ANGEWANDTE CHEMIE
A Journal of the Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z19516

69451 Weinheim, Germany

Supporting Information

Highly Enantioselective Inverse Electron Demand Hetero-Diels—Alder Reactions of α,β-Unsaturated Aldehydes

Karl Gademann, David E. Chavez and Eric N. Jacobsen

Department of Chemistry & Chemical Biology
Harvard University, Cambridge, MA 02138

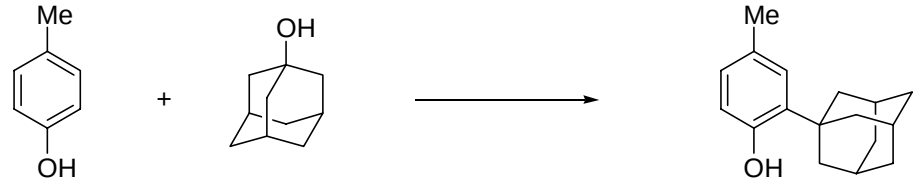
General

Unless otherwise stated, all reagents were purchased from Aldrich, Alfa Aesar or Strem and used without further purification. Powdered 4 Å molecular sieves (> 5 micron, Aldrich) were dried in a vacuum oven (135 ^{o}C) prior to use. Ethyl vinyl ether was stirred over KOH for 30 min. before distillation. Crotonaldehyde, 2-pentenal, 2-hexenal, 4-methyl-2-pentenal, heptenal, tiglic aldehyde, cinnamaldehyde and ethyl-4-oxobutenoate were freshly distilled before use. 4-Nitro-cinnamaldehyde, 2-nitro-cinnamaldehyde, 4-methoxy-cinnamaldehyde, α-bromocinnamaldehyde were purified by column chromatography before use. Aldehyde OTBS[1], OBn[2] and OBz[3] and ethyl-4-oxo-butenoate[4], were prepared according to the literature and used immediately upon isolation. CH_2Cl_2 was distilled from CaH_2. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (0.25 mm thickness) precoated with a fluorescent indicator. The developed plates were examined under a UV light and stained with anisaldehyde stain or $KMnO_4$. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. Mass spectral data were obtained at the Harvard Chemistry Department Mass Spectrometry facility. All ^{1}H and ^{13}C NMR spectra were recorded on Inova 600, Bruker AM 500 or AM 400 FT spectrometers at ambient temperature. IR spectra were recorded as a thin film between NaCl plates on a Matteson FTIR 3000. Optical Rotations were measured using a 2 mL cell with a 1 dm length on a Jasco DIP 370 polarimeter.

Part 1: Experimental Procedures and Analytical Data:

a. Catalyst synthesis.

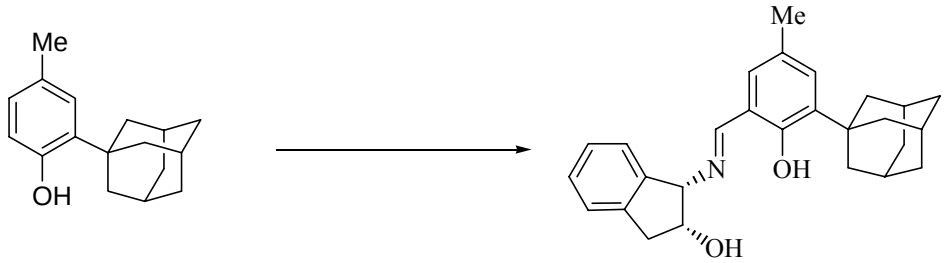
2-Adamantyl-*p*-cresol (5)



5

To a 200-mL round-bottomed flask is added *p*-cresol (11. 09 g, 102.6 mmol), followed by CH_2Cl_2 (90 mL). 1-Adamantanol (16.42 g, 107.8 mmol) is then added. The solution is stirred and concentrated H_2SO_4 (18 M, 6.0 mL) is added dropwise over 20 min. The biphasic mixture is allowed to stir for 20 min and H_2O (100 mL) is added. The mixture is neutralized slowly to pH = 9 by addition of a NaOH (2M). The mixture is extracted with CH_2Cl_2 (3 x 100mL). The combined organics are washed with brine (150 mL), dried with Na_2SO_4 , filtered and concentrated. The crude mixture (~24 g) is triturated with MeOH (100 mL), heated to reflux, allowed to cool to ambient temperature and filtered. The solid is washed with an additional portion of MeOH (100 mL) and the mother liquor concentrated to give a **5** as a white solid (19.4 g, 78%). This material is 97-99% purity by NMR and is used directly in the next step. IR (thin film) 3501, 2904, 2851, 1604, 1504, 1450, 1408, 1346, 1248, 1201, 1180, 1120, 1103, 1035, 976 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.06 (bs, 1H), 6.90 (d, *J* = 8.05 Hz, 1H), 6.56 (d, *J* = 8.05 Hz, 1H), 4.62 (s, 1H), 2.31 (s, 3H), 2.17 (m, 6H), 2.12 (bs, 3H), 1.82 (s, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 152.06, 136.07, 129.63, 127.63, 126.95, 116.60, 40.54, 37.04, 36.51, 29.01, 20.79.

3-(1-Adamantyl)-2-hydroxy-5-methylbenzaldehyde-(1R,2S)-1-aminoindanol imine (6).

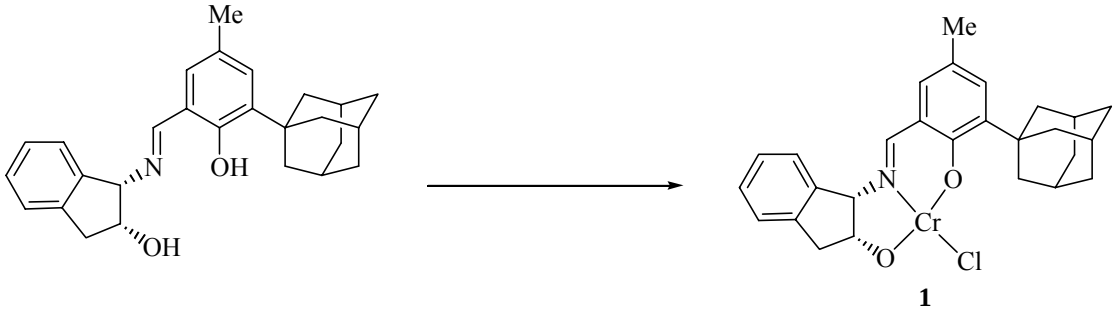


6

An oven-dried, 300-mL, three-necked round-bottomed flask is equipped with a stirbar, fitted with a reflux condenser, a thermometer, sealed with a septum, and placed under a nitrogen atmosphere. The flask is charged with 2-adamantyl-1-*p*-cresol (**5**) (12.1 g, 50.0 mmol, 1 equiv), freshly distilled toluene (110 mL) and 2,6-lutidine (4.28 g, 4.67 mL, 40.00 mmol, 0.8 equiv). $SnCl_4$ (2.60 g, 1.17 mL, 10.00 mmol, 0.2 equiv) was added by syringe over 10 min. The reaction turned pale yellow in color with a pale yellow precipitate. The mixture is allowed to stir at room temperature for 20 min, then solid paraformaldehyde (6.00 g, 200 mmol) is added in one portion and the reaction stirred an additional 10 min. The nitrogen inlet is replaced with a nitrogen balloon, the reaction flask placed in a 90-95 ^{o}C bath and maintained at this temperature for 6 hours. The reaction is allowed to cool to room temperature and filtered through celite-silica gel (1:1, 12 g). The celite-SiO_2 is washed with ethyl acetate (200 ml). The organic filtrate is then washed with water (350 mL), 1N HCl (350 mL) and brine (350mL). The organic layer is dried over anhydrous Na_2SO_4, filtered and concentrated in a 500-mL round-bottomed flask on a rotary-evaporator, followed by removal of trace solvent on a high vacuum pump (0.5 mmHg) (13.4 g crude, 99.5%). The aldehyde can be recrystallized from

