Catalytic Asymmetric Transacetalization

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General Information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography on silica gel pre-coated plastic sheets (0.2 mm, Machery-Nagel). Visualization was accomplished by irradiation with UV light at 254 nm and/or phosphomolybdic acid (PMA) stain. Column chromatography was performed on Merck silica gel (60, particle size 0.040-0.063 mm). Proton, and carbon NMR spectra were recorded on Bruker AV-500 or Bruker AV-400 spectrometer in deuterated solvent. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard (DMSO, δ 2.49 ppm; CD₂Cl₂, δ 5.32 ppm; CDCl₃, δ 7.24). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, q = quartet, m = multiplet), coupling constants (Hz) and integration. ¹³C chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard (DMSO-d₆, δ 39.5 ppm; CD₂Cl₂, 53.8 ppm; CDCl₃, δ 77.0). High resolution mass spectra were determined on a Bruker APEX III FTMS (7 T magnet). The enantiomeric excesses were determined by GC or HPLC analysis employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the appropriate racemic mixtures.

Synthetic Procedures and Spectral Data

Substrates

2a–l

Representative procedure for compounds 2a–l

Preparation of the Grignard reagent

A solution of freshly distilled 3-chloropropionaldehyde diethylacetal (5.0 g, 30.0 mmol) in THF (5 ml) was added to activatedⁱ magnesium turnings (1.46 g, 60 mmol). The temperature of the exothermic reaction mixture was kept between 15–25 °C by cooling with an ice bath.^{ii, iii} After heat development ceased, the mixture was diluted with toluene (10 ml) and the resulting solution (calculated ca. 1.5 mmol/ml) was used immediately.

Addition to ketones

A solution of the Grignard reagent prepared above (7.5 ml, 11.25 mmol)^{iv} was cooled to –30 °C and a solution of ketone (5.0 mmol) in toluene (1.25 ml) was added dropwise.^v The mixture was allowed to warm to 0 °C during 2–4 h. It was then quenched at 0 °C with concentrated aqueous NH₄Cl (5 ml) and H₂O (5 ml), and extracted with Et₂O (2 x 10 ml). The combined organic extracts were washed with conc. Na₂CO₃ (aq.) (5 ml), dried (MgSO₄), filtered, and concentrated directly prior to purification. Flash chromatography on silica gel yielded pure products.^{vi} The products were stored as 0.1–0.2 M solutions in EtOAc or Et₂O, or used immediately for transacetalization reaction.

Notes:

- i) Activation was performed with a few drops of 1,2-dibromoethane.
- ii) For reactions on a larger scale a more efficient dry ice/acetone bath cooling is necessary.
- iii) If there is no exothermic reaction at this point, initiation is performed by adding more 1,2-dibromoethane and fast heating (with a heat gun) and cooling to 25 °C (repeated until reaction becomes exothermic after cooling).
- iv) For all other reactions, except **2j** and **2d**, 1.5 equiv. of the Grignard reagent was used. However, incomplete conversion of the starting ketones was observed. This is probably a result of the decomposition of the Grignard reagent¹ during preparation which leads to variable yields. Addition of more Grignard reagent (which was meanwhile kept at –40 °C) has beneficial effect on conversion.
- v) Ketones that are solids were added in portions to the Grignard reagent diluted with 1.25 ml of toluene.
- vi) TLC visualization: UV (254 nm) and/or PMA stain.

¹ Greiner, A. *Tetrahedron Lett.* **1989**, 30, 3547.

4,4-Diethoxy-1,1-diphenylbutan-1-ol (2a)

Purification: 10% EtOAc/hexane. Colorless oil, 2.12 g (from 10.0 mmol of ketone), 67%. ^1H NMR (400 MHz, DMSO- d_6) δ 7.41 (dd, $J = 8.3, 1.2$ Hz, 4H), 7.26 (t, $J = 7.8$ Hz, 4H), 7.14 (tt, $J = 7.3, 1.2$ Hz, 2H), 5.50 (s, 1H), 4.42 (t, $J = 5.7$ Hz, 1H), 3.51–3.43 (m, 2H), 3.38–3.30 (m, 2H), 2.24–2.20 (m, 2H), 1.47–1.41 (m, 2H), 1.06 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 148.2, 127.7, 126.0, 125.7, 102.4, 76.1, 60.2, 36.0, 28.0, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{20}\text{H}_{26}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$) 337.1774, found 337.1774.

4,4-Diethoxy-1,1-bis(4-methoxyphenyl)butan-1-ol (2b)

Purification: 20 % EtOAc/hexane (mixture loaded on the column as a solution in toluene). Colorless solid, 776 mg (from 5.0 mmol of ketone), 41%. ^1H NMR (400 MHz, DMSO- d_6) δ 7.27 (d, $J = 8.9$ Hz, 4H), 6.81 (d, $J = 8.8$ Hz, 4H), 5.30 (s, 1H), 4.40 (t, $J = 5.6$ Hz, 1H), 3.69 (s, 6H), 3.51–3.43 (m, 2H), 3.38–3.30 (m, 2H), 2.16–2.12 (m, 2H), 1.45–1.40 (m, 2H), 1.06 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 157.4, 140.7, 126.9, 112.9, 102.4, 75.6, 60.1, 54.9, 36.3, 28.1, 15.2. HRMS (ESI+) m/z calculated for $\text{C}_{22}\text{H}_{30}\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$) 397.1985, found 397.1982.

4,4-Diethoxy-1,1-bis(4-fluorophenyl)butan-1-ol (2c)

Purification: 20% EtOAc/hexane (mixture loaded on the column as a solution in toluene). Colorless oil, 781 mg (from 5.0 mmol of ketone), 45%. ^1H NMR (400 MHz, DMSO- d_6) δ 7.43–7.38 (m, 4H), 7.11–7.05 (m, 4H), 5.64 (s, 1H), 4.41 (t, $J = 5.6$ Hz, 1H), 3.50–3.43 (m, 2H), 3.38–3.30 (m, 2H), 2.22–2.17 (m, 2H), 1.43–1.38 (m, 2H), 1.06 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.6 (d, $J = 242.3$ Hz), 144.3 (d, $J = 3.0$ Hz), 127.7 (d, $J = 7.9$ Hz), 114.4 (d, $J = 20.7$ Hz), 102.3, 75.6, 60.2, 36.1, 28.0, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{F}_2\text{Na}$ ($\text{M}+\text{Na}^+$) 373.1586, found 373.1588.

1,1-Bis(4-bromophenyl)-4,4-diethoxybutan-1-ol (2d)

Purification: CH₂Cl₂/hexane/EtOAc 10:10:1. Colorless oil, 823 mg (from 3.15 mmol of ketone), 55%. ¹H NMR (500 MHz, DMSO-d₆) δ 7.46 (d, *J* = 8.6 Hz, 4H), 7.33 (d, *J* = 8.5 Hz, 4H), 5.74 (s, 1H), 4.41 (t, *J* = 5.5 Hz, 1H), 3.50–3.43 (m, 2H), 3.37–3.31 (m, 2H), 2.20–2.17 (m, 2H), 1.41–1.37 (m, 2H), 1.06 (t, *J* = 7.0 Hz, 6H). ¹³C NMR (125 MHz, DMSO-d₆) δ 147.2, 130.8, 128.1, 119.5, 102.2, 75.7, 60.3, 35.5, 27.9, 15.3. HRMS (ESI+) *m/z* calculated for C₂₀H₂₄O₃Br₂Na (M+Na⁺) 492.9985, found 492.9989.

9-(3,3-Diethoxypropyl)-9,10-dihydroanthracen-9-ol (2e)

Purification: 15% EtOAc/hexane (crude product dissolved in 10 % EtOAc/hexane (5 ml), filtered and concentrated prior to chromatography).

Colorless solid, 533 mg (from 5.0 mmol of ketone), 33%. ¹H NMR (400 MHz, DMSO-d₆) δ 7.69 (dd, *J* = 7.6, 1.0 Hz, 2 H), 7.31–7.26 (m, 4H), 7.21 (td, *J* = 7.3, 1.2 Hz, 2H), 5.72 (s, 1H), 4.17 (t, *J* = 5.7 Hz, 1H), 3.94 (s, 2H), 3.39–3.31 (m, 2H), 3.26–3.18 (m, 2H), 1.57–1.53 (m, 2H), 1.38–1.32 (m, 2H), 0.98 (t, *J* = 7.0 Hz, 6H). ¹³C NMR (100 MHz, DMSO-d₆) δ 143.8, 133.7, 127.0, 126.3, 125.9, 125.1, 102.0, 72.6, 60.2, 37.6, 34.3, 28.1, 15.2. HRMS (ESI+) *m/z* calculated for C₂₁H₂₆O₃Na (M+Na⁺) 349.1774, found 349.1776.

