recrystallization in hexane. Yellow solid; mp 26°C; $[\alpha]_D^{25} +24.5$ (c 0.60, HCl); IR (KBr) 2969, 2879, 1715, 1371, 1199 cm^{-1} ; ^1H NMR δ 1.12 (s, 9H), 1.48 (m, 2H), 2.66 (dd, $J_{AB} = 17.7$, $J = 8.4$ Hz, 1H), 2.76 (dd, $J_{AB} = 17.7$, $J = 4.0$ Hz, 1H), 3.78 (dq, $J = 8.4$, 7.7, 4.0 Hz, 1H), ^{13}C NMR δ , 27.7, 35.9, 46.4, 51.1 (q, $J = 32.7$ Hz), 125.8 (q, $J = 280.1$ Hz), 217.1; ^{19}F NMR δ -72.1 (d, $J = 7.7$ Hz).

2-(1-Amino-2,2,2-trifluoroethyl)-cyclohexanone (13a) and (13'a). Following the same procedure as for **9a**, a 3:2 mixture of diastereomers **13a** and **13'a** (106 mg, 46%) was obtained from a 3:2 mixture of **8a** and **8'a** (300 mg, 1.0 mmol) as a white solid. ^1H NMR δ (D_2O) 1.5-2.5 (m, 16H), 3.15 (dm, $J = 7.6$ Hz, 1H_{diast}), 3.36 (dm, $J = 5.5$ Hz, 1H_{diast}), 4.36 (q, $J = 7.6$ Hz, 2H); ^{13}C NMR δ (D_2O) 26.2, 26.4, 29.3, 29.7, 29.8, 32.8, 43.7, 44.3, 49.1, 52.5 (q, $J = 31.5$ Hz), 54.7 (q, $J = 31.5$ Hz), 125.4 (q, $J = 279.5$ Hz), 126.3 (q, $J = 279.3$ Hz), 214.5, 215.8; ^{19}F NMR δ -67.1 (d, $J = 7.6$ Hz) and -69.2 (d, $J = 7.6$).

Configuration assignment of 6a and 7a. To a solution of **3a** (300 mg, 1.0 mmol) in 5 mL of diethyl ether (5 mL) under argon at -78°C, was slowly added PhLi (0.6 mL of a 20% solution in dibutyl ether, 1.0 mmol) or *t*-BuLi (0.67 mL of a 1.5 M solution in pentane, 1.0 mmol). After 45 min of stirring at -78°C, the reaction mixture was poured into 1M HCl (10mL), then a saturated aqueous solution of NaHCO_3 was added until pH became basic. The aqueous layer was extracted with dichloromethane (4x20mL) and the combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by flash chromatography (4:1 petroleum ether/ ethyl acetate) of the crude product obtained from PhLi gave **6a** (152 mg, 45%) and purification by flash chromatography (17:3 petroleum ether/ ethyl acetate) of the crude product obtained from *t*-BuLi gave **7a** (98 mg, 31%).

Synthesis of γ -amino alcohols.

(3R)-4,4,4-Trifluoro-3-((1R)-2-hydroxy-1-phenylethylamino)-butan-1-ol (14) To a solution of **3a** (320 mg, 1.0 mmol) in diethyl ether (40 mL) under argon, was added LiAlH_4 (150 mg, 4.0 mmol). After 24 h of stirring, the reaction mixture was successively treated with water (0.2 mL), a solution of 15% KOH (0.2 mL) and water (0.4 mL). The resulting mixture was filtered on Celite[®], dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification by flash chromatography (3:1 petroleum ether/ ethyl acetate) gave **14** (229 mg,

87%). Colorless oil; $[\alpha]_{\text{D}}^{25}$ -11.2 (*c* 1.3, CHCl₃); IR (neat) 3355, 2933, 2881, 1454, 1129 cm⁻¹; ¹H NMR δ 1.57 (dddd, J_{AB} = 14.3, J = 14.3, 5.5, 3.8 Hz, 1H), 1.89 (m, 1H), 3.51 (m, 1H), 3.6-3.9 (m, 3H), 4.0-4.2 (m, 2H), 7.1-7.5 (m, 10H); ¹³C NMR δ 30.8, 55.5 (q, J = 27.6 Hz), 58.7, 62.5, 67.0, 126.8 (q, J = 283.6 Hz), 127.2, 127.7, 128.8, 140.3; ¹⁹F NMR δ -76.0 (d, J = 7.2 Hz); HRMS calcd for C₁₂H₁₆F₃NO₂ [MH⁺] 264.1211; found 264.1210. Anal. Calcd for C₁₂H₁₆F₃NO₂: C, 54.75; H, 6.13; N, 5.32. Found C, 54.29; H, 6.13; N, 5.08.