hexanes, but purification is not essential for the formation of the Schiff base. The purified aldehyde has the following spectral and physical properties: mp 151.5-152 ^{o}C; IR (KBr) 3200-2500, 1649, 1607, 1524, 1447, 1416, 1356, 1312, 1244, 1221, 1163, 1105, 1084, 1040, 963, 864 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (s, 6H), 2.08 (s, 3H), 2.12 (s, 6H), 2.31 (s, 3H), 7.14 (d, *J* = 1.5 Hz, 1H), 7.26 (d, *J* = 1.5 Hz, 1H), 9.8 (s, 1H), 11.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 28.9, 36.9, 40.1, 120.3, 128.2, 131.2, 135.4, 138.1, 159.3, 197.1; Calculated for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.70; H, 8.16. Ethanol (200 proof, 200 mL) is added and the reaction heated until a solution is obtained, at which point (1*R*, 2*S)*-2-aminoindanol (7.83g, 52.50 mmol, 1.05 equiv) is added in one portion. The reaction is then heated at 80 ^{o}C for 45 min (precipitate forms), cooled to room temperature and allowed to stand for several hours before filtering. The yellow solid is washed with cold ethanol (50 mL) and is air dried (15.1 g, 75.2% over 2 steps). mp 219-221 ^{o}C; $[\alpha]^{26}_{D}$ +70.0^{o} (c 1.00, THF); IR (KBr disk) 3584, 2905, 2849, 1624, 1597cm^{-1}; ^{1}H NMR (500 MHz, DMSO- d_6-) δ1.69 (m, 6H), 1.99 (m, 3H), 2.05 (m, 6H), 2.23 (s, 3H), 2.95 (dd, *J* = 6.0, 15.5 Hz, 1H), 3.11 (dd, *J* = 6.1, 15.5 Hz, 1H), 4.54 ('q', *J* = 5.7 Hz, 1H), 4.73, (d, *J* = 5.5 Hz, 1H), 5.23 (d, *J* = 4.9 Hz, 1H), 7.01 (s, 1H), 7.09 (s, 1H), 7.18-7.31 (m, 4H), 8.61 (s, 1H), 10.94 (s, 1H); ^{13}C NMR (125 MHz) δ 25.4, 33.5, 41.4, 41.7, 79.1, 123.4, 129.9, 130.2, 130.9, 131.9, 133.1, 134.8, 135.2, 141.6, 146.2, 147.2, 153.7; HRMS (m/z) (CI NH_3) calc. for $C_{27}H_{35}NO_2(M)^+$ 401.2355, found 401.2341.

(1*S*,2*R*) Chromium(III) Cl complex (1).



1

To a 200-mL round-bottomed flask is added chromium(III) chloride tetrahydrofuran complex (1:3) (2.80 g, 7.48 mmol, 1equiv) and 3-(1-adamantyl)-2-hydroxy-5-methylbenzaldehyde-(1*S*, 2*R*)-1-aminoindanol imine (**6**) (3.00 g, 7.48 mmol, 1equiv). The flask is placed under a nitrogen atmosphere and CH_2Cl_2 (60 mL) is added followed by dropwise addition of 2,6-lutidine (1.74 mL, 14.96 mmol, 2 equiv). The solution is stirred for 3 h, diluted with CH_2Cl_2 (300 mL) and washed with water (3 x 180 mL) and brine (180 mL). The organic layer is dried over anhydrous Na_2SO_4 , filtered and concentrated. The resulting solid is triturated with ice-cold acetone (10 mL), filtered, washed with an additional portion of cold acetone (10 mL), and air dried to give the chromium complex (**1**) as a brown solid (2.3 g). To the filtrate (20 mL) is added water (2 mL) and the solution allowed to stand, uncovered at 23 ^{o}C overnight. The resulting precipitate is filtered and washed with cold acetone to give an additional 600-800 mg of the chromium complex (**1**) (combined yield 2.9-3.1 g, 75-80%). The complex is isolated as a dimer with a bridging water, and a water molecule coordinated to each Cr atom and shows the following spectral properties: IR (KBr) 3414, 2903, 2847, 1618, 1537, 1433, 1340, 1305, 1228, 1168, 1078 cm^{-1}. LRMS (FAB + NBA) mass calc. for dimer $C_{54}H_{68}Cl_2N_2O_7Cr_2$, $(M\text{-}2Cl\text{-}2H_2O)^+$, 920, found 919. A sample of this complex was treated with TMSCl as described below to provide a sample for elemental analysis: Chlorotrimethylsilane (39.0 μL, 0.31 mmol) was added to a solution of Cr(III)Cl complex (50.0 mg, 0.048 mmol) in dry *tert*-butyl methyl ether (2 mL). The mixture was stirred for 2 h under nitrogen to give a green precipitate. The mixture was concentrated *in vacuo*, suspended in dry *tert*-butyl methyl ether (2 mL), filtered and the residue washed with dry tert-butyl methyl ether. The residue was then dried by high vacuum. Calculated for $[C_{27}H_{29}ClCrNO_2+2HCl)$ (%): C, 57.92; H, 5.58; Cr, 9.29; N 2.50. Found(%): C, 57.49; H, 5.73; Cr, 9.00; N, 2.48. The Cr/N was calculated to be 0.98.

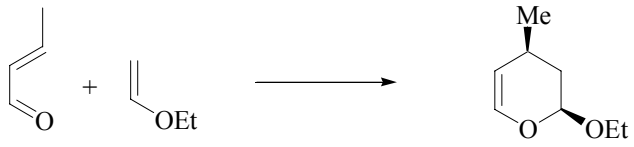
b. Cycloaddition reactions:

-General procedure for the cycloaddition reactions:

To an oven dried 10 mL round botton flask with stirbar is added freshly distilled ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and aldehyde (1.0 mmol, 1 equiv). To this

solution is added *1R,2S* Cr catalyst **1** (24.0 mg, 0.05 mmol) and freshly oven dried powdered 4Å molecular sieves (150 mg). The flask is sealed with a septum or stopper and allowed to stir for the time indicated in the table . The reaction is diluted with pentane or ether, and filtered through celite. The volatiles are removed and the residue purified by distillation or column chromatography on deactivated SiO_2 (deactivated by washing with 5% diethylmethylamine in pentane (3 column volumes)) to provide the cycloadduct.