5,5-Diethoxy-2-methylpentan-2-ol (2f)

Purification: 30% EtOAc/hexane. Colorless oil, 473 mg (from 5.0 mmol of ketone), 50%. ¹H NMR (500 MHz, DMSO-d₆) δ 4.39 (t, *J* = 5.7 Hz, 1H), 4.09 (s,

1H), 3.56–3.50 (m, 2H), 3.42–3.36 (m, 2H), 1.55–1.50 (m, 2H), 1.34–1.31 (m, 2H), 1.09 (t, *J* = 7.0 Hz, 6H), 1.04 (s, 6H). ¹³C NMR (125 MHz, DMSO-d₆) δ 102.7, 68.3, 60.2, 38.3, 29.2, 28.3, 15.2. HRMS (ESI+) *m/z* calculated for C₁₀H₂₂O₃Na (M+Na⁺) 213.1461, found 213.1461.

6,6-Diethoxy-3-ethylhexan-3-ol (2g)

Purification: 20% EtOAc/hexane. Colorless oil, 1.26 g (from 10 mmol of ketone), 58%. ^1H NMR (400 MHz, DMSO- d_6) δ 4.38 (t, J = 5.6 Hz, 1H), 3.80 (s, 1H), 3.56–3.49 (m, 2H), 3.43–3.35 (m, 2H), 1.48–1.42 (m, 2H), 1.32–1.26 (m, 6H), 1.08 (t, J = 7.0 Hz, 6H), 0.74 (t, J = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, DMSO- d_6) δ 102.8, 72.1, 60.3, 32.5, 30.5, 27.5, 15.3, 7.8. HRMS (CI (FE) *i*-butane) m/z calculated for $\text{C}_{12}\text{H}_{27}\text{O}_3$ (M+H) 219.1960, found 219.1962.

6,6-Diethoxy-3-isopropyl-2-methylhexan-3-ol (2h)

Purification: 15% EtOAc/hexane. Colorless oil, 645 mg (from 5.0 mmol of ketone), 52%. ^1H NMR (500 MHz, DMSO- d_6) δ 4.35 (t, J = 5.4 Hz, 1H), 3.56–3.50 (m, 2H), 3.52 (s, 1H), 3.42–3.36 (m, 2H), 1.81–1.72 (m, 2H), 1.51–1.46 (m, 2H), 1.39–1.36 (m, 2H), 1.09 (t, J = 7.0 Hz, 6H), 0.85 (d, J = 6.9 Hz, 6H), 0.83 (d, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 103.0, 75.0, 60.4, 33.4, 28.4, 28.1, 17.6, 17.3, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{14}\text{H}_{30}\text{O}_3\text{Na}$ (M+Na $^+$) 269.2087, found 269.2084.

3-(*tert*-Butyl)-6,6-diethoxy-2,2-dimethylhexan-3-ol (2i)

Purification: 5% EtOAc/hexane. Colorless oil, 231 mg (from 5.0 mmol of ketone), 17%. ^1H NMR (500 MHz, DMSO- d_6) δ 4.40 (t, J = 5.0 Hz, 1H), 3.57–3.50 (m, 2H), 3.42–3.36 (m, 2H), 3.35 (s, 1H), 1.61–1.52 (m, 4H), 1.09 (t, J = 7.1 Hz, 6H), 0.97 (s, 18H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 103.3, 78.1, 60.4, 42.2, 30.4, 28.6, 27.4, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{16}\text{H}_{34}\text{O}_3\text{Na}$ (M+Na $^+$) 297.2400, found 297.2398.

2-Benzyl-5,5-diethoxy-1-phenylpentan-2-ol (2j)

Purification: 15% EtOAc/hexane. Colorless oil, 1.009 g (from 5.0 mmol of ketone), 59%. ^1H NMR (500 MHz, DMSO- d_6) δ 7.24 (d, J = 4.4 Hz, 8H), 7.19–7.15 (m, 2H), 4.29 (s, 1H), 4.23 (t, J = 5.6 Hz, 1H), 3.47–3.41 (m, 2H), 3.35–3.28 (m, 2H), 2.67 (d, J = 13.6 Hz, 2H), 2.63 (d, J = 13.6 Hz, 2H), 1.64–1.60 (m, 2H), 1.20–1.17 (m, 2H), 1.02 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 138.3, 130.6, 127.5, 125.8, 102.8, 73.3, 60.4, 45.3, 32.3, 28.0, 15.2. HRMS (ESI+) m/z calculated for $\text{C}_{22}\text{H}_{30}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$) 365.2087, found 365.2086.

1-(3,3-Diethoxypropyl)cyclohexanol (2k)

Purification: 25% EtOAc/hexane. Colorless oil, 656 mg (from 5.0 mmol of ketone), 57%. ^1H NMR (500 MHz, DMSO- d_6) δ 4.38 (t, J = 5.6 Hz, 1H), 3.83 (s, 1H), 3.55–3.49 (m, 2H), 3.42–3.36 (m, 2H), 1.60–1.49 (m, 4H), 1.45–1.37 (m, 3H), 1.33–1.29 (m, 4H), 1.25–1.16 (m, 3H), 1.09 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 102.8, 68.8, 60.1, 37.0, 36.9, 27.0, 25.7, 21.8, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{13}\text{H}_{26}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$) 253.1774, found 253.1772.

1-(3,3-Diethoxypropyl)-2,3-dihydro-1H-inden-1-ol (2l)

Purification: 25% EtOAc/hexane. Colorless oil, 684 mg (from 5.0 mmol of ketone), 52%. ^1H NMR (500 MHz, DMSO- d_6) δ 7.26–7.23 (m, 1H), 7.19–7.17 (m, 3H), 4.92 (s, 1H), 4.40 (t, J = 5.2 Hz, 1H), 3.54–3.47 (m, 2H), 3.40–3.34 (m, 2H), 2.89–2.84 (m, 1H), 2.73–2.67 (m, 1H), 2.12–2.07 (m, 1H), 2.00–1.94 (m, 1H), 1.74–1.70 (m, 1H), 1.64–1.55 (m, 2H), 1.53–1.47 (m, 1H), 1.073 (t, J = 7.0 Hz, 3H), 1.068 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, DMSO- d_6) δ 148.7, 142.3, 127.3, 126.1, 124.5, 123.1, 102.5, 81.5, 60.5, 60.2, 39.4, 35.4, 29.0, 28.4, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{16}\text{H}_{24}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$) 287.1618, found 287.1616.

2m

3-Chloro-1,1-diethoxypropane (2ma)

A solution of 3-chloropropionaldehyde diethylacetal (4.0 g, 24 mmol) and methanesulfonic acid (156 μ l, 2.4 mmol) in *n*-propanol was stirred at room temperature for 16 h. The volume of the mixture was slowly reduced to ca. 10 ml under reduced pressure at 42 °C. Sodium hydrogencarbonate (403 mg, 4.8 mmol) was then added and the remaining *n*-propanol removed under reduced pressure. Et₂O (20 ml) was added and the resulting solution washed with H₂O (3 x 10 ml), conc. aqueous Na₂CO₃ (5 ml), dried (MgSO₄), and the solvent was removed under reduced pressure. Purified by Kugelrohr distillation (80 °C, reduced pressure). Colorless oil, 3.80 g, 81%. ¹H NMR (400 MHz, CDCl₃) δ 4.66 (t, *J* = 5.6 Hz, 1H), 3.60–3.53 (m, 4 H), 3.42–3.37 (m, 2H), 2.05 (td, *J* = 6.6, 5.7 Hz, 2H), 1.63–1.54 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 100.7, 68.4, 40.9, 36.8, 23.1, 10.7.

