Supporting Information

Highly Enantioselective Transfer Hydrogenation of Fluoroalkyl Ketones

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Metal precursors

[RuCl₂(benzene)]₂ and [RuCl₂(*p*-cymene)]₂ were purchased from Sigma-Aldrich. [RuCl₂(mesitylene)]₂, [RuCl₂(1,3,5-triethylbenzene)]₂ and [RuCl₂(hexamethylbenzene)]₂ were provided by PhosPhoenix.

Chiral ligands

Ligands **1a-d** were prepared according to our published procedure.¹ They are available from PhosPhoenix.

HCO₂H/Et₃N 5:2 and 3:2

HCO₂H/Et₃N 5:2 (azeotrope) was prepared by adding Et₃N (280 mL, 2 mol) to HCO₂H (190 mL, 5 mol) at 0 °C under nitrogen atmosphere and used as such. Similarly, HCO₂H/Et₃N 3:2 was prepared.

NMR measurements

¹H NMR (299.9 MHz; internal Me₄Si), ¹³C NMR (75.43 MHz; internal CDCl₃, δ 77.00) and ¹⁹F NMR (282.2 MHz; internal CFCl₃) spectra were recorded in CDCl₃ on Varian Unity plus 300 spectrometer.

Fluoroalkyl ketones

2,2,2-Trifluoroacetophenone, octafluoroacetophenone, 1,1,1-trifluoro-3-phenyl-propan-2-one, 1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedione, ethyl 4,4,4-trifluoro-3-oxo-butyrate, and ethyl 4,4,5,5,5-pentafluoro-3-oxo-pentanoate were purchased from Sigma-Aldrich.

1,1,1-Trifluorooctan-2-one,² 1,1,1-trifluoro-4-phenyl-butan-2-one,³ cyclohexyl trifluoromethyl ketone,² 3,3,4,4,5,5,5-heptafluoro-1-phenyl-pentan-2-one,⁴ 1,1,1-trifluoro-3-(pyridin-2-yl)propan-2-one,⁵ 1,1,1-

(1) Šterk, D.; Stephan, S. M.; Mohar, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2605-2608.

(2) 1,1,1-Trifluorooctan-2-one prepared as described for 1,1,1-trifluorononan-2-one (Ramachandran, P. V.; Teodorović, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725-1738).

(3) A mixture of 1,1,1-trifluoro-4-phenyl-but-3-yn-2-one (4.0 g) and 10% Pd-C (50 mg) in MeOH (15 mL) was hydrogenated at 2 atm H₂ in a Parr apparatus at rt for 2 h. The mixture was filtered through Celite and the residue distilled (bp 84-86 °C, 12 mbar) affording a colorless oil (3.7 g, 89%). For the synthesis of 1,1,1-trifluoro-4-phenyl-but-3-yn-2-one, see Linderman, R. J.; Lonikar, M. S. *J. Org. Chem.* **1988**, *53*, 6013-6022.

(4) Prepared from benzylmagnesium chloride and ethyl heptafluorobutyrate under similar conditions as described for the synthesis of 1,1,1-trifluoro-3-phenyl-propan-2-one. A mixture of product ketone and its alcohol was obtained

trifluoro-3-(pyridin-2-yl)butan-2-one,⁵ 1,1,1-trifluoro-3-(pyridin-4-yl)propan-2-one,⁵ 1,1,1-trifluoro-3-(pyrimidin-4-yl)propan-2-one,⁵ 3-(benzoxazol-2-yl)-1,1,1-trifluoropropan-2-one,⁵ α -(2,2,2-trifluoroacetyl)- γ -butyrolactone⁶ and α -(2,2,2-trifluoroacetyl)- δ -valerolactone⁷ were prepared according to known procedures.