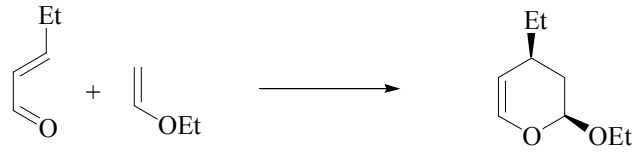
(2*S*, 4*S*)-2-Ethoxy-4-methyl-3,4-dihydro-2*H*-pyran (3a).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and crotonoaldehyde (**2a**) (70.0 mg, 82.7 μL, 1.00 mmol, 1equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2 days, diluted with pentane and filtered through celite. The pentane is removed and the product isolated by vaccum transfer to a flask cooled to -78 ^{o}C at 0.5 mmHg to yield 106 mg (75%) of **3a** as a clear oil and is identical to that previously reported[5]. $[\alpha]^{25}_{D}$ +48.9 ^{o} (c = 0.8, $CHCl_3$); IR (thin film) 2959, 2927, 2872, 1643, 1455, 1378, 1233, 1172, 1121, 1121, 1053, 972, 911 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, *J* = 5.86, 2.2 Hz, 1H), 4.88 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.53 (ddd, *J* = 6.2, 2.2, 1.46 Hz, 1H), 3.90 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.55 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.39 (m, 1H), 2.0 (ddd, *J* = 12.8, 6.2, 1.83 Hz, 1H), 1.47 (ddd, *J* = 12.8, 9.88, 8.8 Hz, 1H), 1.22 (t, *J* = 6.95 Hz, 3H), 1.0 (d, *J* = 6.96 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.30, 107.32, 99.38, 64.22, 36.93, 26.02, 21.22, 15.16.

Assay of enantiomeric excess: Chiral GC analysis (γ-TA, 35 ^{o}C, isothermal, t_R(major) = 12.66 min., t_R(minor) = 13.48 min) 94% ee.

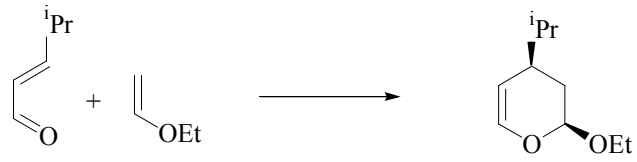
(2*S*, 4*S*)-2-Ethoxy-4-ethyl-3,4-dihydro-2*H*-pyran (3b).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and 2-pentenal (**3a**) (84.0 mg, 98.0 μL, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2 days, diluted with pentane and filtered through celite. The pentane is removed and the product isolated by vaccum transfer to a flask cooled to -78 ^{o}C at 0.5 mmHg to yield 117 mg (75%) of 3b as a clear oil. $[\alpha]^{25}_{D}$ +38.9 ^{o} (c = 0.7, CH_2Cl_2); IR (thin film) 3059, 2965, 2928, 2876, 1645, 1460, 1443, 1379, 1360, 1232, 1168, 1123, 1020, 1015, 1003, 956, 922, 872 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 6.22, 2.2 Hz, 1H), 4.64 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.34 (ddd, *J* = 6.2, 1.83, 1.46 Hz, 1H), 3.67 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.31 (dq, *J* = 9.52, 6.95 Hz, 1H), 1.96 (m, 1H), 1.77 (dddd, , *J* = 12.8, 6.2, 1.83, 1.46 Hz, 1H), 1.2-1.3 (m,1H), 1.0-1.16 (m, 2H), 0.98 (t, *J* = 6.95 Hz, 3H), 0.64 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.71, 105.72, 96.66, 64.33, 34.72, 32.80, 28.57, 15.22, 11.17; HRMS (EI^+) calc. for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1152.

Assay of enantiomeric excess: Chiral HPLC analysis (chiralcel OD, 100% hexane, 1 mL/min, 220 nm, t_R(major) = 6.09 min., t_R(minor) = 5.55 min.) 94% ee.

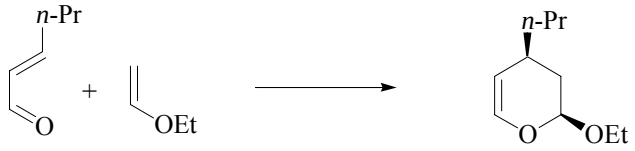
(2*S*, 4*R*)-2-Ethoxy-4-isopropyl-3,4-dihydro-2*H*-pyran (3c).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and 4-methyl-2-pentenal (**2d**) (98.0 mg, 116 μL, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (48.0 mg, 0.05 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2 days, diluted with pentane and filtered through celite. The pentane is removed and the product isolated by Kügelrohr distillation (100 ^{o}C , 0.5 mmHg) to yield 119 mg (73%) of **3d** as a clear oil. $[\alpha]^{25}_{D}$ +28.17 ^{o} (c = 1.06, CH_2Cl_2); IR (thin film) 3065, 2961, 2934, 2874, 1645, 1464, 1442, 1377, 1342, 1234, 1182, 1167, 1126, 1059, 1010, 974, 920, 883, 835 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 6.22, 2.2 Hz, 1H), 4.89 (dd, *J* = 9.52, 2.2 Hz, 1H), 4.6 (ddd, *J* = 6.2, 1.83, 1.83 Hz, 1H), 3.95 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.58 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.15-2.21 (m, 1H), 1.95 (dddd, *J* = 12.8, 6.2, 1.83, 1.83 Hz, 1H), 1.53-1.61 (m, 2H), 1.25 (t, *J* = 6.95 Hz, 3H), 0.89 (d, *J* = 6.59 Hz, 3H), 0.87 (d, *J* = 6.59 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.40, 104.35, 100.12, 64.43, 37.84, 32.02, 31.62, 19.52, 19.11, 15.22; HRMS (EI^+) calc. for $C_{10}H_{18}O_2$ (M^+) 170.1307, found 170.1308.

Assay of enantiomeric excess: Chiral HPLC analysis (chiralcel OD, 100% hexane, 1mL/min, 220 nm, t_R(minor) = 6.40 min., t_R(major) = 6.91 min.) 94% ee.

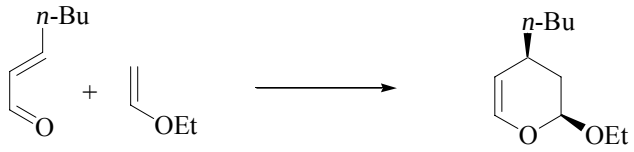
(2*S*, 4*S*)-2-Ethoxy-4-propyl-3,4-dihydro-2*H*-pyran (3d).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and 2-hexenal (**2c**) (98.0 mg, 116 μL, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2 days, diluted with pentane and filtered through celite. The pentane is removed and the product isolated by Kügelrohr distillation (100 ^{o}C , 0.5 mmHg) to yield 124 mg (73%) of **3c** as a clear oil. $[\alpha]^{25}_{D}$ +25.9 ^{o} (c = 0.95, CH_2Cl_2); IR (thin film) 2959, 2932, 2873, 2805, 1678, 1645, 1569, 1464, 1378, 1233, 1176, 1123, 1057, 966, 898, 872 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 6.22, 2.2 Hz, 1H), 4.89 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.59 (ddd, *J* = 6.2, 1.83, 1.46 Hz, 1H), 3.94 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.57 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.26-2.36 (m, 1H), 2.03 (dddd, *J* = 12.8, 6.2, 1.83, 1.46 Hz, 1H), 1.49 (ddd, *J* = 12.8, 10.25, 9.15 Hz, 1H), 1.27-1.37 (m, 4H), 1.24 (t, *J* = 6.95 Hz, 3H), 0.89 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 105.94, 99.64, 64.32, 38.07, 35.13, 30.95, 19.87, 15.21, 14.1; HRMS (EI^+) calc. for $C_{10}H_{18}O_2$ (M^+) 170.1307, found 170.1311.

