Lewis Base-Catalyzed Enantioselective Aldol Addition of Acetaldehyde Derived Silyl Enol Ether to Aldehydes

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SUPPORTING INFORMATION

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General Experimental

All reactions were performed in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon or nitrogen. The following reaction solvents were distilled from the indicated drying agents: dichloromethane (P_2O_5), tetrahydrofuran (sodium, benzophenone), solvents for crystallization benzene (ACS grade), hexanes (ACS grade) were used as received. Solvents for chromatography and filtration were technical grade and distilled from the indicated drying agents: hexane ($CaCl_2$); ethyl acetate (K_2CO_3); dichloromethane ($CaCl_2$); isopropanol (ACS grade) was used as received. Column chromatography was performed using EM Science 230-400-mesh silica gel. Anisaldehyde, benzaldehyde, (*E*)-cinnamaldehyde, 4-chlorobenzaldehyde, 1-naphthaldehyde, and 4-(trifluoromethyl)benzaldehyde were freshly distilled before use. 2-Naphthaldehyde was used as received. Silicon tetrachloride was heated at reflux for 24 h and then distilled prior to use. All reaction temperatures correspond to internal temperatures measured by Teflon-coated thermocouples unless otherwise noted.

^1H NMR, ^{13}C NMR spectra were recorded on 400 MHz, ^1H (100 MHz, ^{13}C), 500 MHz, ^1H (126 MHz, ^{13}C) spectrometers. Spectra were referenced to residual chloroform (δ 7.26 ppm, ^1H ; δ 77.00 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (pentet), m (multiplet), and br (broad). Coupling constants, J , are reported in Hertz. All ^1H and ^{13}C NMR assignments are corroborated by 2D experiments (HETCOR and COSY). Spectra available on request from denmark@scs.uiuc.edu.

Low resolution electron impact (EI) mass spectra were obtained with a typical ionization voltage of 70 eV. Chemical ionization (CI) spectra were obtained using methane as the carrier gas. Data are reported in the form of (m/z). Infrared spectra (IR) are reported in cm^{-1} with indicated relative intensities: s (strong, 67-100%); m (medium, 34-66%); w (weak, 0-33%). Melting points (mp) were determined in sealed tubes and are corrected. Bulb-to-bulb distillations were performed in a Kugelrohr, and boiling points (bp) correspond to the uncorrected air bath temperatures (ABT). Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with 2,4-dinitrophenylhydrazine or KMnO_4 .

Optical rotation data was obtained on a digital polarimeter and are reported as follows: concentration ($c = \text{g}/100 \text{ mL}$), and solvent. Analytical supercritical fluid chromatography (SFC) was performed on packed-column SFC with built-in photometric detector ($\lambda = 220, 258 \text{ nm}$) using Daicel Chiralpak OD and AD columns. Retention times (t_R) and peak areas for SFC were obtained from reporting integrators.

Experimental Procedures

Preparation of Trimethylsilyl Enol ether **1a**¹

To a 500-mL, flame-dried three necked flask fitted with a magnetic stirbar, septum and nitrogen inlet, was charged with dry THF (176 mL) and cooled to 0 °C (ice bath). *n*-Butyllithium (100 mL, 160 mmol) was added slowly via syringe. After the addition, the resulting solution was allowed to warm to room temperature and was stirred for 16 h. A cloudy white solution was observed at this point. The solvent was removed under reduced pressure (0.25 mmHg, room temperature), and a white solid left behind was dissolved in dry diglyme (30 mL). The solution was placed under reduced pressure again to remove further any residual THF. An additional amount of diglyme (120 mL) was added, and the resulting solution was cooled to 0 °C. Freshly distilled chlorotrimethylsilane (15.2 mL, 120 mmol) was then added slowly. A significant amount of white precipitate was observed during the addition. The reaction mixture was allowed to warm to room temperature and aged at this temperature for about 1 h. The product plus a small amount of the solvent was separated from the white precipitate by distillation at first 40 mmHg then gradually reduced to 0.5 mmHg at room temperature. The distillate was further purified by re-distillation at 75 °C (at atmospheric pressure) to provide the desired product as a clear, colorless liquid (7.1 g, 51%).

Data for **1a**

bp: 75 °C (760 mmHg, ABT)

¹H NMR: (400 MHz, CDCl₃)
 6.39 (dd, *J* = 13.7, 5.9, 1 H, H(C1)), 4.42 (d, *J* = 13.7, 1 H, *trans*-H C(2)), 4.13 d, *J* = 5.9, 1 H, *cis*-H C(2)), 0.20 (s, 9 H, H₃C(3))

¹³C NMR: (500 MHz, CDCl₃)
 146.1 (C(1)), 94.9 (C(2)), -0.3 (C(3))

Chiral Phosphoramidate-Catalyzed Crossed-Aldol Additions of **1a** to Aldehydes

General Procedure I

(*R*)-(2,2-Dimethoxyethyl)benzenemethanol (4a)