General procedure for asymmetric transfer hydrogenation of ketones listed in Table 1

Catalyst preparation:

A 100-mL round-bottom flask equipped with a magnetic stirring-bar was charged successively with $[\text{RuCl}_2(\eta^6\text{-arene})]_2$, (1*S*,2*S*)- $\text{R}_2\text{NSO}_2\text{DPEN}$ (**1a-d**) (1.1 equiv. to the Ru atom) and DMF (1 mL). The mixture was degassed by back-filling with nitrogen and heated at 80 °C for 20 min. The tinted color solution was cooled to rt and used directly in catalysis.

Reduction of ketones:

To a DMF solution of $[\text{RuCl}(\eta^6\text{-arene})((S,S)\text{-R}_2\text{NSO}_2\text{DPEN})]$ complex was added the ketone (1 mmol) followed by $\text{HCO}_2\text{H}\cdot\text{Et}_3\text{N}$ 5:2 (420 μL , 5 mmol). The mixture was left to stir at rt (25 °C) with a continuous nitrogen stream. The evolution of the reaction was monitored by GC: aliquots were diluted with CH_2Cl_2 and analyzed on Chirasil-DEX CB (25 m) column with H_2 as carrier gas, except for 1,1,1-trifluorooctan-2-ol which was analyzed as its (1*S*)-camphanic acid ester by ^{19}F NMR.

For working-up the reaction, the mixture was partitioned between diethyl ether (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL), brine (10 mL), dried over MgSO_4 , then concentrated. The product alcohol was purified as indicated below.

Preparation of racemic alcohols as standards

The racemic alcohols were prepared either by NaBH_4 reduction of the ketone in EtOH at 0 °C or by using racemic $[\text{RuCl}(\text{benzene})((\pm)\text{-Me}_2\text{NSO}_2\text{DPEN})]$ catalyst under similar transfer hydrogenation conditions as described above.

(2*S*)-1,1,1-Trifluorooctan-2-ol.

The crude was distilled on Kugelrohr apparatus affording a colorless oil: $[\alpha]^{25}_{\text{D}} -25.0$ (*c* 10.0, CHCl_3) (lit.⁸ *R*-isomer, 97% ee (GC), $[\alpha]^{26}_{\text{D}} +26.3$ (*c* 9.5, CHCl_3)).

^1H NMR δ 0.90 (t, *J* 7.0 Hz, 3H, Me), 1.19-1.40 and 1.45-1.80 (m, 10H, $(\text{CH}_2)_5$), 2.03 (br s, 1H, OH), 3.89 (m, 1H, CHOH); ^{19}F NMR δ -80.58 (d, *J* 6.2 Hz).

After derivatization with (1*S*)-(-)-camphanic acid chloride in $\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$, ee was determined by ^{19}F NMR: δ -77.61 (*S*), -77.68 (*R*); 94% ee.

and they were separated on silica gel eluting with hexane. The ketone was distilled on Kugelrohr apparatus (105 °C, 12 mmHg) affording a colorless oil. For the synthesis of 1,1,1-trifluoro-3-phenyl-propan-2-one, see Xavier, C. *J. Org. Chem.* **1987**, 52, 5026-5030.

(5) Kawase, M.; Teshima, M.; Saito, S.; Tani, S. *Heterocycles* **1998**, 48, 2103-2109.

(6) Archer, S.; Perianayagam, C. Sevenard, D. V.; Lork, E. *J. Fluorine Chem.* **2004**, 125, 125-128.

(7) Archer, S.; Perianayagam, C. *J. Med. Chem.* **1979**, 22, 306-309.

(8) Kuroki, Y.; Sakamaki, Y.; Iseki, K. *Org. Lett.* **2001**, 3, 457-459.

(2S)-1,1,1-Trifluoro-4-phenyl-butan-2-ol.

GC analysis (150 °C): t_R 3.8 min (*R*-isomer), 4.1 min (*S*-isomer); 96% ee.