3-Ethyl-6,6-dipropoxyhexan-3-ol (2m)

Representative procedure for compounds **2a–I** was followed using 3-chloro-1,1-diethoxypropane (**2ma**) and 3-pentanone as substrates. Purification: 15% EtOAc/hexane. Colorless oil, 1.08 g (from 8.125 mmol of ketone), 54%. ¹H NMR (500 MHz, DMSO-d₆) δ 4.38 (t, *J* = 5.6 Hz, 1H), 3.79 (s, 1H), 3.44 (dt, *J* = 9.3, 6.6 Hz, 2H), 3.30 (dt, *J* = 9.3, 6.6 Hz, 2H), 1.52–1.45 (m, 6H), 1.32–1.27 (m, 6H), 0.86 (t, *J* = 7.5 Hz, 6H), 0.75 (t, *J* = 7.5 Hz, 6H). ¹³C NMR (125 MHz, DMSO-d₆) δ 103.0, 72.1, 66.4, 32.5, 30.5, 27.4, 22.7, 10.7, 7.8. HRMS (ESI+) *m/z* calculated for C₁₄H₃₀O₃Na (M+Na⁺) 269.2087, found 269.2084.

2n

Ethyl 5,5-diethoxypentanoate (**2na**)

A solution of methyl 5,5-dimethoxypentanoate (1.76 g, 10 mmol), triethyl orthoformate (2 ml), and p-toluenesulfonic acid monohydrate (172 mg, 1 mmol) in ethanol (25 ml) was heated at reflux. The solvent was slowly distilled off to ca. 10 ml during 8 h. More ethanol (10 ml) was added and further 10 ml of solvent distilled off from the reaction mixture during 6 h. The reaction mixture was cooled to room temperature, sodium carbonate (106 mg, 1 mmol) added and solvent removed under reduced pressure. Diethyl ether (20 ml) was added to the residue, and the solution was washed with 0.5 M aqueous Na₂CO₃ solution (2 x 10 ml), water (3 x 10 ml), brine (10 ml), dried (MgSO₄), and concentrated under reduced pressure. Yellowish liquid, 2.17 g, 99%. ¹H NMR (500 MHz, DMSO-d₆) δ 4.43 (t, *J* = 4.9 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.57–3.50 (m, 2H), 3.42–3.36 (m, 2H), 2.28 (t, *J* = 6.8 Hz, 2H), 1.55–1.47 (m, 4H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (125 MHz, DMSO-d₆) δ 172.8, 101.8, 60.4, 59.6, 33.1, 32.4, 19.8, 15.3, 14.1. HRMS (ESI+) *m/z* calculated for C₁₁H₂₂O₄Na (M+Na⁺) 241.1410, found 241.1409.

5,5-Diethoxy-1,1-bis(4-fluorophenyl)pentan-1-ol (**2n**)

A solution of ethyl 5,5-diethoxypentanoate (**2na**, 437 mg, 2.0 mmol) in Et₂O (5 ml) was added to the 2 M solution of (4-fluorophenyl)magnesium bromide (1196 mg, 6.0 mmol) in Et₂O at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and 40 min at room temperature, then cooled to 0 °C and quenched with a concentrated ammonium chloride solution

(5 ml). Diethyl ether (10 ml) and water (5 ml) were added to the mixture. The organic layer was separated, washed with concentrated sodium carbonate solution (5 ml), dried (MgSO_4), and concentrated under reduced pressure. Purification by silica gel chromatography (15% EtOAc/hexane) yielded a colorless oil, 541 mg, 74%. ^1H NMR (500 MHz, DMSO-d_6) δ 7.44–7.40 (m, 4H), 7.09–7.04 (m, 4H), 5.59 (s, 1H), 4.37 (t, $J = 5.6$ Hz, 1H), 3.51–3.45 (m, 2H), 3.39–3.31 (m, 2H), 2.21–2.17 (m, 2H), 1.50–1.46 (m, 2H), 1.23–1.16 (m, 2H), 1.03 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.6 (d, $J = 242.5$ Hz), 144.5 (d, $J = 2.5$ Hz), 127.7 (d, $J = 7.8$ Hz), 114.4 (d, $J = 20.9$ Hz), 102.1, 75.9, 60.4, 41.0, 33.5, 18.7, 15.3. HRMS (EI (DE)) m/z calculated for $\text{C}_{21}\text{H}_{26}\text{O}_3\text{F}_2$ (M) 364.1850, found 364.1849.

2o

(1-(2,2-Diethoxyethyl)cyclohexyl)methanol (2o)

a) A 2.5 M solution of *n*-BuLi (11.8 ml, 29.4 mmol) in hexanes was added dropwise to a solution of diisopropyl amine (4.53 ml, 32.3 mmol) in dry THF (28 ml) at 0 °C and stirred for 30 min at 0 °C. Then a solution of cyclohexanecarboxylic acid (1.79 g, 14 mmol) in THF (3 ml) was added and the mixture stirred for 30 min at 0 °C and 2 h at room temperature. b) The mixture was cooled to 0 °C and bromoacetaldehyde diethyl acetal (2.32 ml, 3.03 g, 15.4 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C and 12 h at room temperature. c) Lithium aluminum hydride (1.06 g, 28 mmol) was added in small portions and the reaction mixture stirred at 50 °C for 2.5 h. The mixture was cooled to room temperature and poured slowly on the mixture of water (50 ml) and diethyl ether (150 ml). The organic layer was separated by decantation, and the aqueous slurry extracted with diethyl ether (6 x 25 ml). The combined

organic extracts were washed with concentrated aqueous sodium carbonate solution (2 x 25 ml), dried (MgSO_4), and concentrated directly prior to purification. Purification by silica gel chromatography (hexane/EtOAc/MeOH 9:1:0.2, $R_f = 0.31$) yielded a colorless oil, 1.31 g, 41%. ^1H NMR (500 MHz, DMSO-d_6) δ 4.56 (t, $J = 5.3$ Hz, 1H), 4.26 (t, $J = 5.3$ Hz, 1H), 3.56–3.50 (m, 2H), 3.42–3.36 (m, 2H), 3.23 (d, $J = 5.4$ Hz, 2H), 1.51 (d, $J = 5.3$ Hz, 2H), 1.39–1.34 (m, 5H), 1.29–1.22 (m, 5H), 1.08 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 100.3, 66.8, 60.2, 38.2, 36.0, 32.5, 26.0, 21.2, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{13}\text{H}_{26}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}^+$) 253.1774, found 253.1774.

2p

4,4-Diethoxybutan-1-ol (2p)

a) A 1.0 M solution of DIBAL (6 ml, 6.0 mmol) in toluene was added to a solution of 3-cyanopropionaldehyde diethyl acetal (943 mg, 6.0 mmol) in dry DCM (30 ml) at $-78\text{ }^{\circ}\text{C}$ and stirred for 1.5 h at $-78\text{ }^{\circ}\text{C}$. The mixture was allowed to warm to room temperature, treated with concentrated aqueous ammonium chloride solution (10 ml) and water (10 ml), and extracted with DCM (3 x 20 ml). The combined organic extracts were washed with brine (2 x 20 ml), dried (MgSO_4), and concentrated. b) The oily residue was dissolved in methanol (10 ml), NaBH_4 (227 mg, 6 mmol) was added and the mixture was stirred at room temperature. After 1 h water (10 ml) was added to the mixture, methanol was removed under reduced pressure, and the resulting mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with concentrated aqueous sodium carbonate solution (10 ml), dried (MgSO_4), and concentrated. Purification by silica gel chromatography (50% EtOAc/hexane) yielded a colorless oil, 407 mg, 42%. ^1H NMR (500 MHz, DMSO-d_6) δ 4.43 (t, $J = 5.6$ Hz, 1H), 4.37 (t, $J = 5.2$ Hz, 1H), 3.56–3.50 (m, 2H), 3.43–3.35 (m, 4H), 1.53–1.48 (m, 2H), 1.43–1.38 (m, 2H), 1.09 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 102.1, 60.5, 60.3, 29.9, 27.8, 15.3. HRMS (CI (FE) *i*-butane) m/z calculated for $\text{C}_8\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$) 163.1334, found 163.1332.