A 10-mL, 2-necked, round-bottomed flask fitted with a magnetic stirbar, rubber septum, nitrogen inlet and Teflon-coated thermocouple was charged with a stirred solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), freshly distilled benzaldehyde (102 μL , 1 mmol), and *i*-Pr₂EtN (174 μL , 1.0 mmol) in 2 mL of dry methylene chloride at -65°C . Silicon tetrachloride (229 μL , 2.0 mmol, 2.0 equiv) was added slowly via syringe. The resulting solution was stirred for a few minutes before enol ether **1a** (179 μL , 1.2 mmol, 1.2 equiv) was added dropwise via syringe. The reaction mixture was stirred at -65°C under N_2 for 24 h and then was cooled to -78°C whereupon dry methanol (10 mL) was added slowly such that the internal temperature was maintained below -50°C during the addition. The resulting mixture was stirred for 30 min and then allowed to warm to room temperature (23°C). Next, the methanolic mixture was quickly poured into a vigorously-stirred, cold, saturated aqueous, sodium bicarbonate solution (40 mL), and the resulting mixture was stirred at room temperature for about 30 min. A cloudy white solution was observed during this period. The mixture was filtered through Celite and the aqueous layer was separated and extracted with methylene chloride (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel column chromatography (hexanes/ethyl acetate, 3/1) followed by bulb-to-bulb distillation afforded 157.0 mg (80%) of **4a** as a clear, colorless oil.

Data for 4a

bp: 140 °C (0.25 mmHg, ABT)

¹H NMR: (400 MHz, CDCl₃)

7.22-7.28 (m, 4 H, H-Aryl), 7.15-7.20 (m, 1 H, H-Aryl), 4.78 (dd, $J = 9.0, 3.2$, 1 H, HC(1)), 4.46 (t, $J = 5.6$, 1 H, HC(3)), 3.29 (s, 3 H, H₃C(3)), 3.56 (s, 3 H, H₃C(3)), 3.22 (s, br, 1H, (OH)), 1.85-2.02 (m, 2 H, H₂C(2))

¹³C NMR: (400 MHz, CDCl₃)

144.1 (C(5)), 128.4 (C(7)), 127.4 (C(6)), 125.6 (C(8)), 103.4 (C(3)), 70.8 (C(1)), 53.6 (C(4)), 52.9 (C(4)), 41.5 (C(2))

IR: (neat)

3446 (br), 3088 (w), 3064 (w), 3030 (m), 2934 (s), 2834 (s), 2360 (w), 1957 (w), 1651 (w), 1668 (w), 1604 (w), 1495 (w), 1455 (m), 1386 (w), 1193 (w), 1125 (w), 1047 (w), 941 (w), 914 (w), 846 (w), 760 (m)

MS: (FI)

196 (M⁺, 18), 184 (8), 164 (100), 121 (17), 75 (56)

Opt. Rot.: $[\alpha]_D^{24}$ 35.21 ($c = 1.46$, EtOH)

TLC: R_f 0.28 (hexane/EtOAc, 3/1) [silica gel, DNP]

SFC: (*R*)-**4a**, t_R 3.84 min (97.1%); (*S*)-**4a**, t_R 4.53 min (2.88%) (Column: OD, MeOH 5%, pressure 125 psi, flow 2.5 mL/min)

Analysis: C₁₁H₁₆O₃ (196.24)

Calcd: C, 67.32; H, 8.22%

Found: C, 67.28; H, 8.20%

(R)-(2,2-Dimethoxyethyl)-2-naphthylmethanol (4b)

Following General Procedure I, a solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), trimethylsilyl enol ether **1a** (179 μL , 1.2 mmol, 1.2 equiv), *i*-Pr₂EtN (174 μL , 1.0 mmol), silicon tetrachloride (229 μL , 2.0 mmol), and 2-naphthaldehyde (156.2 mg, 1.0 mmol) in 4 mL of $\text{CHCl}_3/\text{CH}_2\text{Cl}_2$ (4/1) was stirred at -65°C under nitrogen for 24 h. Workup and purification by silica gel column chromatography using hexanes/ethyl acetate, 2/1 as eluent provided the desired aldol product, which was further purified by bulb-to-bulb distillation to afford 209 mg (85%) of **4b** as clear, colorless oil.