The crude was filtered through a short pad of silica gel eluting with CH_2Cl_2 , then recrystallized from hexane affording colorless crystals: >99% ee (GC); mp 58-60 °C; $[\alpha]_D^{25}$ -37.8 (*c* 1.0, CHCl_3), $[\alpha]_D^{25}$ -37.9 (*c* 1.70, MeOH) (lit.⁹ *S*-isomer, $[\alpha]_D^{25}$ -70.2 (*c* 1.67, MeOH); lit.³ 96% ee, $[\alpha]_D^{25}$ +36.4 (*c* 0.76, CHCl_3)); ^1H NMR δ 1.95 (m, 2H, PhCH_2CH_2), 2.51 (d, *J* 6.1 Hz, 1H, OH), 2.71 (m, 1H, PhCH_a), 2.89 (m, 1H, PhCH_b), 3.85 (m, 1H, CHOH), 7.16-7.33 (m, 5H, Ph); ^{13}C NMR δ 30.72, 30.87, 69.45 (q, *J* 30.8 Hz), 125.14 (q, *J* 281.8 Hz), 126.29, 128.42, 128.58, 140.36; ^{19}F NMR δ -80.33 (d, *J* 7.6 Hz); EI HRMS (*m/z*) M^+ calcd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{O}$ 204.0762, obsd 204.0771.

(1S)-1-Cyclohexyl-2,2,2-trifluoroethanol.

GC analysis (100 °C): t_R 14.6 min (*S*), 15.2 min (*R*); 65% ee.

The crude was distilled on Kugelrohr apparatus affording a colorless oil: $[\alpha]_D^{25}$ -11.5 (*c* 14.0, CHCl_3) (lit.² *S*-isomer, $\geq 100\%$ ee (GC of its MCF derivative), $[\alpha]_D^{25}$ -17.82 (*c* 9.5, CHCl_3)); ^1H NMR δ 1.06-1.39 and 1.59-1.96 (m, 11H, *c*Hex), 2.82 (br s, 1H, OH), 3.71 (m, 1H, CHOH); ^{19}F NMR δ -75.98 (d, *J* 7.6 Hz).

(1R)-1-Phenyl-2,2,2-trifluoroethanol.

GC analysis (120 °C): t_R 10.0 min (*S*), 10.6 min (*R*); 28% ee.

The crude was filtered through a short pad of silica gel eluting with CH_2Cl_2 affording a colorless oil: $[\alpha]_D^{25}$ -7.3 (*c* 1.0, CCl_4) (lit.⁹ *S*-isomer, >99% ee (GC), $[\alpha]_D^{24}$ +25.1 (*c* 0.81, CCl_4)); ^1H NMR δ 2.65 (br s, 1H, OH), 5.03 (q, *J* 6.7 Hz, 1H, CH), 7.38-7.52 (m, 5H, Ph); ^{19}F NMR δ -78.88 (d, *J* 6.7 Hz).

1-Pentafluorophenyl-2,2,2-trifluoroethanol.

(9) Lin, J. T.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1987**, 52, 3211-3217.

GC analysis (130 °C): t_R 3.3 min, 3.5 min; ~racemic.

The crude was distilled on Kugelrohr apparatus affording a colorless oil: ^1H NMR δ 3.12 (br d, J 9.5 Hz, 1H, OH), 5.42 (m, 1H CH); ^{19}F NMR δ -78.90 (m, 3F), -141.54 (m, 2F), -150.85 (tt, J 21.1, 3.1 Hz, 1F), -160.64 (m, 2F).

(2S)-1,1,1-Trifluoro-3-phenyl-propan-2-ol.

GC analysis (150 °C): t_R 3.3 min (*R*), 3.6 min (*S*); 97% ee.