Assay of enantiomeric excess: Chiral GC analysis (γ–TA, 40 ^{o}C, isothermal, t_R(minor) = 43.4 min., t_R(major) = 46.9 min.) 94% ee.

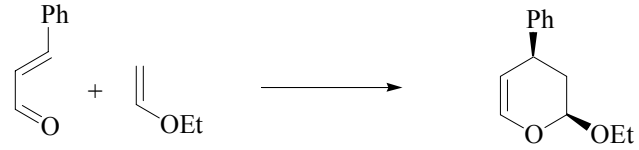
(2*S*, 4*S*)-2-Ethoxy-4-butyl-3,4-dihydro-2*H*-pyran (3e).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and 2-heptenal (**2e**) (112 mg, 130 μL, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.05 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2 days, diluted with pentane and filtered through celite. The pentane is removed and the product isolated by column chromatography (5% Et_2O/ pentane) on deactivated SiO_2 to yield 132 mg (72%) of **3e** as a clear oil. $[\alpha]^{25}_D$ +22.7 ^{o} (c = 1, CH_2Cl_2); IR (thin film) 3059, 2959, 2928, 2860, 1645, 1466, 1377, 1360, 1235, 1169, 1124, 1059, 1036, 974, 910, 872 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.24 (dd, *J* = 6.22, 2.2 Hz, 1H), 4.89 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.59 (ddd, *J* = 6.2, 1.83, 1.46 Hz, 1H), 3.93 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.57 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.22-2.32 (m, 1H), 2.03 (dddd, *J* = 12.8, 6.2, 1.83, 1.46 Hz, 1H), 1.49 (ddd, *J* = 12.8, 10.2, 8.8 Hz, 1H), 1.27-1.37 (m, 6H), 1.24 (t, *J* = 6.95 Hz, 3H), 0.88 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 106.0, 99.64, 64.30, 35.52, 35.15, 31.38, 28.96, 22.70, 15.21, 14.04; HRMS (EI^+) calc. for $C_{11}H_{20}O_2$ (M^+) 184.1463, found 184.1467.

Assay of enantiomeric excess: Chiral GC analysis (γ–TA, 40 ^{o}C, isothermal, t_R(minor) = 99.7 min., t_R(major) = 107.1 min.) 95% ee.

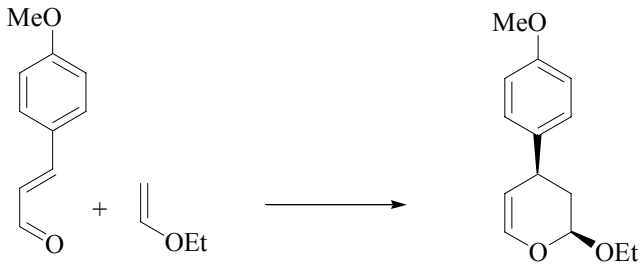
(2*S*, 4*S*)-2-Ethoxy-4-phenyl-3,4-dihydro-2*H*-pyran (3f).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and cinnamaldehyde (**2f**) (132 mg, 126 μL, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (48.0 mg, 0.05 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2 days, diluted with pentane and filtered through celite. The pentane is removed and the product isolated by column chromatography (10% Et_2O/ pentane) on deactivated SiO_2 to yield 153 mg (75%, 90% based on recovered starting material) of **3f** as a clear oil and **2f** (13 mg). The product was identical in all aspects to that previously reported.[5] $[\alpha]^{25}_D$ +25.55 ^{o} (c = 3.64, CH_2Cl_2); IR (thin film) 3062, 3028, 2977, 2931, 2871, 1644, 1603, 1495, 1453, 1441, 1377, 1360, 1343, 1234, 1160, 1135, 1099, 1031, 1008, 969, 913, 869, 830 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.08-7.21 (m, 5H), 6.43 (dd, *J* = 6.22, 2.2 Hz, 1H), 4.87 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.68 (ddd, *J* = 6.2, 1.83, 1.83 Hz, 1H), 3.93 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.37-3.45 (m, 2H), 2.14 (dddd, *J* = 13.8, 6.2, 1.83, 1.46 Hz, 1H), 2.01 (ddd, *J* = 13.8, 10.62, 9.15 Hz, 1H), 1.13 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.95, 142.61, 128.72, 128.24, 128.00, 127.76, 127.51, 126.68, 104.96, 99.75, 64.18, 38.32, 38.08, 15.37.

Assay of enantiomeric excess: Chiral GC analysis (γ-TA, 80 ^{o}C, isothermal, t_R(minor) = 76.08 min., t_R(major) = 81.38 min) 98% ee.

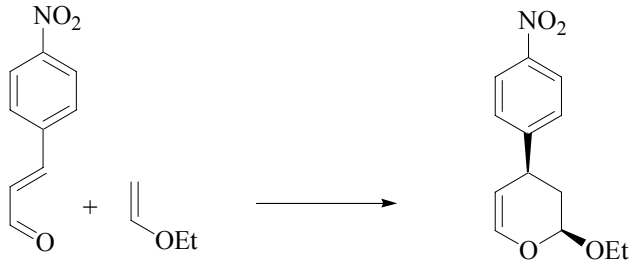
(2*S*, 4*S*)-2-Ethoxy-4-(4-methoxy-phenyl)-3,4-dihydro-2*H*-pyran (3g).



According to the general procedure ethyl vinyl ether (0.96 mL, 10 mmol, 10 equiv) and 4-methoxy-cinnamaldehyde (**2g**) (162 mg, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stir bar. To this solution is added **1** (48.0 mg, 0.05 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 4 days, diluted with ether and filtered through celite. The volatiles are removed and the product isolated by column chromatography (10% Et_2O/ pentane) on deactivated SiO_2 to yield 93.6 mg (40%, 95% based on recovered starting material) of **3g** and 90 mg recovered **2g**. $[\alpha]^{25}_D$ -37.6^o (c = 1.45, CH_2Cl_2); IR (thin film) 2978, 2929, 2903, 2875, 2836, 1644, 1611, 1512, 1464, 1443, 1377, 1303, 1250, 1233, 1175, 1158, 1096, 1034, 912, 870, 829, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.43 (dd, *J* = 6.22, 2.2 Hz, 1H), 5.03 (dd, *J* = 9.15, 1.83 Hz, 1H), 4.72 (ddd, *J* = 6.22, 2.2, 1.83 Hz, 1H), 3.96 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.79 (s, 3H), 3.56-3.65 (m, 2H), 2.23 (dddd, *J* = 13.2, 6.22, 1.83, 1.46 Hz, 1H), 1.85 (ddd, *J* = 13.2, 10.95, 9.15 Hz, 1H), 1.25 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.17, 141.97, 136.45, 128.09, 113.82, 105.38, 99.53, 64.35, 55.22, 38.00, 37.01, 15.16 ; HRMS (EI$^+$) calc. for $C_{13}H_{15}NO_4$ (M^+) 249.1001, found 249.1001.

Assay of enantiomeric excess: Chiral GC analysis (γ-TA, 125 ^{o}C, isothermal, t_R(minor) = 33.74 min., t_R(major) = 35.24 min) 98% ee.