Data for 4b

bp: 220°C (0.25 mmHg, ABT)

¹H NMR: (500 MHz, CDCl_3)

7.81-7.86 (m, 4 H, H-Aryl), 7.45-7.50 (m, 3 H, H-Aryl), 5.08 (dt, $J = 9, 6.2$, 1 H, HC(1)), 4.60 (t, $J = 6.0$, 1 H, H(C(3))), 3.42 (s, 3 H, $\text{H}_3\text{C}(3)$), 3.38 (s, 3 H, $\text{H}_3\text{C}(3)$), 2.14-2.20 (m, 1 H, HC(2)), 2.06-2.11 (m, 1 H, HC(2))

¹³C NMR: (400 MHz, CDCl_3)

141.4 (C(5)), 133.3 (C(7)), 132.9 (C(12)), 128.2 (C(6)), 127.9 (C(8)), 127.6 (C(11)), 126.1 (C(13)), 125.7 (C(14)), 124.2 (C(9)), 123.9 (C(10)), 103.5 (C(3)), 70.9 (C(1)), 53.7 (C(4)), 53.1 (C(4)), 41.4 (C(2))

IR: (neat)

3436 (br), 3056 (m), 2933 (s), 2927 (w), 1633 (w), 1602 (w), 1509 (w), 1445 (w), 1385 (m), 12714 (w), 1190 (w), 1124 (s), 1058 (m), 959 (w), 899 (w), 859(w), 821 (m), 750 (m)

MS: (FI)

246 (M^+ , 25), 214 ($\text{M}^+ - \text{MeOH}$, 37), 182 (35) 155 (97), 129 (97), 89(41), 75 (90)

Opt. Rot.: $[\alpha]_{\text{D}}^{24}$ 43.47 ($c = 1.12$, EtOH)

TLC: R_f 0.22 (hexane/EtOAc, 2/1) [silica gel, DNP]

SFC: (*S*)-**4b**, t_R 2.74 min (2.9%); (*R*)-**4b**, t_R 10.59 min (97.1%) (Column: OD, MeOH 5%, pressure 125 psi, flow 3.0 mL/min)

Analysis: C₁₅H₁₈O₃ (246.30)

Calcd: C, 73.15; H, 7.37%

Found: C, 72.93; H, 7.36%

(*R*)-(2,2-Dimethoxyethyl)-1-naphthylmethanol (4c)

Following General Procedure I, a solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), trimethylsilyl enol ether **1a** (179 μ L, 1.2 mmol, 1.2 equiv), *i*-Pr₂EtN (174 μ L, 1.0 mmol), silicon tetrachloride (229 μ L, 2.0 mmol), and 1-naphthaldehyde (156.2 mg, 1.0 mmol) in 4 mL of CHCl₃/CH₂Cl₂ (4/1) was stirred at - 65 °C under nitrogen for 24 h. Workup and purification by silica gel column chromatography using hexanes/ethyl acetate, 2/1 as eluent provided the desired aldol product, which was further purified by bulb-to-bulb distillation to afford 192 mg (78%) of **4c** as clear, colorless oil.

Data for 4c

bp: 180 °C (0.1 mmHg, ABT)

¹H NMR: (500 MHz, CDCl₃)

7.05 (d, J = 8.3, 1 H, HC(7)), 7.87 (dt, J = 7.8, 1.5, 1 H, HC(10)), 7.78 (d, J = 8.3, 1 H, HC(12)), 7.72 (d, J = 8.3, 1 H, H(C(14))), 7.47-7.54 (m, 3 H, H-Aryl), 5.71 (d, J = 8.8, 1 H, HC(1)), 4.69 (t, J = 5.4, 1 H, HC(3)), 3.43 (s, 3 H, H₃C(4)), 3.42 (s, 3 H, H₃C(4)), 3.41 (br, 1H, (OH)), 2.13-2.25 (m, 2 H, H₂C(2))

¹³C NMR: (500 MHz, CDCl₃)

139.6 (C(5)), 133.7 (C(11)), 130.0 (C(6)), 128.9 (C(10)), 127.8 (C(12)), 126.0 (C(8)), 125.5 (C(9)), 125.5 (C(13)), 122.9 (C(7)), 122.7 (C(14)), 103.9 (C(3)),

67.5 (C(1)), 54.0 (C(4)), 53.4 (C(4)), 40.9 (C(2))

IR: (neat)

3436 (br), 3051 (w), 2935 (s), 2833 (m), 1948 (w), 1597 (w), 1512 (w), 1446 (w), 1386 (m), 1228 (w), 1191 (w), 1164 (w), 1125 (s), 1097 (s), 1055 (s), 1005 (w), 969 (w), 913 (w), 867 (w), 801 (m), 778 (s), 736 (w)

MS: (FI)

246 (M⁺, 98), 182 (5)

Opt. Rot.: $[\alpha]_D^{24}$ 108.08 (*c* = 1.10, EtOH)

TLC: *R_f* 0.32 (hexane/EtOAc, 2/1) [silica gel, DNP]

SFC: (*S*)-**4c**, *t_R* 10.81 min (7.8%); (*R*)-**4c**, *t_R* 11.48 min (92.2%) (Column: AD, MeOH 3%, pressure 125 psi, flow 3.0 mL/min)

Analysis: C₁₅H₁₇O₃ (246.30)

Calcd: C, 73.15; H, 7.37%

Found: C, 72.86; H, 7.46%

(*R*)-(2,2-Dimethoxyethyl)-4-trifluoromethylphenylmethanol (4d)

Following General Procedure I, a solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), trimethylsilyl enol ether **1a** (179 μL, 1.2 mmol, 1.2 equiv), *i*-Pr₂EtN (174 μL, 1.0 mmol), silicon tetrachloride (229 μL, 2.0 mmol), and aldehyde **2d** (156.2 mg, 1.0 mmol) in 4 mL of CHCl₃/CH₂Cl₂ (4/1) was stirred at -65 °C under nitrogen for 24 h. Workup and purification by silica gel column chromatography using hexanes/ethyl acetate, 2/1 as eluent provided the desired aldol product, which was further purified by bulb-to-bulb distillation to afford 221 mg (84%) of **4d** as clear, colorless oil.