The crude was distilled on Kugelrohr apparatus affording a colorless oil: $[\alpha]_D^{25}$ -44.8 (c 1.0, CHCl_3) (lit.¹⁰ *S*-isomer, 98% ee (GC), $[\alpha]_D^{25}$ -45.5 (c 0.95, CHCl_3)); ^1H NMR δ 2.12 (br s, 1H, OH), 2.85 (dd, J 14.0, 10.1 Hz, 1H, CH_a), 3.07 (dd, J 14.0, 2.8 Hz, 1H, CH_b), 4.14 (m, 1H, CHOH), 7.23-7.39 (m, 5H, Ph); ^{19}F NMR δ -80.10 (d, J 6.7 Hz).

(2S)-3,3,4,4,5,5,5-Heptafluoro-1-phenyl-pentan-2-ol.

GC analysis (120 °C): t_R 12.2 min (*R*), 14.0 min (*S*); 98% ee.

The crude was distilled on Kugelrohr apparatus affording a colorless oil: $[\alpha]_D^{25}$ -27.8 (c 2.0, MeOH) (lit.¹¹ *S*-isomer, $[\alpha]_D^{20}$ -28.1 (c 2.0, MeOH)); ^1H NMR δ 2.87 (dd, J 14.0, 10.3 Hz, 1H, CH_a), 3.13 (m, 1H, CH_b), 4.30 (m, 1H, CHOH), 7.23-7.39 (m, 5H, Ph); ^{19}F NMR δ -81.38 (dd, J 11.1, 8.4 Hz, 3F), -121.22 (dm, J 282.2 Hz, 1F), -125.43 (ddd, J 291.4, 8.9, 4.3 Hz, 1F), -127.20 (dd, J 291.4, 10.6 Hz, 1F), -128.40 (dm, J 282.2 Hz, 1F).

(2S)-1,1,1-Trifluoro-3-(pyridin-2-yl)propan-2-ol.

GC analysis (150 °C): t_R 3.0 min (*R*), 3.3 min (*S*); 99% ee.

The crude was purified on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 95:5 (R_f 0.38), then recrystallized from hexane/DCM 95:5 to yield colorless crystals: >99.9 % ee (GC); mp 93-95 °C; $[\alpha]_D^{23}$ -68.9 (c 1.0, MeOH); ^1H NMR δ 3.09 (dd, J 15.6, 8.2 Hz, 1H, CH_a), 3.14 (dd, J 15.6, 3.8 Hz, 1H, CH_b), 4.45 (m, 1H, CHOH), 6.49 (br s, 1H, OH), 7.23 (m, 2H), 7.69 (td, J 7.7, 1.8 Hz, 1H), 8.48 (m, 1H); ^{13}C NMR δ 35.20 (q, J 2.2 Hz), 69.92 (q, J 31.5 Hz), 122.25, 123.93, 124.89 (q, J 281.3 Hz), 137.37, 148.38, 157.49; ^{19}F NMR δ -79.64 (d, J 6.8 Hz); EI HRMS (m/z) M^+ calcd for $\text{C}_8\text{H}_8\text{F}_3\text{NO}$ 191.0558, obsd 191.0553.

(10) Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. *J. Org. Chem.* **2000**, 65, 157-163.

(11) Bravo, P.; Frigerio, M.; Resnati, G. *Synthesis* **1988**, 955-960.

(+)-*erythro*-1,1,1-Trifluoro-3-(pyridin-2-yl)butan-2-ol.

GC analysis (150 °C): t_R 2.8 min (minor) and 3.0 min (major) (*threo*: 2*S*,3*S* or 2*R*,3*R*),
 t_R 3.9 min (minor) and 4.2 min (major) (*erythro*: 2*S*,3*R* or 2*R*,3*S*);
erythro/*threo* = 78:22, *erythro*: 99% ee, *threo*: 84% ee.