Products

General procedure for catalytic enantioselective intramolecular transacetalization

Molecular sieves 4 Å (150 mg) and a solution of (S)-TRIP (2.38 mg, 0.003 mmol, co-crystallized with CH₃CN 1:1) in dry benzene (4 ml), were added to the solution of **2** (0.3 mmol) in dry benzene (8 ml) and stirred at 20 °C. Et₃N (42 µl) was added to the reaction mixture after complete conversion of the starting material (in most cases within 9–24 h).ⁱ

– For non-volatile products:ⁱⁱ The reaction mixture was concentrated under reduced pressure and the product was purified by silica gel (5 g) chromatography with EtOAc/hexane as the eluent.ⁱⁱⁱ

– For volatile products:ⁱⁱ The reaction mixture was directly loaded on silica gel (5 g, preconditioned with pentane) column. The crude mixture was first eluted with some pentane to remove benzene, and then with Et₂O/pentane to isolate the product.ⁱⁱⁱ

Notes:

- *i*) Reaction progress monitored by TLC (EtOAc/hexane), visualization: UV (254 nm) and/or PMA stain.
- *ii*) Use of DCM or CHCl₃ as a solvent during sample preparation for the chiral GC might lead to product epimerization as these solvents tend to contain HCl as an impurity.
- *iii*) Molecular sieves hinder solvent flow when the crude reaction mixture is loaded onto the column. For reactions on a larger scale, a small pad of Celite on top of the silica column was used to prevent column clogging.

Preparation of the racemates

Diphenyl phosphate (1.25 mg, 0.005 mmol) was added to the solution of **2** (0.025 mmol) in benzene (1 ml). After 1h sample of the product for HPLC was isolated by TLC (eluent as used for purification of enantioenriched products).

(R)-5-Ethoxy-2,2-diphenyltetrahydrofuran (3a)

Reaction time: 24 h. Purification: 3% EtOAc/hexane. Colorless oil, 76.7 mg, 95%.

^1H NMR (400 MHz, CD_2Cl_2) δ 7.46–7.41 (m, 4H), 7.31–7.27 (m, 4H), 7.22–7.17 (m, 2H), 5.35 (dd, $J = 5.0, 1.9$ Hz, 1H), 3.87–3.80 (m, 1H), 3.57–3.49 (m, 1H),

2.72–2.65 (m, 1H), 2.61–2.55 (m, 1H) 2.04–1.90 (m, 2H), 1.13 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 147.8, 147.2, 128.35, 128.25, 126.94, 126.92, 126.4, 126.0, 104.5, 89.3, 63.3, 37.5, 32.9, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{18}\text{H}_{20}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$) 291.1356, found 291.1358. HPLC (OJ-H), *n*-heptane/*i*-PrOH 90:10, 0.5 ml/min, $\lambda = 210$ nm, $t_{\text{minor}} = 15.3$ min, $t_{\text{major}} = 28.2$ min, er = 94.5:5.5.

(R)-5-Ethoxy-2,2-bis(4-methoxyphenyl)tetrahydrofuran (3b)

Reaction time: 24 h. Purification: 10% EtOAc/hexane. Colorless oil, 94.1 mg,

96%. ^1H NMR (400 MHz, CD_2Cl_2) δ 7.34–7.27 (m, 4H), 6.83–6.79 (m, 4H)

5.31 (dd, $J = 5.2, 2.0$ Hz, 1H), 3.86–3.78 (m, 1H), 3.77 (s, 3H), 3.76 (s, 3H),

3.55–3.48 (m, 1H), 2.65–2.58 (m, 1H), 2.53–2.47 (m, 1H), 2.03–1.88 (m, 2H),

1.15 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 158.70, 158.68, 140.2, 127.7, 127.2, 113.55, 113.45, 104.5, 88.9, 63.2, 55.5, 37.8, 33.0, 15.4. HRMS (ESI+) m/z calculated for $\text{C}_{20}\text{H}_{24}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$)

351.1567, found 351.1563. HPLC (OJ-H), *n*-heptane/*i*-PrOH 60:40, 0.5 ml/min, λ = 210 nm, t_{minor} = 22.5 min, t_{major} = 32.9 min, er = 95.5:4.5.

(*R*)-5-Ethoxy-2,2-bis(4-fluorophenyl)tetrahydrofuran (3c)

Reaction time: 24 h. Purification: 5% EtOAc/hexane. Colorless oil, 89.4 mg, 98%.

^1H NMR (400 MHz, CD_2Cl_2) δ 7.42–7.34 (m, 4H), 7.01–6.95 (m, 4H), 5.33 (dd, J = 5.1, 2.2 Hz, 1H), 3.84–3.76 (m, 1H), 3.55–3.48 (m, 1H), 2.69–2.62 (m, 1H), 2.55–2.49 (m, 1H), 2.03–1.90 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100

MHz, CD_2Cl_2) δ 162.0 (d, J = 244.1 Hz), 143.5 (d, J = 3.2 Hz), 142.8 (d, J = 3.1 Hz), 128.2 (d, J = 8.0 Hz), 127.8 (d, J = 8.0 Hz), 115.0 (d, J = 21.3 Hz), 114.9 (d, J = 21.2 Hz), 104.6, 88.5, 63.4, 37.9, 32.9, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{F}_2\text{Na}$ ($\text{M}+\text{Na}^+$) 327.1167, found 327.1168. HPLC (OJ-H), *n*-heptane/*i*-PrOH 98:2, 0.5 ml/min, λ = 210 nm, t_{minor} = 12.3 min, t_{major} = 14.8 min, er = 97:3.

(*R*)-2,2-Bis(4-bromophenyl)-5-ethoxytetrahydrofuran (3d)

Reaction performed on 0.9 mmol scale. Reaction time: 24 h. Purification: 5%

EtOAc/hexane. Colorless oil, 381 mg, 99% (Crystallizes at $-20\text{ }^\circ\text{C}$, remains solid when reheated to room temperature). ^1H NMR (500 MHz, CD_2Cl_2) δ 7.43–4.41

(m, 4H), 7.32–7.26 (m, 4H), 5.33 (dd, J = (overlap), 2.0 Hz, 1H), 3.81–3.75 (m,

1H), 3.54–3.48 (m, 1H), 2.68–2.62 (m, 1H), 2.53–2.48 (m, 1H), 2.01–1.90 (m, 2H), 1.12 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 146.4, 145.8, 131.5, 131.4, 128.3, 127.9, 121.0, 104.6, 88.4, 63.4,

37.5, 32.8, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$) 446.9566, found 446.9570.

HPLC (OJ-H), *n*-heptane/*i*-PrOH 98:2, 0.5 ml/min, λ = 220 nm, t_{minor} = 11.8 min, t_{major} = 13.0 min, er = 97:3.

(R)-5'-Ethoxy-4',5'-dihydro-3'H,10H-spiro[anthracene-9,2'-furan] (3e)

Reaction time: 7 days. Purification: 30% CH₂Cl₂/hexane. Colorless oil, 72.1 mg, 86%. To remove the solvent from the product, the sample was dissolved several times in Et₂O and concentrated. Further extensive drying of this product resulted in the formation of a small amount of impurity (see Copies of NMR Spectra). ¹H NMR (500 MHz, CD₂Cl₂) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.34–7.21 (m, 6H), 5.68 (d, *J* = 5.0 Hz, 1H), 4.22–4.15 (m, 1H), 4.01 (d, *J* = 17.9 Hz, 1H), 3.92 (d, *J* = 17.9 Hz, 1H), 3.79–3.73 (m, 1H), 2.17–2.10 (m, 1H), 2.10–2.02 (m, 1H), 2.02–1.96 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, CD₂Cl₂) δ 144.3, 143.4, 134.7, 134.6, 127.7, 127.2, 126.9, 126.8, 126.3, 124.2, 124.0, 105.8, 86.1, 64.0, 37.9, 36.0, 32.0, 15.5. HRMS (ESI+) *m/z* calculated for C₁₉H₂₀O₂Na (M+Na⁺) 303.1355, found 303.1355. HPLC (OD-3), *n*-heptane/*i*-PrOH 90:10, 0.5 ml/min, λ = 210 nm, *t*_{minor} = 5.50 min, *t*_{major} = 6.58 min, er = 95.5:4.5.

(R)-5-Ethoxy-2,2-dimethyltetrahydrofuran (3f)

Reaction time: 10 h. Purification: 10% Et₂O/pentane. Colorless oil, 38.3 mg, 84%. ¹H NMR (500 MHz, CD₂Cl₂) δ 5.01 (d, *J* = 4.9 Hz, 1H), 3.71–3.65 (m, 1H), 3.38–3.32 (m, 1H), 2.05–1.98 (m, 1H), 1.91–1.84 (m, 2H), 1.71–1.66 (m, 1H), 1.31 (s, 3H), 1.17 (s, 3H), 1.14 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CD₂Cl₂) δ 104.2, 82.1, 62.3, 36.6, 33.4, 30.1, 28.9, 15.4. HRMS (EI (FE) *i*-butane) *m/z* calculated for C₈H₁₇O₂ (M+H) 145.1228, found 145.1227. Chiral GC (Column: 29.5 m BGB-176 SE/SE52 (2,3-dimethyl-6-*tert*-butyldimethylsilyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.15 μm; Detector: FID; Temperature: injector 230 °C, detector 350 °C, oven 60 °C; gas: 0.6 bar H₂), *t*_{minor} = 4.76 min, *t*_{major} = 5.57 min, er = 94.5:5.5.