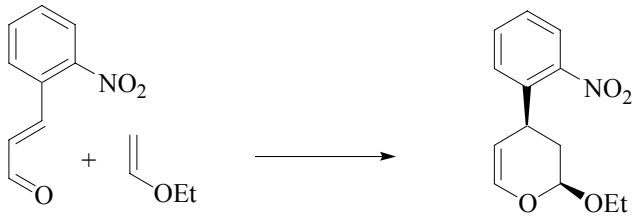
(2*S*, 4*S*)-2-Ethoxy-4-(4-nitro-phenyl)-3,4-dihydro-2*H*-pyran (3h).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and 4-nitro-cinnamaldehyde (**2h**) (177 mg, 1.00 mmol, 1 equiv) and CH_2Cl_2 (1 mL) are placed in an oven dried 10 mL flask with stir bar. To this solution is added **1** (48.0 mg, 0.05 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 3 days, diluted with ether and filtered through celite. The volatiles are removed and the product isolated by column chromatography (10% Et_2O/ pentane) on deactivated SiO_2 to yield 224 mg (90%) of **3h** as a clear oil. $[\alpha]^{25}_D$ -65 ^{o} (c = 1, CH_2Cl_2); IR (thin film) 3075, 2977, 2931, 2881, 1645, 1608, 1520, 1493, 1442, 1376, 1283, 1236, 1159, 1096, 1033, 1011, 973, 913, 856, 826, 754, 700 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.50 (dd, *J* = 6.22, 1.83 Hz, 1H), 5.05 (dd, *J* = 7.6, 2.2 Hz, 1H), 4.77 (m, 1H), 3.90 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.70 (m, 1H), 3.55 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.28 (dd, *J* = 13.2, 6.59 Hz, 1H), 1.89 (ddd, *J* = 13.2, 8.8, 8.0 Hz, 1H), 1.18 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.62, 146.88, 143.28, 128.52, 123.90, 103.26, 98.72, 64.57, 37.06, 15.32; HRMS (EI^+) calc. for $C_{13}H_{15}NO_4$ (M^+) 249.1001, found 249.1001.

Assay of enantiomeric excess: Chiral GC analysis (γ-TA, 150 ^{o}C, isothermal, t_R(minor) = 38.3 min., t_R(major) = 40.21 min) 98% ee.

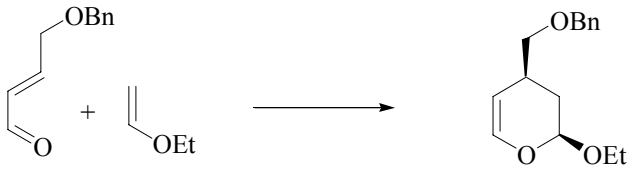
(2*S*, 4*S*)-2-Ethoxy-4-(2-nitro-phenyl)-3,4-dihydro-2*H*-pyran (3i).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and 2-nitro-cinnamaldehyde (**2i**) (177 mg, 1.00 mmol, 1 equiv) and CH_2Cl_2 (1 mL) are placed in an oven dried 10 mL flask with stir bar. To this solution is added **1** (48.0 mg, 0.05 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 4 days, diluted with ether and filtered through celite. The volatiles are removed and the product isolated by column chromatography (10% Et_2O/ pentane) on deactivated SiO_2 to yield 199 mg (80%) of **3i** as a clear oil .$[\alpha]^{25}_D$ -103.8 ^{o} (c = 2.6, CH_2Cl_2); IR (thin film) 3065, 2978, 2932, 2901, 2884, 1645, 1607, 1578, 1538, 1481, 1445, 1377, 1352, 1306, 1236, 1163, 1124, 1099, 1032, 972, 912, 854, 827, 787 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.05, 1.1 Hz, 1H), 7.5-7.6 (m, 2H), 7.31-7.36 (m, 1H), 6.53 (dd, *J* = 6.22, 2.2 Hz, 1H), 5.04 (dd, *J* = 8, 2.2 Hz, 1H), 4.68 (ddd, *J* = 6.22, 2.2, 1.46 Hz, 1H), 4.10-4.15 (m, 1H), 3.92 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.70 (m, 1H), 3.58 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.52 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.85 (ddd, *J* = 13.8, 9.15, 8.4 Hz, 1H), 1.20 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.43, 143.30, 139.04, 132.79, 129.99, 127.27, 124.09, 103.65, 98.83, 64.39, 36.35, 32.31, 15.08; HRMS (EI^+) calc. for $C_{13}H_{15}NO_4$ (M^+) 249.1001, found 249.1004.

Assay of enantiomeric excess: Chiral GC analysis (γ-TA, 135 ^{o}C, isothermal, t_R(minor) = 31.15 min., t_R(major) = 32.79 min) 98% ee.

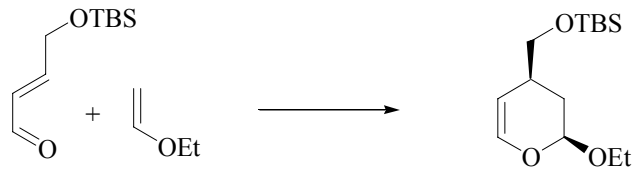
(2*S*, 4*R*)-2-Ethoxy-4-((benzylyloxy)-methyl-3,4-dihydro-2*H*-pyran (3j).



According to the general procedure ethyl vinyl ether (0.96 mL, 10 mmol, 10 equiv) and aldehyde **2j** (176 mg, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 1 day, diluted with pentane and filtered through celite. The pentane is removed and the product purified by column chromatography (5% Et_2O/ pentane) on deactivated SiO_2 to yield 223 mg (90%) of **3j** as a clear oil. $[\alpha]^{25}_{D}$ +14.85 ^{o} (c = 1.05, CH_2Cl_2); IR (thin film) 3063, 3030, 2976, 2928, 2859, 1647, 1454, 1377, 1362, 1232, 1164, 1111, 1047, 1034, 910, 872, 852 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28-7.38 (m, 5H), 6.30 (dd, *J* = 6.22, 1.83 Hz, 1H), 4.96 (dd, *J* = 7.7, 2.2 Hz, 1H), 4.71 (dd, *J* = 6.2, 2.93 Hz, 1H), 4.52 (s, 2H), 3.90 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.56 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.42 (d, *J* = 6.2 Hz, 2H), 2.58-2.7 (m, 1H), 2.09 (m, 1H), 1.68 (ddd, *J* = 13.9, 8.42, 8.05 Hz, 1H), 1.23 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.66, 138.4, 128.32, 127.54, 127.50, 102.27, 98.66, 74.16, 73.04, 64.20, 31.50, 31.41, 15.18. HRMS (EI^+) calc. for $C_{15}H_{20}O_3$ $(M)^+$ 248.1413, found 248.1406

Assay of enantiomeric excess: Chiral GC analysis (Cyclodex β, 100 ^{o}C, 90 min, 100-200 ^{o}C, 5 ^{o}C/min., t_R(major) = 107.49 min., t_R(minor) = 107.7 min) 95% ee.

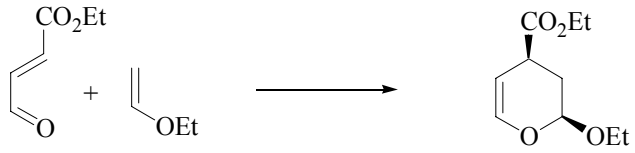
(2*S*, 4*R*)-2-Ethoxy-4-((*tert*-butyl-dimethylsilyloxy)-methyl-3,4-dihydro-2*H*-pyran (3k).