The crude was purified on silica gel eluting with CH_2Cl_2 (R_f 0.17), then recrystallized from hexane to yield colorless crystals: ee >99% (GC); mp 101-102 °C; $[\alpha]_D^{25} +8.5$ (c 1.0, CHCl_3); ^1H NMR δ 1.40 (dq, J 7.2, 1.2 Hz, 3H, Me), 3.29 (qd, J 7.2, 2.3 Hz, 1H, CHMe), 4.45 (qd, J 7.6, 2.3 Hz, 1H, CHOH), 6.09 (br s, 1H, OH), 7.23 (m, 2H), 7.70 (td, J 7.7, 1.8 Hz, 1H), 8.48 (m, 1H); ^{13}C NMR δ 14.71 (q, J 2.0 Hz), 39.51 (q, J 1.7 Hz), 72.30 (q, J 30.0 Hz), 122.17, 122.28, 124.93 (q, J 282.4 Hz), 137.52, 148.34, 163.51; ^{19}F NMR δ -75.92 (dq, J 7.6, 1.2 Hz); EI HRMS (m/z) M^+ calcd for $\text{C}_9\text{H}_{10}\text{F}_3\text{NO}$ 205.0714, obsd 205.0719.

Configuration of the major diastereomer was determined to be *erythro* by X-ray analysis. Due to the transfer hydrogenation trend of the catalyst, we suppose that the absolute configuration is (2*S*,3*R*).

threo-Isomer:

Yellowish oil (R_f 0.43): ^1H NMR δ 1.51 (d, J 7.2 Hz, 3H, Me), 3.21 (qd, J 7.2, 2.1 Hz, 1H, CHMe), 4.15 (qd, J 7.7, 2.1 Hz, 1H, CHOH), 7.13-7.23 (m, 2H), 7.32 (br s, 1H, OH), 7.68 (td, J 7.7, 1.8 Hz, 1H), 8.45 (m, 1H); ^{13}C NMR δ 20.36, 37.78 (q, J 1.5 Hz), 75.12 (q, J 29.7 Hz), 122.12, 123.06, 125.22 (q, J 284.2 Hz), 137.63, 148.00, 162.78; ^{19}F NMR δ -77.65 (d, J 7.7 Hz).

(2*S*)-1,1,1-Trifluoro-3-(pyridin-4-yl)propan-2-ol.

GC analysis (160 °C): t_R 5.1 min (*R*), 5.5 min (*S*); 98% ee.

The crude was purified on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 4:6 (R_f 0.38) to yield a yellowish oil: $[\alpha]_D^{25} -42.6$ (c 1.8, CHCl_3); ^1H NMR δ 2.87 (dd, J 14.0, 10.2 Hz, 1H, CH_a), 3.00 (dd, J 14.0, 2.6 Hz, 1H, CH_b), 4.15 (m, 1H, CHOH), 7.21 (m, 2H), 8.21 (m, 2H); ^{13}C NMR δ 35.73, 69.97 (q, J 30.8 Hz), 125.02 (q, J 283.46 Hz), 125.18, 147.15, 148.50; ^{19}F NMR δ -80.08 (d, J 6.7 Hz); EI HRMS (m/z) M^+ calcd for $\text{C}_8\text{H}_8\text{F}_3\text{NO}$ 191.0558, obsd 191.0552.

(2*S*)-1,1,1-Trifluoro-3-(pyrimidin-4-yl)propan-2-ol.

GC analysis (150 °C): t_R 4.1 min (*R*), 4.7 min (*S*); 98% ee.

The crude was purified on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 6:4 (R_f 0.30) to yield a yellowish oil: $[\alpha]_D^{25} -39.5$ (c 0.8, CHCl_3); ^1H NMR δ 3.09 (dd, J 15.3, 8.8 Hz, 1H, CH_a), 3.18 (dd, J 15.3, 3.4 Hz, 1H, CH_b), 4.56 (m, 1H, CHOH), 4.9 (br s, 1H, OH), 7.30 (dd, J 5.2, 1.1 Hz, 1H), 8.68 (d, J 5.2 Hz, 1H), 9.11 (d, J 1.1 Hz, 1H); ^{13}C NMR δ 36.13, 69.01 (q, J 31.9 Hz), 121.78, 124.69 (q, J 281.3 Hz), 157.32, 157.97, 165.80; ^{19}F NMR δ -79.71 (d, J 6.7 Hz); EI HRMS (m/z) M^+ calcd for $\text{C}_7\text{H}_7\text{F}_3\text{N}_2\text{O}$ 192.0510, obsd 192.0517.