(R)-5-Ethoxy-2,2-diethyltetrahydrofuran (3g)

Reaction time: 16 h. Purification: 3% EtOAc/hexane. Colorless oil, 47.6 mg, 92%. ^1H

NMR (500 MHz, CD_2Cl_2) δ 5.02 (d, $J = 4.9$ Hz, 1H), 3.73–3.66 (m, 1H), 2.38–3.32 (m, 1H), 1.98–1.90 (m, 1H), 1.86–1.75 (m, 2H), 1.69–1.51 (m, 3H), 1.51–1.38 (m, 2), 1.13 (t, $J = 7.1$ Hz, 3H), 0.87 (t, $J = 7.5$ Hz, 3H), 0.82 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 104.0, 87.6, 62.3, 33.3, 33.0, 32.5, 30.8, 15.4, 8.9, 8.7. HRMS (EI (FE) *i*-butane) m/z calculated for $\text{C}_{10}\text{H}_{21}\text{O}_2$ ($\text{M}+\text{H}$) 173.1542, found 173.1540. Chiral GC (Column: 29.5 m BGB-176 SE/SE52 (2,3-dimethyl-6-*tert*-butyldimethylsilyl- β -cyclodextrin), i.D. 0.25 mm, df. 0.15 μm ; Detector: FID; Temperature: injector 220 $^\circ\text{C}$, detector 320 $^\circ\text{C}$, oven 90 $^\circ\text{C}$; gas: 0.8 bar H_2), $t_{\text{minor}} = 5.49$ min, $t_{\text{major}} = 5.98$ min, er = 97:3.

(R)-5-Ethoxy-2,2-diisopropyltetrahydrofuran (3h)

Reaction time: 12 h. Purification: 10% Et_2O /pentane. Colorless oil, 55.8 mg, 93%. ^1H

NMR (500 MHz, CD_2Cl_2) δ 5.05 (d, $J = 5.8$ Hz, 1H), 3.75–3.69 (m, 1H), 3.39–3.33 (m, 1H), 2.06–1.99 (m, 1H), 2.00–1.85 (m, 2H), 1.85–1.73 (m, 2H), 1.62–1.57 (m, 1H) 1.14 (t, $J = 7.1$ Hz, 3H), 0.91 (t, $J = 7.6$ Hz, 6H), 0.83 (t, $J = 6.7$ Hz, 6H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 105.3, 93.1, 62.9, 34.7, 34.3, 33.9, 26.4, 18.4, 18.2, 17.9, 17.7, 15.3. HRMS (ESI+) m/z calculated for $\text{C}_{12}\text{H}_{24}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}^+$) 223.1669, found 223.1667. Chiral GC (Column: 29.5 m BGB-176 SE/SE52 (2,3-dimethyl-6-*tert*-butyldimethylsilyl- β -cyclodextrin), i.D. 0.25 mm, df. 0.15 μm ; Detector: FID; Temperature: injector 250 $^\circ\text{C}$, detector 350 $^\circ\text{C}$, oven 100 $^\circ\text{C}$; gas: 0.6 bar H_2), $t_{\text{minor}} = 9.02$ min, $t_{\text{major}} = 9.28$ min, er = 98:2.

(R)-2,2-Di-*tert*-butyl-5-ethoxytetrahydrofuran (3i)

Reaction time: 9 h. Purification: 2% EtOAc/hexane. Colorless oil, 61.7 mg, 90%. ^1H

NMR (500 MHz, CD_2Cl_2) δ 5.13 (dd, $J = 6.5$ Hz, 4.0 Hz, 1H), 3.79–3.73 (m, 1H), 3.45–3.39 (m, 1H), 2.17–2.10 (m, 1H), 1.98–1.92 (m, 1H), 1.86–1.80 (m, 1H), 1.78–1.71 (m, 1H), 1.16 (t, $J = 7.1$ Hz, 3 H), 1.06 (s, 9H), 1.00 (s, 9H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 107.0, 96.8, 63.7, 42.5,

41.0, 34.7, 29.6, 29.2, 28.7, 15.5. HRMS (ESI+) m/z calculated for $C_{14}H_{28}O_2Na$ ($M+Na^+$) 251.1981, found 251.1977. Chiral GC (Column: 30 m BGB-176 SE/SE52 (2,3-dimethyl-6-*tert*-butyldimethylsilyl- β -cyclodextrin), i.D. 0.25 mm, df. 0.25 μ m; Detector: FID; Temperature: injector 230 °C, detector 350 °C, oven 90 °C; gas: 0.5 bar H_2), t_{minor} = 65.11 min, t_{major} = 66.38 min, er = 98:2.

(*R*)-2,2-Dibenzyl-5-ethoxytetrahydrofuran (3j)

Reaction time: 14 h. Purification: 5% EtOAc/hexane. Colorless oil, 87.2 mg,

98%. 1H NMR (500 MHz, CD_2Cl_2) δ 7.34–7.29 (m, 4H), 7.25–7.17 (m, 6H),

4.90 (d, J = 5.0 Hz, 1H), 3.85–3.78 (m, 1H), 3.44–3.37 (m, 1H), 3.04 (d, J =

13.6 Hz, 1H), 2.94 (d, J = 13.6 Hz, 1H), 2.73 (d, J = 13.6 Hz, 1H), 2.56 (d, J = 13.6 Hz, 1H), 1.99–1.93

(m, 1H), 1.79–1.75 (m, 1H), 1.56–1.52 (m, 1H), 1.14 (t, J = 7.1 Hz, 3H), 1.02–0.94 (m, 1H). ^{13}C NMR

(125 MHz, CD_2Cl_2) δ 138.9, 138.6, 131.0, 130.9, 128.2, 128.1, 126.5, 126.4, 104.8, 87.3, 62.8, 49.2,

45.3, 33.1, 32.4, 15.4. HRMS (ESI+) m/z calculated for $C_{20}H_{24}O_2Na$ ($M+Na^+$) 319.1668, found

319.1668. HPLC (OJ-H), *n*-heptane/*i*-PrOH 98:2, 0.5 ml/min, λ = 220 nm, t_{minor} = 9.6 min, t_{major} = 11.9

min, er = 97:3.

(*R*)-2-Ethoxy-1-oxaspiro[4.5]decane (3k)

Reaction time: 12 h. Purification: 10% Et_2O /pentane. Colorless oil, 52.0 mg, 94%. 1H

NMR (500 MHz, CD_2Cl_2) δ 5.01 (d, J = 4.9 Hz, 1H), 3.72–3.66 (m, 1H), 3.39–3.32

(m, 1H), 1.99–1.91 (m, 1H), 1.88–1.83 (m, 1H), 1.81–1.75 (m, 1H), 1.72–1.68 (m, 1H), 1.68–1.61 (m,

3H), 1.59–1.54 (m, 1H), 1.50–1.46 (m, 1H), 1.43–1.36 (m, 5H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125

MHz, CD_2Cl_2) δ 103.6, 84.2, 62.2, 40.1, 38.2, 34.4, 32.8, 26.0, 24.3, 15.5. HRMS (EI (FE)) m/z

calculated for $C_{11}H_{20}O_2$ (M) 184.1463, found 184.1465. Chiral GC (Column: 29.5 m BGB-176 SE/SE52

(2,3-dimethyl-6-*tert*-butyldimethylsilyl- β -cyclodextrin), i.D. 0.25 mm, df. 0.25 μ m; Detector: FID;

Temperature: injector 220 °C, detector 320 °C, oven 90 °C; gas: 0.8 bar H₂), $t_{\text{minor}} = 10.06$ min, $t_{\text{major}} = 10.34$ min, er = 97:3.

(1'*S*,5*R*)-5-Ethoxy-2',3',4,5-tetrahydro-3H-spiro[furan-2,1'-indene] + (1'*R*,5*R*)-5-ethoxy-2',3',4,5-tetrahydro-3H-spiro[furan-2,1'-indene] (3l)

Reaction time: 20 h. Purification: 8% EtOAc/hexane.