According to the general procedure ethyl vinyl ether (0.96 mL, 10 mmol, 10 equiv) and aldehyde **2k** (200 mg, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 1 day, diluted with pentane and filtered through celite. The pentane is removed and the product purified by column chromatography (5% Et_2O/ pentane) on deactivated SiO_2 to yield 258 mg (95%) of **3k** as a clear oil. $[\alpha]^{25}_D$ +20.4 ^{o} (c = 1.22, CH_2Cl_2); IR (thin film) 2957, 2930, 2887, 2859, 1649, 1472, 1442, 1379, 1362, 1256, 1232, 1169, 1109, 1082, 1049, 1004, 981, 839 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.28 (dd, *J* = 6.22, 2.2 Hz, 1H), 4.94 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.65 (ddd, *J* = 6.2, 2.2, 1.09 Hz, 1H), 3.90 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.46-3.59 (m, 2H), 2.4-2.5 (m, 1H), 2.00-2.06 (m, 1H), 1.60 (ddd, *J* = 13.9, 8.8, 6 Hz, 1H), 1.23 (t, *J* = 6.95 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.54, 102.36, 98.87, 66.97, 64.23, 33.82, 31.31, 25.90, 18.30, 15.19, -5.38. HRMS (EI^+) calc. for $C_{14}H_{28}O_3Si$ $(M)^+$ 272.1808, found 272.1810

Assay of enantiomeric excess: Chiral GC analysis (Cyclodex β, 100 ^{o}C, isothermal, t_R(major) = 57.3 min., t_R(minor) = 60.92 min) 91% ee.

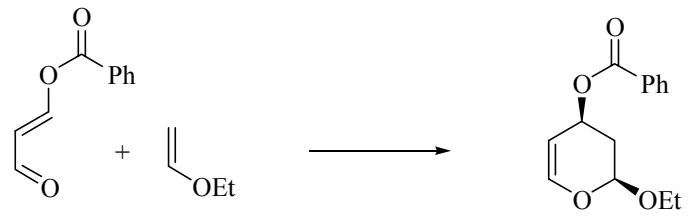
(2*S*, 4*S*)-2-Ethoxy-4-((*tert*-butyl-dimethylsilyloxy)-methyl-3,4-dihydro-2*H*-pyran (3l).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and aldehyde **2l** (128 mg, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 1 day, diluted with ether and filtered through celite. The solvent is removed and the product purified by column chromatography (5% Et_2O/ pentane) on deactivated SiO_2 to yield 180 mg (90%) of **3l** as a clear oil. $[\alpha]^{25}_D$ +43.43 ^{o} (c= 2.05, CH_2Cl_2); IR (thin film) 3073, 2980, 2936, 2907, 2878, 1735, 1651, 1447, 1371, 1342, 1300, 1265, 1236, 1188, 1121, 1047, 947, 872 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 6.22, 1.83 Hz, 1H), 5.01 (dd, *J* = 5.0, 2.0 Hz, 1H), 4.92 (dd, *J* = 6.2, 4.0 Hz, 1H), 4.1-4.2 (m, 2H), 3.82 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.56 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.04-3.1 (m, 1H), 2.35 (ddd, *J* = 13.5, 5.85, 5.49 Hz, 1H), 2.10 (ddd, *J* = 13.5, 6.95, 2.2 Hz, 1H), 1.23 (t, *J* = 6.95 Hz, 3H), 1.17 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 141.42, 99.18, 96.63, 63.63, 60.65, 34.61, 29.72, 14.93, 14.08. HRMS (EI^+) calc. for $C_{15}H_{20}O_3$ $(M)^+$ 248.1413, found 248.1406

Assay of enantiomeric excess: Chiral GC analysis (γ–TA, 85 ^{o}C isothermal, t_R(major) = 18.29 min., t_R(minor) = 20.53 min) 95% ee.

(2*S*, 4*S*)-2-ethoxy-4-benzoyl-3,4-dihydro-2*H*-pyran (3m).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and aldehyde **2m** (176 mg, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2 days, diluted with ether and filtered through celite. The ether is removed and the product isolated by column chromatography (10% Et_2O/ pentane) on deactivated SiO_2 to yield 198 mg (80%) of **3m**. $[\alpha]^{25}_D$ -59.37 ^{o} (c = 1.12 , CH_2Cl_2); IR (thin film) 3069, 2978, 2934, 1713, 1649, 1603, 1452, 1379, 1346, 1275, 1230, 1176, 1113, 978, 924, 870 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.04-8.08 (m, 2H), 7.52-7.58 (m, 1H), 7.40-7.45 (m, 2H), 6.46 (dd, *J* = 6.22, 1.10 Hz, 1H), 5.52 (m, 1H), 5.16 (dd, *J* = 4.39, 3.29 Hz, 1H), 5.08 (m, 1H), 3.91 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.26-2.34 (m, 2H), 1.27 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 166.09, 144.40, 132.72, 131.44, 130.06, 128.4, 101.09, 96.79, 64.26, 62.98, 33.198, 15.19; HRMS (CI^+) calc. for $C_{14}H_{16}O_4$ $(M+NH_4)^+$ 266.1393, found 266.1393

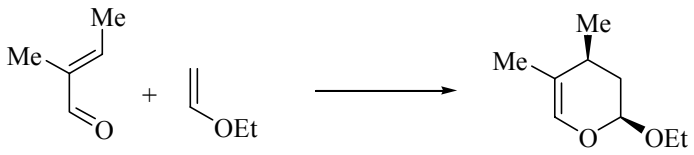
Assay of enantiomeric excess: Chiral GC analysis (Cyclodex β, 125 ^{o}C, isothermal, t_R(minor) = 75.4 min., t_R(major) = 74.0 min) 88% ee.

(2*S*, 4*R*)-5-Bromo-2-ethoxy-4-phenyl-3,4-dihydro-2*H*-pyran (3n).

According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and 2-bromo-cinnamaldehyde (**2n**) (211 mg, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (24.0 mg, 0.025 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 2.5 days, diluted with ether and filtered through celite. The ether is removed and the product isolated by column chromatography (5% Et_2O/ pentane) on deactivated SiO_2 to yield 142 mg (50 %) of **3n**. $[\alpha]^{25}_D$ +73.9 ^{o} (c = 1.3, CH_2Cl_2); IR (thin film) 3063, 3028, 2976, 2934, 2880, 1637, 1493, 1454, 1379, 1360, 1344, 1182, 1128, 1057, 1035, 995, 966, 916, 873, 843, 822 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.2-7.40 (m, 5H), 6.76 (d, *J* = 1.83 Hz, 1H), 5.08 (dd, *J* = 7.69, 2.2 Hz, 1H), 3.90 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.72 (m, 1H), 3.56 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.41 (ddd, *J* = 13.5, 7.32, 2.2 Hz, 1H), 2.16 (ddd, *J* = 13.5, 8.42, 7.32 Hz, 1H), 1.20 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.25, 141.62, 128.32, 128.13, 126.95, 103.68, 98.60, 64.53, 44.45, 38.68, 14.99; HRMS (EI^+) calc. for $C_{13}H_{15}O_2Br$ $(M)^+$ 282.0255, found 282.0244

Assay of enantiomeric excess: Chiral GC analysis (γ-TA, 100 ^{o}C, isothermal, t_R(minor) = 99.53 min., t_R(major) = 102.61 min) 98% ee.