(2S)-3-(Benzoxazol-2-yl)-1,1,1-trifluoropropan-2-ol.

GC analysis (150 °C): t_R 9.7 min (*R*), 9.3 min (*S*); 96% ee.

The crude was filtered through a short pad of silica gel eluting with CH_2Cl_2 (R_f 0.23), then recrystallized from hexane/ CH_2Cl_2 affording colorless crystals: >99% ee (GC); mp 128-129 °C; $[\alpha]_D^{25}$ -41.6 (*c* 1.0, CHCl_3); ^1H NMR (CD_3OD) δ 3.23 (dd, *J* 15.4, 9.7 Hz, 1H, CH_a), 3.36 (dd, *J* 15.4, 3.7 Hz, 1H, CH_b), 4.64 (m, 1H, CHOH), 7.36 (m, 2H), 7.57 (m, 1H), 7.65 (m, 1H); ^{13}C NMR (CD_3OD) δ 31.36 (q, *J* 2.2 Hz), 69.04 (q, *J* 31.5 Hz), 111.75, 120.42, 125.85, 126.48 (q, *J* 281.8 Hz), 126.48, 142.01, 152.35, 164.71; ^{19}F NMR (CD_3OD) δ -79.85 (d, *J* 7.0 Hz); EI HRMS (*m/z*) M^+ calcd for $\text{C}_{10}\text{H}_8\text{F}_3\text{NO}_2$ 231.0507, obsd 231.0512.

(5S)-6,6,6-Trifluoro-5-hydroxy-2,2-dimethyl-3-hexanone.

GC analysis (100 °C): t_R 10.0 min (*R*), 11.0 min (*S*); 99% ee.

The crude was filtered through a short pad of silica gel eluting with CH_2Cl_2 , then recrystallized from hexane affording colorless crystals: >99.9% ee (GC); mp 37-38 °C; $[\alpha]_D^{23}$ -24.8 (*c* 1.0, MeOH) (lit.¹² *R*-isomer, >95% ee, $[\alpha]_D$ +18.3 (*c* 1.03, MeOH)); ^1H NMR δ 1.18 (s, 9H, CMe_3), 2.78 (dd, *J* 17.9, 2.7 Hz, 1H, CH_a), 2.93 (dd, *J* 17.9, 9.2 Hz, 1H, CH_b), 3.57 (br s, 1H, OH), 4.48 (m, 1H, CHOH); ^{19}F NMR δ -79.82 (d; *J* 6.9 Hz).

Ethyl (3S)-4,4,4-trifluoro-3-hydroxybutyrate.

GC analysis (120 °C): t_R 3.0 min (*R*), 3.1 min (*S*); 98% ee.

The crude was distilled on Kugelrohr apparatus affording a colorless oil: $[\alpha]_D^{25}$ -20.9 (*c* 0.7, CHCl_3) (lit.¹³ *R*-isomer, >95% ee, $[\alpha]_D^{20}$ +20.8 (*c* 0.7, CHCl_3)); ^1H NMR δ 1.30 (t, *J* 7.3 Hz, 3H, Me), 2.67 (dd, *J* 16.7, 8.3 Hz, 1H, CH_a), 2.74 (dd, *J* 16.7, 4.2 Hz, 1H, CH_b), 3.54 (br s, 1H, OH), 4.22 (q, *J* 7.3 Hz, 2H, OCH_2), 4.44 (m, 1H, CHOH); ^{19}F NMR δ -80.26 (d, *J* 6.5 Hz).

Ethyl (3S)-4,4,5,5,5-pentafluoro-3-hydroxypentanoate.