Colorless oil, 62.9 mg, 96%. ¹H NMR (500 MHz, CD₂Cl₂) δ 7.36–7.33 (m, 0.49H, major isomer), 7.25–7.18 (m, 3.26H), 5.26 (dd, $J = 5.3, 2.0$ Hz, 0.45H, minor isomer), 5.17 (dd, $J =$

4.1, 0.9 Hz, 0.50H, major isomer), 3.80–3.73 (m, 1H), 3.48–3.40 (m, 1H), 3.00–2.91 (m, 1H), 2.85–2.76 (m, 1H), 2.36–2.27 (m, 1H), 2.25–2.01 (m, 5H), 1.23 (t, $J = 7.1$ Hz, 1.56H, major isomer), 1.19 (t, $J = 7.1$ Hz, 1.41H, minor isomer). ¹³C NMR (125 MHz, CD₂Cl₂) δ 147.8, 147.1, 143.6, 143.2, 128.3, 128.0, 127.1, 126.9, 125.0, 124.8, 124.0, 123.0, 104.6, 103.9, 93.8, 92.8, 63.0, 62.7, 41.4, 40.7, 36.3, 36.1, 33.9, 33.8, 30.2, 29.7, 15.5, 15.4. Diastereomeric ratio = 1.1:1, determined by ¹H NMR, protons on acetal carbon stereocenter, δ 5.26 (0.4519H) and δ 5.17 (0.4957H). Relative stereochemistry of diastereomers determined by NOESY experiment: only one of the acetal protons, the one of minor diastereomer (δ 5.26) has a cross-peak with aromatic proton indicating *trans* relationship between OEt and aromatic substituent (see the copy of NOESY spectra). HRMS (ESI+) m/z calculated for C₁₄H₁₈O₂Na (M+Na⁺) 241.1199, found 241.1198. Chiral GC for *cis* diastereomer (Column: 30 m Chiraldex G-BP (gamma-cyclodextrin-butyryl), i.D. 0.25 mm, df. 0.25 μ m; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 80 °C; gas: 0.9 bar H₂), $t_{\text{major}} = 211.3$ min, $t_{\text{minor}} = 225.1$ min, er (*cis*) = 91:9. Chiral GC for *trans* diastereomer (Column: 24.8 m Hydrodex-B-TBDAC-CD (Heptakis-(2,3-di-*O*-acetyl-6-*O*-*t*-butyldimethyl-silyl)- β -cyclodextrin), i.D. 0.25 mm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 100 °C; gas: 0.5 bar H₂), $t_{\text{major}} = 109.0$ min, $t_{\text{minor}} = 112.4$ min, er (*trans*) = 96:4.

(R)-2,2-diethyl-5-propoxytetrahydrofuran (3m)

Reaction time: 24 h. Purification: 10% Et₂O/pentane. Colorless oil, 54.5 mg, 95%. ¹H NMR (400 MHz, CD₂Cl₂) δ 5.01 (dd, *J* = 4.9, 1.1 Hz, 1H), 3.60 (dt, *J* = 9.4, 6.8 Hz, 1H), 3.25 (dt, *J* = 9.4, 6.6 Hz, 1H), 1.99–1.90 (m, 1H), 1.88–1.82 (m, 1H), 1.82–1.74 (m, 1H), 1.70–1.51 (m, 5H), 1.51–1.38 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (100 MHz, CD₂Cl₂) δ 104.4, 87.7, 68.8, 33.4, 33.0, 32.7, 30.8, 23.4, 10.9, 9.0, 8.7. HRMS (CI (FE) *i*-butane) *m/z* calculated for C₁₁H₂₃O₂ (M+H) 187.1698, found 187.1697. Chiral GC (Column: 30 m BGB-177/BGB-15 (2,6-dimethyl-3-pentyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.25 μm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 115 °C; gas: 0.6 bar H₂), *t*_{minor} = 7.06 min, *t*_{major} = 7.34 min, er = 95:5.

(R)-6-Ethoxy-2,2-bis(4-fluorophenyl)tetrahydro-2H-pyran (3n)

Reaction time: 4 days. Purification: 5% EtOAc/hexane. Colorless oil, 92.1 mg, 96%. ¹H NMR (500 MHz, CD₂Cl₂) δ 7.43–7.39 (m, 2H), 7.32–7.28 (m, 2H), 7.09–7.04 (m, 2H), 6.97–6.92 (m, 2H), 4.46 (dd, *J* = 9.7, 2.1 Hz, 1H), 4.07–4.01 (m, 1H), 3.51–3.44 (m, 1H), 2.61–2.57 (m, 1H), 1.86–1.81 (m, 1H), 1.79–1.66 (m, 3H), 1.54–1.46 (m, 1H), 1.21 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CD₂Cl₂) δ 162.1 (d, *J* = 246.2 Hz), 161.7 (d, *J* = 243.9 Hz), 145.2 (d, *J* = 2.7 Hz), 139.4 (d, *J* = 3.3 Hz), 129.2 (d, *J* = 8.1 Hz), 126.9 (d, *J* = 7.7 Hz), 115.7 (d, *J* = 21.8 Hz), 114.9 (d, *J* = 21.1 Hz), 97.9, 80.3, 64.1, 34.9, 31.5, 20.1, 15.5. HRMS (EI (DE)) *m/z* calculated for C₁₉H₂₀O₂F₂ (M) 318.1431, found 318.1431. HPLC (OJ-H), *n*-heptane/*i*-PrOH 99.7:0.3, 0.5 ml/min, λ = 220 nm, *t*_{minor} = 13.9 min, *t*_{major} = 17.3 min, er = 82:18.

(R)-3-Ethoxy-2-oxaspiro[4.5]decane (3o)

Reaction time: 30 min. Purification: 10% Et₂O/pentane. Colorless oil, 51.9 mg, 94%.

¹H NMR (500 MHz, CD₂Cl₂) δ 5.07 (dd, *J* = 5.8, 2.6 Hz, 1H), 3.70–3.64 (m, 1H), 3.60 (d, *J* = 8.3 Hz, 1H), 3.56 (d, *J* = 8.3 Hz, 1H), 3.41–3.34 (m, 1H), 1.89 (dd, *J* = 13.3, 5.7 Hz, 1H), 1.60 (dd, *J* = 13.3, 2.6 Hz, 1H), 1.53–1.36 (m, 10 H), 1.15 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (125 MHz, CD₂Cl₂) δ 104.7, 77.1, 63.1, 45.5, 43.1, 37.2, 36.4, 26.3, 24.5, 23.9, 15.5. HRMS (ESI+) *m/z* calculated for C₁₁H₂₀O₂Na (M+Na⁺) 207.1356, found 207.1355. Chiral GC (Column: 29.5m BGB-176 SE/SE52 (2,3-dimethyl-6-*tert*-butyldimethylsilyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.15 μm; Detector: FID; Temperature: injector 220 °C, detector 350 °C, oven 110 °C; gas: 0.5 bar H₂), *t*_{minor} = 14.64 min, *t*_{major} = 15.19 min, er = 82.5:17.5.

(R)-2-Ethoxytetrahydrofuran (3p)

Reaction time: 7 h. Purification: product is highly volatile but it can be isolated as a solution in organic solvent (e.g. dichloromethane): (1/6 (2 ml) of the reaction mixture was directly loaded on silica gel (0.5 g, preconditioned with pentane) column and product eluted with CD₂Cl₂). Yield 76%: determined by ¹H NMR using Ph₃CH (0.05 mmol) as internal standard and comparing relative area of Ph₃CH and proton on acetal carbon stereocenter. ¹H NMR (500 MHz, CD₂Cl₂) δ 5.08 (dd, *J* = 4.7, 1.4 Hz, 1H), 3.85–3.78 (m, 2H), 3.69–3.63 (m, 1H), 3.42–3.36 (m, 1H), 1.97–1.86 (m, 2H), 1.84–1.76 (m, 2H), 1.14 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (125 MHz, CD₂Cl₂) δ 103.9, 67.0, 62.7, 32.7, 23.9, 15.4. GC-MS (EI) *m/z* 116. Chiral GC (Column: 30 m BGB-176 SE/SE52 (2,3-dimethyl-6-*tert*-butyldimethylsilyl-β-cyclodextrin), i.D. 0.25 mm, df. 0.25 μm; Detector: FID; Temperature: injector 220 °C, detector 320 °C, oven 70 °C; gas: 0.5 bar H₂), *t*_{minor} = 5.20 min, *t*_{major} = 5.79 min, er = 79:21.