(3R)-4,4,4-Trifluoro-3-((1R)-2-hydroxy-1-phenylethylamino)-1-phenylbutan-1-ol (16).

Following the same procedure described for **14**, **16** was obtained from **6a** (340 mg, 1.0 mmol) as a mixture of diastereomers. Separation of the two diastereomers by flash chromatography (4:1 petroleum ether/ ethyl acetate) gave isolated major diastereomer **16a** (194 mg, 57%) and isolated minor diastereomer **16b** (119 mg, 35%). **16a** Colorless oil; $[\alpha]_{\text{D}}^{25}$ -46.8 (*c* 1.0, CHCl₃); IR (neat) 3315, 3032, 2926, 1455, 1259, 1126 cm⁻¹; ¹H NMR δ 1.82 (ddd, J_{AB} = 14.6, J = 10.4, 3.0 Hz, 1H), 2.00 (ddd, J_{AB} = 14.6, J = 8.1, 2.7 Hz, 1H), 2.9 (br, 3H), 3.60 (ddq, J = 10.4, 7.2, 2.7 Hz, 1H), 3.67 (dd, J_{AB} = 10.7, J = 8.6 Hz, 1H), 3.74 (dd, J_{AB} = 10.7, J = 4.1 Hz, 1H), 4.13 (dd, J = 8.6, 4.1 Hz, 1H), 4.95 (dd, J = 8.1, 3.0 Hz, 1H), 7.1-7.5 (m, 10H); ¹³C NMR δ 37.7, 53.0 (q, J = 26.7 Hz), 62.6, 66.8, 70.1, 125.3, 127.0 (q, J = 285.8 Hz), 127.2, 127.9, 128.1, 128.7, 129.3, 138.9, 143.5; ¹⁹F NMR δ -73.9 (d, J = 7.2); MS (EI 70 eV) *m/z* 340 (M⁺+1), 309, 308, 233, 230, 187, 121, 104, 77. **16b**. $[\alpha]_{\text{D}}^{25}$ -38.5 (*c* 1.0, CHCl₃); ¹H NMR δ 1.76 (m, 1H), 2.00 (m, 1H), 3.28 (m, 1H), 3.71 (dd, J_{AB} = 10.4, J = 9.0 Hz, 1H), 3.80 (dd, J_{AB} = 10.4, J = 3.9 Hz, 1H), 4.28 (dd, J = 9.0, 3.9 Hz, 1H), 4.64 (dd, J = 9.9, 1.7 Hz, 1H), 7.1-7.5 (m, 10H); ¹³C NMR δ 37.3, 56.0 (q, J = 27.4 Hz), 62.3, 67.1, 73.6, 124.8 (q, J = 284.9 Hz), 126.1, 127.7, 128.2, 128.6, 128.9, 129.5, 137.7, 143.3; ¹⁹F NMR δ -73.7 (d, J = 6.3 Hz).

(5R)-6,6,6-Trifluoro-5-((1R)-2-hydroxy-1-phenylethylamino)-2,2-dimethylhexan-3-ol (17).