GC analysis (120 °C): t_R 2.7 min (*R*), 2.9 min (*S*); 99% ee.

The crude was distilled on Kugelrohr apparatus affording a colorless oil: $[\alpha]_D^{25}$ -9.8 (*c* 1.5, CHCl_3); ^1H NMR δ 1.30 (t, *J* 7.2 Hz, 3H, Me), 1.74 (m, 2H, CF_3CHCH_2), 3.62 (br s, 1H, OH), 4.23 (q, *J* 7.2 Hz, 2H, OCH_2),

(12) Lin, J. T.; Yamazaki, T.; Takeda, M.; Kitazume, T. *J. Fluorine Chem.* **1989**, *44*, 113-120.

(13) Xu, C.; Yuan, C. *Tetrahedron* **2005**, *61*, 2169-2186.

4.55 (m, 1H, *CHOH*); ^{13}C NMR δ 13.91, 34.06, 61.63, 66.41 (dd, J 28.6, 23.1 Hz), 113.28 (ddq, J 260.4, 254.9, 26.3 Hz), 118.84 (qdd, J 286.2, 36.3, 34.6 Hz), 171.18; ^{19}F NMR δ -82.24 (s, 3F), 123.15 (dd, J 277.7, 5.5 Hz, 1F), -131.93 (dd, J 277.7, 18.3 Hz, 1F); EI HRMS (m/z) M^+ calcd for $\text{C}_7\text{H}_9\text{F}_5\text{O}_3$ 236.0472, obsd 236.0477.

(*S*)- α -[(1*S*)-2,2,2-Trifluoro-1-hydroxy-ethyl]- γ -butyrolactone.

GC analysis (150 °C): t_R 2.8 min (minor) and 2.9 min (major) (*anti*),
 t_R 7.1 min (*S,S*-major) and 8.2 min (*R,R*-minor) (*syn*);
syn/anti 89:11, *syn*: 98% ee (*S,S*), *anti*: 81% ee.

The crude was purified on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 95:5 (R_f 0.36) to yield *syn*-diastereomer as a colorless oil: 98% ee (GC), $[\alpha]_D^{25}$ -7.6 (c 2.0, CHCl_3); ^1H NMR δ 2.29 and 2.65 (2m, 2H, $\text{CH}_2\text{CH}_2\text{O}$), 2.96 (m, 1H, CH), 3.75 (br s, 1H, OH), 4.27 and 4.45 (2m, 2H, CH_2O), 4.62 (m, 1H, *CHOH*); ^{13}C NMR δ 21.09, 40.91, 67.21 (q, J 32.1 Hz), 67.68, 124.52 (q, J 281.8 Hz), 177.60; ^{19}F NMR δ -78.32 (d, J 7.1 Hz); EI HRMS (m/z) ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_6\text{H}_8\text{F}_3\text{O}_3$ 185.0426, obsd 185.0431.

anti-Diastereomer:

Colorless oil (R_f 0.48): ^1H NMR δ 2.22 and 2.48 (2m, 2H, $\text{CH}_2\text{CH}_2\text{O}$), 2.90 (m, 1H, CH), 4.18 (m, 1H, *CHOH*), 4.29 and 4.51 (2m, 2H, CH_2O), 4.83 (s, 1H, OH); ^{13}C NMR δ 25.91, 39.51, 67.45, 70.81 (q, J 31.9 Hz), 123.79 (q, J 281.28), 178.17; ^{19}F NMR δ -78.51 (d, J 6.1 Hz).

(*S*)- α -[(1*S*)-2,2,2-Trifluoro-1-hydroxy-ethyl]- δ -valerolactone.

GC analysis (150 °C): t_R 4.4 min (minor) and 4.5 min (major) (*anti*),
 t_R 7.2 min (*S,S*-major) and 8.3 min (*R,R*-minor) (*syn*);
syn/anti 89:11, *syn*: 97% ee (*S,S*), *anti*: 95% ee.