Data for **4d**

bp: 150 °C (0.25 mmHg, ABT)

¹H NMR: (400 MHz, CDCl₃)

7.60 (d, *J* = 8.1, 2 H, HC(7)), 7.48 (d, *J* = 8.6, 2 H, HC(6)), 4.97 (dd, *J* = 9.0, 3.2, 1 H, HC(1)), 4.58 (t, *J* = 5.1, 1 H, HC(3)), 3.55 (br, 1 H, OH), 3.42 (s, 3 H, H₃C(4)), 3.37 (s, 3 H, H₃C(4)), 1.95-2.09 (m, 2 H, H₂C(2))

¹³C NMR: (400 MHz, CDCl₃)

148.1 (C(5)), 125.9 (C(8)), 125.4 (C(6)), 125.4 (C(7)), 122.8 (C(9)), 103.5 (C(3)), 70.2 (C(1)), 54.0 (C(4)), 53.2 (C(4)), 41.5 (C(2))

IR: (neat)

3436 (s), 2939 (s), 2837 (s), 2360 (s), 2342 (s), 1925 (w), 1447 (w), 1447 (m), 1387 (w), 1326 (s), 1165 (s), 1124 (s), 1067 (s), 1018 (m), 971 (w), 914 (w), 848 (m), 759 (w)

MS: (EI)

263 (M⁺- H, 1), 232 (M⁺-MeOH, 13), 189 (7), 175 (18), 173 (13), 145 (8), 127 (26), 75(100), 59 (30), 58(32)

Opt. Rot.: [α]_D²⁴ 31.99 (*c* = 2.46, EtOH)

TLC: *R_f* 0.35 (hexane/EtOAc, 2/1) [silica gel, DNP]

SFC: (*R*)-**4d**, *t_R* 5.11 min (98.1%); (*S*)-**4d**, *t_R* 5.52 min (1.9%) (Column: AD, MeOH 1%, pressure 125 psi, flow 3.0 mL/min)

Analysis: C₁₂H₁₅F₃O₃ (264.24)

Calcd: C, 54.54; H, 5.72 F, 21.57%

Found: C, 54.64; H, 5.83 F, 21.22%

(R)-(2,2-Dimethoxyethyl)-4-chlorophenylmethanol (4e)

Following General Procedure I, a solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), trimethylsilyl enol ether **1a** (179 μL , 1.2 mmol, 1.2 equiv), *i*-Pr₂EtN (174 μL , 1.0 mmol), silicon tetrachloride (229 μL , 2.0 mmol), and aldehyde **2e** (140.6 mg, 1.0 mmol) in 4 mL of $\text{CHCl}_3/\text{CH}_2\text{Cl}_2$ (4/1) was stirred at -65°C under nitrogen for 24 h. Workup and purification by silica gel column chromatography using hexanes/ethyl acetate, 2/1 as eluent provided the desired aldol product, which was further purified by bulb-to-bulb distillation to afford 187 mg (81%) of **4e** as clear, colorless oil.

Data for 4e

bp: 170°C (0.35 mmHg, ABT)

¹H NMR: (500 MHz, CDCl_3)

7.26-7.30 (m, 4 H, Aryl-H), 4.83 (dt, $J = 9.0, 3.0$, 1 H, HC(1)), 4.52 (t, $J = 5.4$, 1 H, H(C(3))), 3.48 (d, $J = 3$, 1 H, OH), 3.37 (s, 3 H, H₃C(4)), 3.34 (s, 3 H, H₃C(4)), 1.89-2.04 (m, 2 H, H₂C(2))

¹³C NMR: (400 MHz, CDCl_3)

142.6 (C(5)), 132.9 (C(8)), 128.5 (C(6)), 127.0 (C(7)), 103.3 (C(3)), 70.0 (C(1)), 53.7 (C(4)), 53.1 (C(4)), 41.4 (C(2))

IR: (neat)

3435 (br), 2959 (m), 2834 (m), 1906 (w), 1597 (w), 1579 (w), 1490 (m), 1455 (w), 1386 (w), 1317 (w), 1230 (w), 1194 (w), 1125 (m), 1090 (m), 1014 (m), 968 (w), 943 (w), 912 (w), 832 (m), 780 (w)

MS: (FI)