Following the same procedure described for **14**, **17** was obtained from **7a** (310 mg, 1.0 mmol) as a mixture of diastereomers. Separation of the two diastereomers by recrystallization in pentane gave isolated major diastereomer **17a** (172 mg, 55%) and isolated minor diastereomer **17b** (110 mg, 35%). **17a**. yellow oil; $[\alpha]_{\text{D}}^{25}$ +3.6 (*c* 1.0, CHCl₃); IR (neat) 3377, 3275, 3034, 2964, 2874, 1604, 1475, 1162 cm⁻¹; ¹H NMR δ 0.96 (s, 9H), 1.58 (ddd, J_{AB} = 14.3, J = 11.3, 3.3 Hz, 1H), 1.75 (ddd, J_{AB} = 14.3, J = 10.5, 2.7 Hz, 1H), 3.5-3.9 (m, 4H), 4.25 (dd, J = 6.7, 3.4 Hz, 1H), 7.2-7.5 (m, 5H); ¹³C NMR δ 25.6, 29.4, 34.5, 55.2 (q, J = 26.8 Hz), 62.2, 67.3, 74.7, 127.2, 127.3 (q, J = 284.2 Hz), 127.7, 128.5, 140.8; ¹⁹F NMR δ -75.4 (d, J = 7.2 Hz); MS (EI 70 eV) *m/z* 320 (M⁺+1), 288, 230, 200, 186 (100), 166, 121, 103, 77. **17b**. Yellow solid; mp 91-92°C; $[\alpha]_{\text{D}}^{25}$ +8.0 (*c* 0.6, CHCl₃); ¹H NMR δ 0.92 (s, 9H), 1.41 (dt, J_{AB}

= 14.4, $J = 10.3$ Hz, 1H), 1.93 (ddd, $J_{AB} = 14.4$, $J = 3.0$, 1.7 Hz, 1H), 3.52 (dd, $J = 10.3$, 1.7 Hz, 1H), 2.60 (t, $J = 5.9$ Hz), 3.60 (ddq, $J = 10.3$, 7.2, 3.0 Hz, 1H), 3.75 (ddd, $J_{AB} = 11.0$, $J = 6.7$, 5.9 Hz, 1H), 3.85 (ddd, $J_{AB} = 11.0$, $J = 5.9$, 5.1 Hz, 1H), 4.14 (dd, $J = 6.7$, 5.1 Hz, 1H), 7.4 (m, 5H); ^{13}C NMR δ 25.5, 30.3, 34.9, 58.8 (q, $J = 27.4$ Hz), 62.6, 67.2, 79.5, 126.0 (q, $J = 284.7$ Hz), 127.2, 128.4, 128.8, 140.0; ^{19}F NMR δ -75.8 (d, $J = 7.2$ Hz). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{F}_3\text{NO}_2$: C, 60.17; H, 7.57; N, 4.39. Found C, 60.46; H, 7.40; N, 4.21.

(3R)-3-Amino-4,4,4-trifluorobutan-1-ol hydrochloride (15).

To a solution of **14** (260 mg, 1.0 mmol) in a 2:1 MeOH/ CH_2Cl_2 mixture (5 mL) at 0°C, was added $\text{Pb}(\text{OAc})_4$ (620 mg, 1.4 mmol). After 20 min of stirring at 0°C, the reaction mixture was poured into a buffer aqueous solution pH=7 (10 mL) at room temperature, then filtered on Celite®. The aqueous layer was extracted with dichloromethane (4x10mL) and the combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Then, 3N HCl (5 mL) was added. After 30 min of stirring at room temperature, the organic layer was extracted with diethyl ether (3x5 mL) and the aqueous extracts was concentrated under reduced pressure to afford **15** (141 mg, 79%) as a white powder. $[\alpha]_{\text{D}}^{25} +11.4$ (c 0.5, HCl 1N); ^1H NMR δ (D_2O) 1.82 (dddd, $J_{AB} = 15.3$, $J = 8.4$, 6.6, 5.7 Hz, 1H); 1.95 (dddd, $J_{AB} = 15.3$, $J = 6.6$, 5.7, 4.7 Hz, 1H), 3.58 (dd, $J = 6.6$, 5.7 Hz, 1H), 4.02 (ddq, $J = 8.4$, 7.2, 4.7, 1H); ^{13}C NMR δ (D_2O) 27.2, 49.9 (q, $J = 32.2$ Hz), 56.3, 122.7 (q, $J = 279.9$ Hz); ^{19}F NMR δ (D_2O) -75.1 (d, $J = 7.2$ Hz).