The crude was purified on silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 95:5 (R_f 0.38), then recrystallized from hexane/ CH_2Cl_2 9:1 to yield *syn*-diastereomer as colorless crystals: >99.9% ee and >99.9% de (GC); mp 97-98 °C; $[\alpha]_D^{25}$ -45.5 (c 1.0, CHCl_3); ^1H NMR δ 1.87-2.24 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 2.90 (m, 1H, CH), 4.15 (d, J 6.4 Hz, 1H, OH), 4.38 (m, 2H, OCH_2), 4.85 (m, 1H, *CHOH*); ^{13}C NMR δ 17.86 (q, J 1.7 Hz), 21.94, 41.55 (q, J 1.1 Hz), 68.54 (q, J 31.32 Hz), 69.54, 124.72 (q, J 282.4 Hz), 172.27; ^{19}F NMR δ -76.13 (d, J 7.6 Hz); EI HRMS (m/z) ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_7\text{H}_{10}\text{F}_3\text{O}_3$ 199.0582, obsd 199.0587.

anti-Diastereomer:

Colorless oil (R_f 0.52): ^1H NMR δ 1.80 (m, 1H), 2.00 (m, 2H), 2.24 (m, 1H), 2.86 (m, 1H, CH), 4.22 (m, 1H, *CHOH*), 4.39 (m, 2H, OCH_2), 4.60 (d, J 6.4 Hz, 1H, OH); ^{13}C NMR δ 20.51 (q, J 2.2 Hz), 21.30, 40.82 (q, J 1.1 Hz), 68.28, 70.62 (q, J 31.3 Hz), 124.28 (q, J 282.4 Hz), 173.43; ^{19}F NMR δ -75.82 (d, J 6.7 Hz).

Preparation of (1*S*)-camphanic acid ester of the *syn*-diastereomer for X-ray analysis:

To a solution of (*S*)- α -[(1*S*)-2,2,2-trifluoro-1-hydroxy-ethyl]- δ -valerolactone (50 mg, 0.25 mmol) and Et_3N (35 μl , 0.25 mmol) in CH_2Cl_2 (0.7 ml) was added (1*S*)-(-)-camphanic chloride (54 mg, 0.25 mmol) and DMAP (1 mg). The mixture was stirred at rt for 4 h. Water was added and the product extracted with CH_2Cl_2 , dried over Na_2SO_4 , and purified on silica gel eluting with CH_2Cl_2 (R_f 0.29). Recrystallization from hexane yielded colorless crystals (25 mg, 26%): mp 143-144 °C; ^1H NMR δ 0.93, 1.08 and 1.12 (3s, 9H,

3Me), 1.71 (m, 1H), 1.89-2.18 (m, 5H), 2.26 (m, 1H), 2.43 (m, 1H), 3.08 (m, 1H), 4.34 (m, 2H, OCH₂), 6.28 (qd, *J* 7.5, 2.1 Hz, 1H, CF₃CH); ¹³C NMR δ 9.65, 16.32, 16.49, 19.27 (q, *J* 1.7 Hz), 21.90, 28.83, 30.99, 40.08, 54.72, 54.88, 68.44 (q, *J* 33.0 Hz), 69.04, 90.56, 123.24 (q, *J* 282.4 Hz), 165.13, 169.20, 177.93; ¹⁹F NMR δ -73.98 (d, *J* 7.5 Hz); EI MS (*m/z*) M⁺ 378 (73%). X-Ray diffraction analysis revealed the *S,S* configuration of the *syn*-diastereomer.

Figure 1: X-ray crystallographic structure of the major diastereomer of 1,1,1-trifluoro-3-(pyridin-2-yl)butan-2-ol showing *threo* relative configuration.

Figure 2: X-ray crystallographic structure of (1*S*)-camphanic acid ester of *syn*- α -(2,2,2-trifluoro-1-hydroxy-ethyl)- δ -valerolactone showing *S,S* absolute configuration.