230 (M^+ , 100), 199 (19), 198 (60), 170 (7), 155 (30), 75(90)

Opt. Rot.: $[\alpha]_{\text{D}}^{24}$ 30.47 ($c = 2.11$, EtOH)

TLC: R_f 0.24 (hexane/EtOAc, 2/1) [silica gel, DNP]

SFC: (R)-**4e**, t_R 3.76 min (97.9%); (S)-**4e**, t_R 4.14 min (2.1%) (Column: AD, MeOH 5%, pressure 125 psi, flow 3.0 mL/min)

Analysis: $C_{11}H_{15}ClO_3$ (230.69)

Calcd: C, 57.27; H, 6.55; Cl, 15.37%

Found: C, 57.27; H, 6.58; Cl, 15.57%

(R)-2,2-Dimethoxy-1-phenyl-1-penten-3-ol (4f)

Following General Procedure I, a solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), trimethylsilyl enol ether **1a** (179 μ L, 1.2 mmol, 1.2 equiv), *i*-Pr₂EtN (174 μ L, 1.0 mmol), silicon tetrachloride (229 μ L, 2.0 mmol), and aldehyde **2f** (126 μ L, 1.0 mmol) in 4 mL of $CHCl_3/CH_2Cl_2$ (4/1) was stirred at $-65^\circ C$ under nitrogen for 24 h. Workup and purification by silica gel column chromatography using hexanes/ethyl acetate, 2/1 as eluent provided the desired aldol product, which was further purified by bulb-to-bulb distillation to afford 134 mg (60%) of **4f** as clear, colorless oil.

Data for 4f

bp: $177^\circ C$ (0.01 mmHg, ABT)

1H NMR: (400 MHz, $CDCl_3$)

7.22-7.40 (m, 5 H, Aryl-H), 6.63 (d, $J = 15.9$, 1 H, HC(1)), 6.22 (dd, $J = 15.9$, 6.1, 1 H, HC(2)), 4.63 (t, $J = 5.4$, 1 H, HC(5)), 4.49 (q, $J = 6.0$, 1 H, H(C(3))), 3.39 (s, 3 H, $H_3C(6)$), 3.38 (s, 3 H, $H_3C(6)$), 3.03 (br, $J = 2.0$, 1 H, OH), 1.93-1.96 (m, 2 H, $H_2C(4)$)

^{13}C NMR: (400 MHz, $CDCl_3$)

136.7 (C(7)), 131.6 (C(1)), 129.9 (C(9)), 128.6 (C(10)), 127.6 (C(8)), 126.5 (C(2)), 103.4 (C(5)), 69.3 (C(3)), 53.6 (C(6)), 53.2 (C(6)), 39.5 (C(4))

IR: (neat)

3436 (br), 3083 (w), 3060 (w), 3027 (m), 2955 (s), 2833 (s), 1951 (w), 1881 (w), 1811 (w), 1652 (w), 1599 (m), 1578 (w), 1495 (s), 1448 (s), 1386 (s), 1315 (w), 1226 (w), 1191 (m), 1124 (s), 1048 (s), 967 (m), 914(w), 817 (w), 750 (m)

MS: (FI)

222.2 (M^+ , 100), 220 (18), 190 (9), 162 (4), 158 (4)

Opt. Rot.: $[\alpha]_D^{24}$ - 5.65 ($c = 2.2$, EtOH)

TLC: R_f 0.23 (hexane/EtOAc, 2/1) [silica gel, DNP]

SFC: (*R*)-**4f**, t_R 3.57 min (98.3%); (*R*)-**4f**, t_R 5.09 min (1.7%) (Column: OD, MeOH 8%, pressure 125 psi, flow 3.0 mL/min)

Analysis: $C_{13}H_{18}O_3$ (222.28)

Calcd: C, 70.24; H, 8.16%

Found: C, 70.22; H, 7.92%

(*R*)-(2,2-Dimethoxyethyl)-4-methoxyphenylmethanol (4g**)**

To a stirred solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), freshly distilled anisaldehyde (122 μ L, 1 mmol), and *i*-Pr₂EtN (174 μ L, 1.0 mmol) in 2 mL of dry methylene chloride in a 10-mL, 2-necked round bottomed flask fitted with a magnetic stirbar, rubber septum, nitrogen inlet and Teflon-coated thermocouple at -65 $^{\circ}$ C was added silicon tetrachloride (172 μ L, 1.5 mmol) slowly via syringe. The resulting solution was stirred for few minutes before enolate **1a** (179 μ L, 1.2 mmol, 1.2 equiv) was added dropwise via syringe. The reaction mixture was stirred at -65 $^{\circ}$ C under N₂ for 24 h and first cooled to -78 $^{\circ}$ C and then diluted with dry methylene chloride (10 mL) before dry methanol (10 mL) was added slowly such that the internal temperature was maintained below -65 $^{\circ}$ C during the addition. The resulting mixture was stirred for 30 min and then allowed to warm to 0 $^{\circ}$ C and aged at this temperature for 25 min before continuing to let the solution to warm to room temperature (23 $^{\circ}$ C). Next, the methanolic

mixture was quickly poured into a vigorously stirred, cold, saturated sodium bicarbonate (50 mL), and the resulting solution was stirred at room temperature for about 1 h. A cloudy white solution was observed during this period. The mixture was filtered through Celite and the aqueous layer was separated and extracted with methylene chloride (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel column chromatography using hexanes/ethyl acetate (5/1) then (3/1) followed by bulb-to-bulb distillation afforded **4g** (68 mg, 30%) as a clear, colorless oil.