(3R)-3-Amino-4,4,4-trifluoro-1-phenylbutan-1-ol hydrochloride (18). Following the same procedure described for **15**, **18a** (110 mg, 86%) was obtained from **16a** (200 mg, 0.5 mmol) and **18b** (110 mg, 86%) was obtained from **16b** (200 mg, 0.5 mmol). **18a**. White powder; $[\alpha]_{\text{D}}^{25} -32.9$ (c 0.5, HCl 1N); IR (KBr) 3382, 3030, 2914, 1602, 1538, 1280, 1205 cm^{-1} ; ^1H NMR δ (D_2O) 2.19 (ddd, $J_{AB} = 15.3$, $J = 9.1$, 4.4 Hz, 1H), 3.32 (ddd, $J_{AB} = 15.3$, $J = 8.5$, 3.8 Hz, 1H), 4.12 (ddq, $J = 9.1$, 6.3, 3.8 Hz, 1H), 4.96 (dd, $J = 8.5$, 4.4 Hz, 1H), 7.4 (m, 10H); ^{13}C NMR δ (D_2O) 34.4, 50.1 (q, $J = 31.7$ Hz), 68.9, 123.9 (q, $J = 279.9$ Hz), 125.9, 128.6, 129.2, 142.9; ^{19}F NMR δ (D_2O) -75.0 (d, $^3J_{\text{HF}} = 6.3$). **18b**. White powder; $[\alpha]_{\text{D}}^{25} +27.1$ (c 1.0, HCl 1N); ^1H NMR δ (D_2O) 2.15 (ddd, $J_{AB} = 15.0$, $J = 9.3$, 3.5 Hz, 1H); 2.35 (ddd, $J_{AB} = 15.0$, $J = 10.3$, 3.9 Hz, 1H), 4.35 (ddq, $J = 9.3$, 6.3, 3.9 Hz, 1H), 4.98 (dd, $J = 10.3$, 3.5 Hz, 1H), 7.3-7.5 (m, 10H); ^{13}C NMR δ (D_2O) 31.9, 50.1 (q, $J = 32.2$ Hz), 69.5, 121.7 (q, $J = 280.0$ Hz), 123.9, 126.6, 127.0, 140.7; ^{19}F NMR δ (D_2O) -75.3 (d, $J = 6.3$ Hz).

(5R)-5-Amino-6,6,6-trifluoro-2,2-dimethylhexan-3-ol (19). Following the same procedure described for **15**, **19a** (83 mg, 71%) was obtained from **17a** (117 mg, 0.5 mmol) and **19b** (81

mg, 70%) was obtained from **17b** (117 mg, 0.5 mmol). **19a**. White solid; $[\alpha]_{\text{D}}^{25} +35.7$ (*c* 1.6, HCl 1N); IR (KBr) 3494, 2965, 2877, 1565, 1202, 1145 cm^{-1} ; ^1H NMR $\delta(\text{D}_2\text{O})$ 0.78 (s, 9H), 1.82 (ddd, $J_{AB} = 15.0$, $J = 10.8$, 2.6 Hz, 1H), 1.97 (ddd, $J_{AB} = 15.0$, $J = 10.0$, 2.0 Hz, 1H), 3.36 (dd, $J = 10.8$, 2.0 Hz, 1H), 4.14 (ddq, $J = 10.0$, 7.2, 2.6 Hz, 1H), ^{13}C NMR $\delta(\text{D}_2\text{O})$ 24.9, 28.1, 34.6, 50.7 (q, $J = 31.7$ Hz), 73.9, 124.9 (q, $J = 279.9$ Hz); ^{19}F NMR $\delta(\text{D}_2\text{O})$ -75.0 (d, $J = 7.2$ Hz). **19b**. White solid; $[\alpha]_{\text{D}}^{25} -2.4$ (*c* 1.0, HCl 1N), ^1H NMR $\delta(\text{D}_2\text{O})$ 0.84 (s, 9H), 1.74 (ddd, $^2J_{\text{HH}} = 14.9$, $^3J_{\text{HH}} = 10.4$, 10.0, 1 H), 2.17 (ddd, $J_{AB} = 14.9$, $J = 2.8$, 1.4 Hz, 1H), 3.55 (dd, $J = 10.4$, 1.4 Hz, 1H), 4.21 (ddq, $J = 10.0$, 7.2, 3.8 Hz, 1H); ^{13}C NMR $\delta(\text{D}_2\text{O})$ 27.5, 30.2, 37.4, 55.4 (q, $J = 31.7$ Hz), 80.3, 126.6 (q, $J = 281.0$ Hz); ^{19}F NMR $\delta(\text{D}_2\text{O})$ -75.1 (d, $J = 7.2$ Hz).