(2*S*, 4*S*)-2-Ethoxy-4,5-methylyl-3,4-dihydro-2*H*-pyran (3o).



According to the general procedure ethyl vinyl ether (0.96 mL, 10.0 mmol, 10 equiv) and tiglic aldehyde (**2o**) (84.0 mg, 96.5 μL, 1.00 mmol, 1 equiv) are placed in an oven dried 10 mL flask with stirbar. To this solution is added **1** (27.0 mg, 0.037 mmol) and powdered 4 Å MS (150 mg). The reaction is allowed to stir 4 days, diluted with pentane and filtered through celite. The pentane is removed and the product isolated by column chromatography (5% Et_2O/ pentane) on deactivated SiO_2 to yield 117 mg (75%) of **3o** as a clear oil. $[\alpha]^{25}_D$ +72.5 ^{o} (c = 1.42, CH_2Cl_2); IR (thin film) 2961, 2932, 2878, 2862, 1663, 1456, 1439, 1344, 1310, 1288, 1236, 1138, 1099, 1076, 1061, 1024, 995, 957, 933, 860, 844 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.03 (t, *J* = 1.46 Hz, 1H), 4.87 (dd, *J* = 7.3, 2.2 Hz, 1H), 3.87 (dq, *J* = 9.52, 6.95 Hz, 1H), 3.53 (dq, *J* = 9.52, 6.95 Hz, 1H), 2.20-2.30 (m, 1H), 2.01 (dddd, , *J* = 13.2, 6.59, 2.56, 2.2 Hz, 1H), 1.60 (ddd, *J* = 13.2, 8.05, 7.3 Hz, 1H), 1.53 (t, *J* = 1.46 Hz, 3H), 1.22 (t, *J* = 6.95 Hz, 3H), 1.06 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.18, 113.28, 98.54, 63.98, 36.54, 29.26, 18.93, 15.61, 15.21; HRMS (EI$^+$) calc. for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1151.

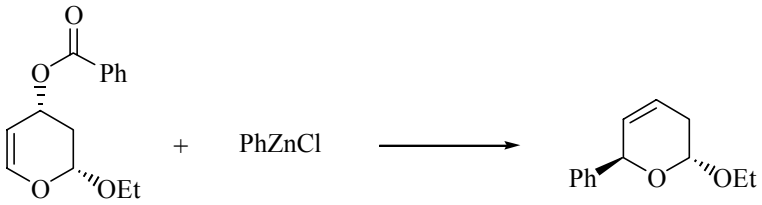
Assay of enantiomeric excess: Chiral GC analysis (γ–TA, 40 °C, isothermal, t_R(major) = 18.1 min., t_R(major) = 23.4 min.) 92% ee.

c. Organozinc addition to 3m

General Procedure:

The organozinc reagents were prepared according to the literature and the cycloadditions were conducted according to the procedure developed by Dubois, et al.[6] A typical experimental is given as follows:

(2*R*, 6*S*)-6-ethoxy-2-phenyl-3,4-dihydro-2*H*-pyran.

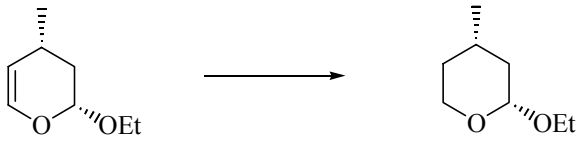


To a stirred solution of bromobenzene (128 mg, 0.82 mmol) in diethyl ether (0.8 mL is added *t*BuLi dropwise (1.7 M in pentane, 960 μL) at –78 °C. A solution of $ZnCl_2$ (116 mg, 0.85 mmol) in diethyl ether (1.2 mL) was added via cannula at –78 °C. Following the addition of $ZnCl_2$ the reaction was allowed to warm to to RT and stirred for 20 min. **2m** is added as a solution in diethyl ether (1 mL). The reaction is allowed to stir for 2h, quench with saturated NH_4Cl (5mL) and with CH_2Cl_2. The combined organics were dried with $MgSO_4$, filtered and concetrated to give a residue that was purified by column chromatography (5% EtOAc/Hexanes) to give the 82 mg (85%) of the addition product. $[\alpha]^{25}_D$ +31.7 ° (c = 0.55 , CH_2Cl_2); IR (thin film) 3036, 2976, 2907, 1493, 1452, 1371,

1273, 1217, 1180,1113, 1053, 1026, 972 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.3-7.42 (m, 5H), 5.84 (s, 2H), 5.24 (m, 1H), 5.07 (bd,1H), 3.93 (dq, *J* = 9.5, 6.95 Hz, 1H), 3.58 (dq, *J* = 9.5, 6.95 Hz, 1H), 2.56 (m, 1H), 2.18 (m,1H), 1.29 (t, *J* = 6.95 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.97, 128.46, 128.44, 127.81, 127.36, 121.75, 95.8, 70.39, 63.11, 29.92, 15.19.

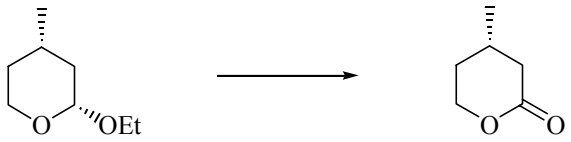
Part 2. Proof of Absolute Stereochemistry

(2*R*, 4*S*)-2-Ethoxy-4-methyl-tetrahydropyran (S1).



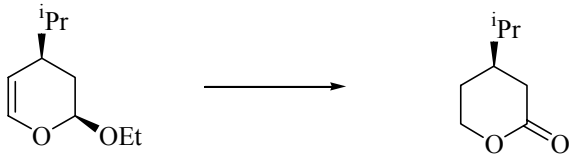
Vinyl ether **3a** (400 mg, 2.81 mmol) is dissolved in ether (10 mL) and Pd/C (5% wt, 60 mg) is added. The reaction was stirred under a H_2 atmosphere for 6 h, is filtered through celite, and the celite washed with ether. The ether was distilled to give 400 mg (99%) as a clear oil, identical in all aspects to that previously reported.[7] $[\alpha]^{25}_{D}$ –31.7 ^{o} (c = 2.4, CH_2Cl_2), lit. $[\alpha]^{25}_{D}$ –19.2 ^{o} (c = 0.45, $CHCl_3$) ; IR (thin film) 2955, 2929, 2871, 2843, 1458, 1444, 1413, 1378, 1307, 1258, 1167, 1142, 1077, 1026, 988, 976, 926, 892, 877 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (dd, *J* = 9.52, 2.19 Hz, 1H), 4.00 (ddd, *J* = 11.72, 4.76, 1.83 Hz, 1H), 3.92 (dq, *J* = 9.52, 7.32 Hz, 1H), 3.51 (dq, *J* = 9.52, 7.32 Hz, 1H), 3.38-3.48 (m, 2H), 1.76-1.82 (m, 1H), 1.59-1.7 (m, 1H), 1.45-1.51 (m, 1H), 1.22 (t, *J* = 7.32 Hz, 3H), 1.05-1.15 (m, 1H), 0.95 (d, *J* = 6.59 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 101.57, 65.33, 64.04, 40.12, 33.77, 29.4, 21.87, 15.28.

(4*S*)-4-Methyltetrahydro-2*H*-pyran-2-one (4a).