Data for 4g

bp: 165°C (0.12 mmHg, ABT)

¹H NMR: (500 MHz, CDCl₃)

7.29 (d, *J* = 8.8, 2 H, HC(6)), 6.88 (d, *J* = 8.8, 2 H, HC(7)), 4.84 (dt, *J* = 9.3, 2.7, 1 H, HC(1)), 4.55 (t, *J* = 5.1, 1 H, HC(3)), 3.80 (s, 3 H, H₃C(9)), 3.40 (s, 3 H, H₃C(4)), 3.36 (s, 3 H, H₃C(4)), 3.10 (t, *J* = 2.7, 1 H, OH), 1.93-2.11 (m, 2 H, H₂C(2))

¹³C NMR: (400 MHz, CDCl₃)

158.9 (C(8)), 136.2 (C(5)), 126.9 (C(6)), 113.8 (C(7)), 103.5 (C(3)), 70.5 (C(1)), 55.3 (C(4)), 53.7 (C(4)), 53.0 (C(9)), 41.5 (C(2))

IR: (neat)

3435 (br), 3014 (m), 2957 (m), 2836 (m), 2341 (w), 1613 (m), 1587 (w), 1514 (s), 1464 (w), 1386 (w), 1303 (w), 1247 (s), 1177 (m), 1126 (s), 1035 (m), 967 (w), 940 (w), 912 (w), 834 (m)

MS: (FI)

226 (100)

Opt. Rot.: [α]_D²⁴ +32.64 (*c* = 1.61, EtOH)

TLC: *R*_f 0.13 (hexane/EtOAc, 2/1) [silica gel]

SFC: (*R*)-**4g**, *t*_R 4.96 min (91.2%); (*S*)-**4g**, *t*_R 5.50 min (8.8%) (Column: OD, MeOH 2.5%, pressure 125 psi, flow 2.5 mL/min)

Analysis: C₁₂H₁₈O₄ (226.27)

Calcd: C, 63.70; H, 8.02%

Found: C, 63.42; H, 8.08%

Determination of the configuration of aldol products**(*R*)-1-Phenylpropane-1,3-diol (**5**)**

To a stirred solution of **3** (126.4 mg, 0.15 mmol, 0.15 equiv), freshly distilled benzaldehyde (102 μL , 1 mmol), and *i*-Pr₂EtN (174 μL , 1.0 mmol) in 2 mL of dry methylene chloride in a 10-mL, 2-necked round bottomed flask fitted with a magnetic stirbar, rubber septum, nitrogen inlet and Teflon-coated thermocouple at -65°C was added silicon tetrachloride (172 μL , 1.5 mmol) slowly via syringe. The resulting solution was stirred for few minutes before enolate **1a** (179 μL , 1.2 mmol, 1.2 equiv) was added dropwise via syringe. The reaction mixture was stirred at -67°C under N_2 for 24 h and then cooled to -75°C before a mixture of $\text{THF/Et}_3\text{N/H}_2\text{O}$ (8.5/1/0.5, 10 mL total) was added slowly such that the internal temperature was maintained below -65°C during the addition. The resulting mixture was stirred for 15 min, then sodium borohydride (121 mg, 3.2 mmol) was added at -75°C . The reaction was allowed to warm to 0°C and stirred at this temperature for 2 h. The reaction mixture was then quickly poured into a vigorously stirred, cold, saturated sodium bicarbonate (50 mL), and the resultant solution was stirred at room temperature for about 1 h. Next, the solution was filtered through Celite, and the aqueous layer of the filtrate was separated and extracted with methylene chloride (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Silica gel column chromatography using hexanes/ethyl acetate (1/2) afforded **5** (84 mg, 55%) as a clear, colorless oil.