X-Ray Data for Compound **3d**

Absolute configuration determination of **3d** by X-ray single-crystal structure analysis

Figure 1. Crystal structure of **3d**, showing the absolute configuration of the sample. Anisotropic displacement parameters are drawn at the 50% probability level and hydrogen atoms omitted for clarity.

Crystals of **3d** were obtained as fine needles after keeping the oil in the freezer at $-20\text{ }^{\circ}\text{C}$. The compound remains solid when warmed up to room temperature. More crystals in the form of prisms were obtained by dissolving a few milligrams of the product in dichloromethane, evaporating the solvent, and keeping the remaining oil at $-20\text{ }^{\circ}\text{C}$ overnight. The absolute configurations of four crystals picked at random from the sample were investigated, and all showed the configuration shown in Figure 1. The Flack parameter x and the Hooft factor y for the four crystals were as follows: (1) $x = -0.018(12)$ (3048 reflections), $y = -0.026(4)$ (1447 Bijvoet pairs)(Cu); (2) $x = -0.009(11)$ (6792 reflections), $y = -0.0120(1)$ (3304 Bijvoet pairs)(Mo); (3) $x = -0.07(4)$ (2168 reflections), $y = -0.096(22)$ (1036 Bijvoet pairs)(Cu); (4) $x = -0.003(20)$ (2797 reflections), $y = -0.004(12)$ (1226 Bijvoet pairs)(Cu).

X-ray Crystal Structure Analysis of 3d: [C₁₈H₁₈Br₂O₂], $M_r = 426.14 \text{ g} \cdot \text{mol}^{-1}$, colorless prism, crystal size 0.060 x 0.204 x 0.573 mm³, tetragonal, space group $P4_1$, $a = 10.8373(9) \text{ \AA}$, $c = 14.8921(13) \text{ \AA}$, $V = 1749.0(3) \text{ \AA}^3$, $T = 100 \text{ K}$, $Z = 4$, $D_{\text{calc}} = 1.618 \text{ g} \cdot \text{cm}^{-3}$, $\lambda = 1.54178 \text{ \AA}$, $\mu = 5.909 \text{ mm}^{-1}$, Gaussian absorption correction ($T_{\text{min}} = 0.10636$, $T_{\text{max}} = 0.70728$), scaling SADABS, Bruker AXS ProteumX8 diffractometer, $4.08 < \theta < 66.52^\circ$, 40020 measured reflections, 3048 independent reflections, 3046 reflections with $I > 2\sigma(I)$, $R_{\text{int}} = 0.0405$. Structure solved by direct methods and refined by full-matrix least-squares against F^2 to $R_1 = 0.0168 [I > 2\sigma(I)]$, $wR_2 = 0.0407$, 200 parameters.² The Flack parameter is -0.018(12).³ The Hooft factor y based on 1447 Bijvoet pairs is -0.026(4).⁴ H atoms riding, $S = 1.133$, residual electron density +0.26 / -0.22 e $\text{\AA}^{-3}$. CCDC 771853.

The supplementary crystallographic data for 3d (CCDC 771853 can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

² Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.

³ Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.

⁴ Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Cryst.* **2008**, *41*, 96.

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{18}H_{18}Br_2O_2$	
Color	colourless	
Formula weight	$426.14 \text{ g} \cdot \text{mol}^{-1}$	
Temperature	100 K	
Wavelength	$1.54178 \text{ \AA}$	
Crystal system	Tetragonal	
Space group	P4₁, (no. 76)	
Unit cell dimensions	$a = 10.8373(9) \text{ \AA}$	$\alpha = 90^\circ$
	$b = 10.8373(9) \text{ \AA}$	$\beta = 90^\circ$
	$c = 14.8921(13) \text{ \AA}$	$\gamma = 90^\circ$
Volume	$1749.0(3) \text{ \AA}^3$	
Z	4	
Density (calculated)	$1.618 \text{ Mg} \cdot \text{m}^{-3}$	
Absorption coefficient	5.909 mm^{-1}	
F(000)	848 e	
Crystal size	$0.973 \times 0.204 \times 0.060 \text{ mm}^3$	
θ range for data collection	4.08 to 66.52°	
Index ranges	$-12 \leq h \leq 12, -12 \leq k \leq 12, -17 \leq l \leq 17$	
Reflections collected	40020	
Independent reflections	3048 [$R_{\text{int}} = 0.0405$]	
Reflections with $I > 2\sigma(I)$	3046	
Completeness to $\theta = 66.52^\circ$	99.6 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.71 and 0.11	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3048 / 1 / 200	
Goodness-of-fit on F^2	1.133	
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0168$	$wR^2 = 0.0407$
R indices (all data)	$R_1 = 0.0168$	$wR^2 = 0.0407$
Absolute structure parameter	$-0.018(12)$	
Largest diff. peak and hole	0.256 and $-0.216 \text{ e} \cdot \text{\AA}^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($\text{\AA}^2$).

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
Br(1)	0.0872(1)	-0.3557(1)	1.1153(1)	0.033(1)
Br(2)	0.3290(1)	0.1452(1)	0.5970(1)	0.036(1)
C(1)	0.2644(2)	0.1691(2)	1.0105(2)	0.022(1)
C(2)	0.1805(2)	0.2743(2)	1.0443(2)	0.026(1)
C(3)	0.2454(2)	0.3136(2)	1.1306(2)	0.028(1)
C(4)	0.3788(2)	0.2997(2)	1.1047(2)	0.024(1)
C(5)	0.5412(2)	0.4053(2)	1.0296(2)	0.033(1)
C(6)	0.5751(2)	0.5339(2)	1.0007(2)	0.038(1)
C(7)	0.2797(2)	0.1664(2)	0.9089(2)	0.023(1)
C(8)	0.3915(2)	0.1288(2)	0.8713(2)	0.024(1)
C(9)	0.4060(2)	0.1220(2)	0.7788(2)	0.027(1)
C(10)	0.3082(2)	0.1537(2)	0.7241(2)	0.028(1)
C(11)	0.1959(2)	0.1907(2)	0.7589(2)	0.031(1)
C(12)	0.1829(2)	0.1961(2)	0.8519(2)	0.027(1)
C(13)	0.2198(2)	0.0419(2)	1.0420(1)	0.020(1)
C(14)	0.2959(2)	-0.0374(2)	1.0902(2)	0.024(1)
C(15)	0.2555(2)	-0.1547(2)	1.1144(2)	0.026(1)
C(16)	0.1389(2)	-0.1914(2)	1.0901(1)	0.025(1)
C(17)	0.0600(2)	-0.1141(2)	1.0436(2)	0.026(1)
C(18)	0.1011(2)	0.0015(2)	1.0195(2)	0.025(1)
O(1)	0.3837(1)	0.1913(1)	1.0508(1)	0.023(1)
O(2)	0.4137(1)	0.4050(1)	1.0552(1)	0.025(1)

Table 3. Bond lengths [Å] and angles [°].