Data for **5**

¹H NMR: (500 MHz, CDCl_3)

7.27-7.38 (m, 5 H, Aryl-H), 4.98 (dd, $J = 8.8, 3.7$, 1 H, HC(1)), 3.88 (t, $J = 5.9$, 2 H, HC(3)), 1.93-2.07 (m, 2 H, $\text{H}_2\text{C}(3)$)

¹³C NMR: (500 MHz, CDCl₃)
 144.3 (C(4)), 128.5 (C(6)), 127.6 (C(5)), 125.7 (C(7)), 74.4 (C(1)), 61.5 (C(3)),
 40.4 (C(2))

MS: (FI)
 152 (100)

Opt. Rot.: [α]_D²⁴ +36.05 (*c* = 1.12, EtOH), + 65.11 (*c* = 1.05, CHCl₃)
 Literature reported value for (*R*)-**5**, + 69.0 at 23 °C (*c* = 1.51, CHCl₃)²

TLC: *R_f* 0.34 (EtOAc/hexane, 2/1) [silica gel]

Spectroscopic Detection of Chlorohydrin Chlorosilyl Aldolate Intermediate **i**

To a dry NMR tube was added catalyst **3** (6 mg, 0.007 mmol, 0.05 equiv). This material was dissolved in deuterated methylene chloride (0.6 mL). To this solution was added benzaldehyde (13 μ L, 0.13 mmol, 1 equiv.), silicon tetrachloride (33 μ L, 0.26 mmol, 2 equiv), and Hunig base (11 μ L, 0.065 mmol, 0.5 equiv.) at -78 °C. The resulting solution was mixed thoroughly using a vortex. Next, trimethyl silyl enol ether **1a** (36 μ L, 0.20 mmol, 1.5 equiv) was added and mixed again in the same manner as described before. The reaction was run for 31 h at -78 °C, then the sample was inserted into the NMR probe at -78 °C. Three chlorohydrin intermediates *trans-i*, *cis-i*, and a third unidentified chlorohydrin (see attachments) were observed in a ratio of about 1/5.3/8.4 respectively. When the reaction was warmed to -40 °C for 5 min, the ratio of *trans-i* : *cis-i* : unknown changed to 1/4.2/5.4, and this ratio was about 6.5/1.6/1 at 0 °C for 5 min. A significant amount of compound *trans-i* formed at the expense of compounds *cis-i* and the unknown at this temperature. After 20 min at 0 °C, compounds *trans-i* and *cis-i*, were observed in about >95/5 ratio whereas unknown intermediate was not observed at this temperature.

Data for *trans-i* : *cis-i* : unknown

¹H NMR: (500 MHz, CD₂Cl₂) recorded at -40 °C.

Scheme 1

trans-ia (signal 1)

observed

 H_a 5.92 (dd, $J = 11.3, 2.1, 1$ H) H_b 6.37 (t, $J = 2.3, 1$ H) *cis-i* (signal 2)

observed

 H_a 5.31 (dd, $J = 10.7, 2.6, 1$ H) H_b 6.04 (dd, $J = 9.2, 2.6, 1$ H)

calculated coupling constants	dihedral angles	calculated coupling constants	dihedral angles
H_a $J = 9.2, 1.1$	-178.98° and 65.31°	H_a $J = 9.2, 1.0$	-177.84° and 66.49°
H_b $J = 1.6, 2.5$	61.15° and -54.32°	H_b $J = 9.0, 2.4$	-170.24° and -54.69°

unknown (signal 3)

observed

 H_a 5.37 (dd, $J = 8.9, 4.9, 1$ H) H_b 5.77 (dd, $J = 6.9, 4.7, 1$ H)

Scheme 2

trans-ia (signal 1) *cis-i* (signal 2)

unknown (signal 3)

At - 78 °C (31 h)	<i>trans-i</i>	<i>cis-i</i>	unknown
ratio	1	5.3	8.4
%	6.8%	36.2%	57%
At - 40 °C (5 min)	<i>trans-ia</i>	<i>cis-i</i>	unknown
ratio	1	4.2	5.4
%	9.4%	39.6%	50.9%
% increase (↑) or decrease (↓)	2.6%↑	3.4%↑	6.1%↓
At 0 °C (5 min)	<i>trans-ia</i>	<i>cis-i</i>	unknown
ratio	6.5	1.6	1
%	71%	17.9%	10.9%
% increase (↑) or decrease (↓)	61.6%↑	22%↓	39.7%↓
At 0 °C (20 min)	<i>trans-ia</i>	<i>cis-i</i>	unknown
ratio	> 95%	5%<	not observed

In-situ Trapping of the Intermediate with *tert*-Butylisocyanide

(3*R*,5*R*)-Dihydro-3-hydroxy-5-phenylfuran-2-one (6) and (4*R*)-*N*-*tert*-butyl-2,4-dihydroxy-4-phenylbutanamide (7)

To a stirred solution of **3** (168.5 mg, 0.20 mmol, 0.20 equiv), freshly distilled benzaldehyde (102 μL , 1 mmol), and *i*-Pr₂EtN (87 μL , 0.5 mmol) in 2 mL of dry methylene chloride in a 10-mL, 2-necked, round-bottomed flask fitted with a magnetic stirbar, rubber septum, nitrogen inlet and Teflon-coated thermocouple was added silicon tetrachloride (229 μL , 2.0 mmol) slowly via syringe at $-60\text{ }^\circ\text{C}$. The resulting solution was stirred for few minutes before enolate **1a** (179 μL , 1.2 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at $-60\text{ }^\circ\text{C}$ under N₂ for 16 h. Next, a solution of *tert*-butyl isocyanide (170 μL , 1.5 mmol, 1.5 equiv) in 1 mL dry methylene chloride was added slowly, and the reaction mixture was allowed to warm to $-46\text{ }^\circ\text{C}$ and was stirred at this temperature for 8 h. The mixture was first cooled to $-75\text{ }^\circ\text{C}$ and dry methanol (3 mL) was then added dropwise. The resulting solution was stirred at this temperature for about 40 min. Next, the reaction mixture was transferred slowly to a vigorously stirred, cold, saturated, aqueous, sodium bicarbonate solution (25 mL) via a cannula. The mixture was then stirred at room temperature for about 1 h and then was filtered through Celite. The aqueous layer of the filtrate was separated and extracted with methylene chloride (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification of the product by silica gel column chromatography (ether/hexane, 3/2) followed by recrystallization (hexane/ethyl acetate, 4/1) afforded 89.1 mg (50%) of **6** and 25.1 mg (10%) of **7** as a white solid.³

Data for 6

mp: 100 °C

¹H NMR: (500 MHz, CDCl₃)

7.36-7.44 (m, 5 H, H-Aryl), 5.37 (dd, $J = 10.9, 5.1$, 1 H, HC(4)), 4.70 (ddd, $J = 11.2, 8.1, 2.9$, 1 H, HC(2)), 3.01 (ddd, $J = 12.6, 8.3, 5.7$, 1 H, H₂C(3)), 2.77 (d, $J = 2.9$, 1 H, (OH)), 2.21-2.30 (m, 1 H, H₂C(3))

¹³C NMR: (500 MHz, CDCl₃)

176.9 (C(1)), 137.7 (C(5)), 129.1 (C(7)), 128.9 (C(6)), 125.9 (C(8)), 77.7 (C(4)), 69.0 (C(2)), 39.5 (C(3))

IR: (nujol)

3411 (br), 2952 (s), 2924 (s), 2854 (s), 1760 (w), 1459 (m), 1377 (w), 1324 (w), 1310 (w), 1223 (w), 1195 (w), 1124 (w), 992 (w), 937 (w)

MS: (FI)

178 (100)

Opt. Rot.: $[\alpha]_D^{24} +38.02$ ($c = 1.38$, EtOH)

TLC: R_f 0.12 (Et₂O/hexane, 3/2) [silica gel, ceric ammonium molybdate]

Analysis: C₁₀H₁₀O₃ (178.18)

Calcd: C, 67.41; H, 5.66%

Found: C, 67.19; H, 5.34%

Difference NOE Experiments with Lactone 6

Irradiation at the signal of H_a results in the enhancement of the signal for H_b (0.31%). Likewise, irradiation of H_b gives rise to the enhancement of the signal for H_a (0.34%). Note that this is a difference NOE experiment, whose measurement of percentage of enhancement is reliable to below 1%.⁴

Data for 7

mp: 126 °C

¹H NMR: (400 MHz, CDCl₃)

7.27-7.34 (m, 5 H, H-Aryl), 6.63 (br, 1 H, (HN)), 4.99 (dd, *J* = 10.3, 2.2, 1 H, HC(4)), 4.57 (br, 1 H, (OH)), 4.23 (dd, *J* = 9.8, 2.2, 1 H, HC(2)), 3.23 (br, 1 H, (OH)), 2.26 (dt, *J* = 14.6, 2.4, 1 H, H₂C(3)), 1.82-1.91 (m, 1 H, H₂C(3)), 1.34 (s, 9 H, 3 x (H₃C(10)))

¹³C NMR: (400 MHz, CDCl₃)

172.2 (C(1)), 143.7 (C(5)), 128.6 (C(7)), 127.9 (C(6)), 125.5 (C(8)), 75.3 (C(4)), 72.9 (C(2)), 50.7 (C(9)), 42.8 (C(3)), 28.6 (C(10))

IR: (nujol)

3359 (br), 3194 (br), 2917 (s), 2855 (s), 2725 (w), 2672 (w), 2362 (w), 1955 (w), 1891 (w), 1651 (m), 1532 (w), 1461 (s), 1376 (s), 1366 (m), 1342 (w), 1293 (w), 1283 (w), 1228 (w), 1213 (w), 1200 (w), 1170 (w), 1151 (w), 1094 (w), 1070 (w), 1024 (w), 1008 (w), 996 (w)

MS: (FI)

251 (100)

Opt. Rot.: [α]_D²⁴ +38.64 (*c* = 2.5, EtOH)

TLC: *R*_f 0.17 (Et₂O/hexane, 3/2) [silica gel, ceric ammonium molybdate]

Analysis: C₁₄H₂₄N₃O₃ (251.32)

Calcd: C, 66.91; H, 8.42 N, 5.57%

Found: C, 66.60; H, 8.55 N, 5.66%

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