Br(1)-C(16)	1.9047(19)	Br(2)-C(10)	1.908(2)	C(1)-
O(1)	1.446(2)	C(1)-C(7)	1.523(3)	C(1)-
C(13)	1.534(3)	C(1)-C(2)	1.543(3)	C(2)-
C(3)	1.526(3)	C(3)-C(4)	1.504(3)	C(4)-
O(2)	1.411(3)	C(4)-O(1)	1.424(3)	C(5)-
O(2)	1.434(3)	C(5)-C(6)	1.504(3)	C(7)-
C(12)	1.387(3)	C(7)-C(8)	1.395(3)	C(8)-
C(9)	1.389(4)	C(9)-C(10)	1.379(3)	C(10)-
C(11)	1.382(3)	C(11)-C(12)	1.394(4)	C(13)-
C(14)	1.390(3)	C(13)-C(18)	1.399(3)	C(14)-
C(15)	1.392(3)	C(15)-C(16)	1.374(3)	C(16)-
C(17)	1.383(3)	C(17)-C(18)	1.377(3)	
O(1)-C(1)-C(7)	108.57(16)	O(1)-C(1)-C(13)	107.74(16)	C(7)-
C(1)-C(13)	108.74(17)	O(1)-C(1)-C(2)	105.59(17)	C(7)-
C(1)-C(2)	113.69(17)	C(13)-C(1)-C(2)	112.25(17)	C(3)-
C(2)-C(1)	102.06(17)	C(4)-C(3)-C(2)	101.53(18)	O(2)-
C(4)-O(1)	111.24(18)	O(2)-C(4)-C(3)	108.08(16)	O(1)-
C(4)-C(3)	105.23(16)	O(2)-C(5)-C(6)	108.22(18)	C(12)-
C(7)-C(8)	118.6(2)	C(12)-C(7)-C(1)	121.41(19)	C(8)-
C(7)-C(1)	119.90(19)	C(9)-C(8)-C(7)	120.8(2)	C(10)-
C(9)-C(8)	119.0(2)	C(9)-C(10)-C(11)	121.8(2)	C(9)-
C(10)-Br(2)	118.83(18)	C(11)-C(10)-Br(2)	119.32(18)	C(10)-
C(11)-C(12)	118.3(2)	C(7)-C(12)-C(11)	121.4(2)	C(14)-
C(13)-C(18)	118.39(18)	C(14)-C(13)-C(1)	121.73(18)	C(18)-
C(13)-C(1)	119.84(18)	C(13)-C(14)-C(15)	120.78(19)	C(16)-
C(15)-C(14)	119.03(19)	C(15)-C(16)-C(17)	121.70(18)	C(15)-
C(16)-Br(1)	119.33(16)	C(17)-C(16)-Br(1)	118.89(15)	C(18)-
C(17)-C(16)	118.79(19)	C(17)-C(18)-C(13)	121.3(2)	C(4)-
O(1)-C(1)	109.78(14)	C(4)-O(2)-C(5)	113.50(15)	

Table 4. Anisotropic displacement parameters ($\text{\AA}^2$).

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}].$$

	U ₁₁	U ₂₂	U ₃₃	U ₂₃	U ₁₃	U ₁₂
Br(1)	0.046(1)	0.021(1)	0.032(1)	0.003(1)	0.000(1)	-0.009(1)
Br(2)	0.051(1)	0.032(1)	0.026(1)	0.005(1)	0.000(1)	-0.013(1)
C(1)	0.015(1)	0.020(1)	0.032(1)	0.001(1)	0.000(1)	0.001(1)
C(2)	0.021(1)	0.020(1)	0.039(1)	0.002(1)	0.007(1)	0.003(1)
C(3)	0.033(1)	0.021(1)	0.030(1)	0.002(1)	0.009(1)	0.002(1)
C(4)	0.029(1)	0.020(1)	0.023(1)	0.000(1)	0.002(1)	0.001(1)
C(5)	0.022(1)	0.031(1)	0.045(2)	0.011(1)	-0.005(1)	-0.003(1)
C(6)	0.029(1)	0.034(1)	0.051(2)	0.016(1)	-0.007(1)	-0.007(1)
C(7)	0.022(1)	0.015(1)	0.031(1)	0.004(1)	0.000(1)	-0.002(1)
C(8)	0.019(1)	0.021(1)	0.032(1)	0.002(1)	-0.001(1)	0.001(1)
C(9)	0.027(1)	0.021(1)	0.033(1)	0.002(1)	0.003(1)	-0.002(1)
C(10)	0.036(1)	0.021(1)	0.028(1)	0.004(1)	0.000(1)	-0.009(1)
C(11)	0.030(1)	0.027(1)	0.034(1)	0.008(1)	-0.008(1)	-0.006(1)
C(12)	0.020(1)	0.025(1)	0.037(1)	0.006(1)	-0.001(1)	-0.001(1)
C(13)	0.022(1)	0.018(1)	0.021(1)	-0.003(1)	0.003(1)	0.001(1)
C(14)	0.024(1)	0.022(1)	0.027(1)	-0.001(1)	-0.003(1)	-0.002(1)
C(15)	0.033(1)	0.024(1)	0.022(1)	0.001(1)	-0.004(1)	0.002(1)
C(16)	0.034(1)	0.017(1)	0.022(1)	0.000(1)	0.002(1)	-0.003(1)
C(17)	0.022(1)	0.026(1)	0.029(1)	-0.002(1)	0.002(1)	-0.004(1)
C(18)	0.020(1)	0.025(1)	0.029(1)	0.000(1)	0.000(1)	0.001(1)
O(1)	0.018(1)	0.018(1)	0.032(1)	-0.004(1)	-0.002(1)	0.000(1)
O(2)	0.023(1)	0.020(1)	0.033(1)	0.004(1)	-0.003(1)	-0.002(1)

Copies of NMR Spectra

NOESY (1.2s) on COC-CB-140-01

ppm

5.2

5.4

5.6

5.8

6.0

6.2

6.4

6.6

6.8

7.0

7.2

7.4

7.6

Current Data Parameters
NAME COC14001
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20100219
Time 16.34
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG noesygpph
TD 2048
SOLVENT CD2Cl2
NS 10
DS 16
SWH 4401.409 Hz
FIDRES 2.149125 Hz
AQ 0.2327028 sec
RG 181
DW 113.600 usec
DE 10.00 usec
TE 302.0 K
D0 0.00010150 sec
D1 10.10000038 sec
D8 1.20000005 sec
D16 0.00020000 sec
IN0 0.00022720 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.50 usec
P2 19.00 usec
PL1 -3.00 dB
SFO1 400.1322007 MHz

===== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1000.00 usec

F1 - Acquisition parameters
ND0 1
TD 2048
SFO1 400.1322 MHz
FIDRES 2.149148 Hz
SW 11.000 ppm
FnMODE States-TPPI

F2 - Processing parameters
SI 4096
SF 400.1300150 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 400.1300150 MHz
WDW QSINE
SSB 2
LB 0.00 Hz
GB 0

ppm

HPLC and GC Traces

1 220nm 4nm

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area %
1	11.75	2.92
2	13.01	97.08
Total		100.00

1 220nm 4nm

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area %
1	11.72	48.65
2	12.97	51.35
Total		100.00

3f

Peak #	Ret. Time/min	Area/%
1	4.76	5.39
2	5.57	94.6

racemic

Peak #	Ret. Time/min	Area/%
1	5.09	50.1
2	6.01	49.9

Peak #	Ret. Time/min	Area/%
1	9.02	1.88
2	9.28	98.1

Peak #	Ret. Time/min	Area/%
1	9.02	50.0
2	9.29	50.0

Peak #	Ret. Time/min	Area/%
1	65.11	2.32
2	66.38	97.8

Peak #	Ret. Time/min	Area/%
1	65.08	50.3
2	66.28	49.7

1 220nm 4nm

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area %
1	9.55	3.18
2	11.90	96.82
Total		100.00

1 210nm 4nm

PDA Ch1 210nm 4nm

Peak #	Ret. Time	Area %
1	9.60	51.33
2	12.02	48.67
Total		100.00

Peak #	Ret. Time/min	Area/%
1	10.06	3.24
2	10.34	96.8

Peak #	Ret. Time/min	Area/%
1	10.04	49.9
2	10.39	50.1

isomer	Peak #	Ret. Time/min	Area/%
<i>cis</i>	1	211.3	50.7
	2	225.1	4.99
<i>trans</i>	3	288.9	44.3

isomer	Peak #	Ret. Time/min	Area/%
<i>cis</i>	1	214.1	27.4
	2	227.2	27.5
<i>trans</i>	3	292.9	21.7
	4	297.2	23.4

isomer	Peak #	Ret. Time/min	Area/%
<i>cis</i>	1	93.9	53.1
<i>trans</i>	2	109.0	44.9
	3	112.4	1.99

isomer	Peak #	Ret. Time/min	Area/%
<i>cis</i>	1	94.0	54.3
<i>trans</i>	2	108.8	22.7
	3	112.3	23.0

Peak #	Ret. Time/min	Area/%
1	7.06	5.06
2	7.34	94.9

Peak #	Ret. Time/min	Area/%
1	6.94	50.0
2	7.28	50.0

1 220nm 4nm

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area %
1	13.90	18.00
2	17.30	82.00
Total		100.00

1 220nm 4nm

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area %
1	13.01	49.69
2	17.08	50.31
Total		100.00

Peak #	Ret. Time/min	Area/%
1	14.64	17.7
2	15.19	82.3

Peak #	Ret. Time/min	Area/%
1	14.67	50.0
2	15.30	50.0

Peak #	Ret. Time/min	Area/%
1	5.20	20.8
2	5.79	79.2

Peak #	Ret. Time/min	Area/%
1	5.19	49.9
2	5.78	50.1