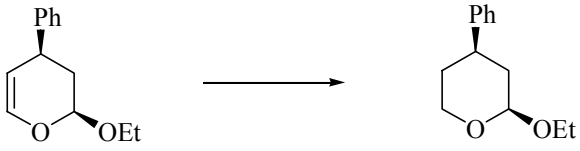
S1 (400 mg, 2.87 mmol) is dissolved in acetone/H_2O (1:1, 10 mL). *p*-Toluenesulfonic acid (22.0 mg, 0.16 mmol) is added and the reaction stirred 24 h at 25 ^oC. The reaction was diluted with ether (50 mL), washed with saturated $NaHCO_3$, and the organic collected. The aqueous layer was extracted with ether (2 x 30 mL), and the combined organics were with brine, dried with anhydrous $MgSO_4$, filtered and concentrated by rotary-evaporation below 20 ^oC. The residue is taken up in CH_2Cl_2 (15 mL) and pyridinium chlorochromate (860 mg, 4.00mmol) is added. The reaction is allowed to stir 16 h at 25 ^oC, is diluted with pentane (20 mL), filtered through celite, the solvent is concentrated by rotary-evaporation below 20 ^oC, and the residue purified by column chromatography (70% ether/pentane). The fractions are collected and the solvent distilled to give 217 mg (65 %) as a clear oil identical in all aspects to that previously reported.[8] $[\alpha]^{25}_D$ –25.2 ^{o} (c = 0.45, CH_2Cl_2), lit. $[\alpha]^{25}_D$ –19.2 ^{o} (c = 0.45, $CHCl_3$) ; IR (thin film) 2960, 2930, 2910, 2876, 1742, 1479, 1458, 1402, 1342, 1287, 1258, 1229, 1177, 1153, 1089, 1065, 995, 912, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.4 (m, 1H), 4.26 (m, 1H), 2.67 (m, 1H), 2.06-2.14 (m, 2H), 1.86-1.94 (m, 1H), 1.47-1.56 (m, 1H), 1.06 (d, *J* = 6.22 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.21, 68.57, 38.24, 30.65, 26.58, 21.45.

(4*R*)-4-(1-Methylethyl)tetrahydro-2*H*-pyran-2-one (4b).



Vinyl ether **2c** (100 mg, 0.59 mmol) is dissolved in ether (2 mL) and Pd/C (5% wt, 12 mg) is added. The reaction was stirred under a H_2 atmosphere for 6 h, is filtered through celite, and the celite washed with ether. The ether was distilled and the residue dissloved in acetone/H_2O (1:1, 2 mL) and *p*-toluenesulfonic acid (6.5 mg, 0.03 mmol) is added. The reaction is stirred 24 h, diluted with ether (20 mL) and washed with saturated $NaHCO_3$. The aqueous layer is extracted with ether (2x), the combined organics are washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue is dissolved in CH_2Cl_2 (5 mL) and pyridinium chlorochromate (253 mg, 1.17 mmol) added. The reaction is stirred 16 h, diluted with pentane (10 mL), filtered through celite and concentrated. Purification by column chromatography (ether/pentane 1:1) gave 57 mg (70%) as a clear oil identical in all aspects to that previously reported.[8] $[\alpha]^{25}_D$ +26.6 ^{o} (c = 0.68, CH_2Cl_2), lit. $[\alpha]^{25}_D$ +24.6^o (c = 0.75, $CHCl_3$) ; IR (thin film) 2962, 2876, 1739, 1472, 1442, 1402, 1371, 1258, 1225, 1179, 1149, 1082, 970, 935, 875 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (ddd, *J* = 11.35, 4.76, 4.0 Hz, 1H), 4.22 (ddd, *J* = 11.35, 10.62, 3.66 Hz, 1H), 2.66 (dddd, *J* = 17.2, 6.22, 1.83, 1.46 Hz, 1H), 2.21 (dd, *J* = 17.2, 10.62 Hz, 1H), 1.87-1.96 (m, 1H), 1.69-1.79 (m, 1H), 1.49-1.61 (m, 1H), 0.92 (d, *J* = 6.95 Hz, 3H), 0.91 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.00, 68.69, 37.85, 34.08, 32.30, 26.33, 19.26, 19.15.

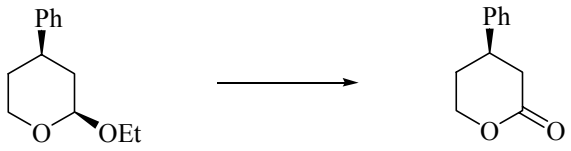
(2*S*, 4*R*)-2-Ethoxy-4-phenyl-tetrahydropyran (S2).



Vinyl ether (**3f**) (140 mg, 0.93 mmol) is dissolved in ether (4 mL) and Pd/C (5% wt, 40 mg) is added. The reaction was stirred under a H_2 atmosphere for 6 h, is filtered through celite, and the celite washed with ether. The ether was distilled to give 184 mg (97%) of **S2** as a clear oil. $[\alpha]^{25}_D$ +24 ^{o} (c = 2.16, CH_2Cl_2); IR (thin film) 3028, 2974, 2925, 2849, 1496, 1453, 1381, 1353, 1252, 1147, 1119, 1074, 980, 960, 915, 892, 862,

830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.2-7.34 (m, 5H), 4.51 (dd, *J* = 9.52, 2.19 Hz, 1H), 4.14 (ddd, *J* = 11.72, 3.29, 2.93 Hz, 1H), 3.98 (dq, *J* = 9.52, 6.59 Hz, 1H), 3.51-3.63 (m, 2H), 2.78-2.86 (m, 1H), 2.04 (m, 1H), 1.64-1.75 (m, 2H), 1.26 (t, *J* = 6.59 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.65, 128.49, 126.65, 126.37, 101.7, 65.50, 64.14, 40.62, 38.58, 33.19, 15.24. HRMS (CI^+) calc. for $C_9H_{16}O_2$ ($M+NH_4^+$) 224.1651, found 224.1653.

(4*R*)-4-Phenyltetrahydro-2*H*-pyran-2-one (4c).



S2 (20 mg, 0.1 mmol) is dissolved in acetone/H_2O (1:1, 1 mL). *p*-Toluenesulfonic acid (1.0 mg, 0.005 mmol) is added and the reaction stirred 24 h at 25 ^oC. The reaction was diluted with ethyl acetate (12 mL), washed with saturated $NaHCO_3$, and the organic collected. The aqueous layer was extracted with ethyl acetate (2 x 8 mL), and the combined organics were dried with anhydrous Na_2SO_4, filtered and concentrated by rotary-evaporation. The crystalline solid is taken up in CH_2Cl_2 (1.5 mL) and pyridinium chlorochromate (40 mg, 0.2 mmol) is added. The reaction is allowed to stir for 16 h at 25 ^oC, is diluted with pentane/ether (20 mL) and filtered through celite. The solvent is concentrated by rotary-evaporation, and the residue purified by column chromatography (2:1 hexanes/ethyl acetate) to give 14 mg (80 %) as a clear oil identical in all aspects to that previously reported.[8] $[\alpha]^{25}_D$ –3.2 ^{o} (c = 0.28, CH_2Cl_2), lit. $[\alpha]^{25}_D$ –3.4^o (c = 0.34, $CHCl_3$) ; IR (thin film) 3060, 3031, 2960, 2918, 2853, 1738, 1496, 1476, 1455, 1403, 1256, 1220, 1173, 1072, 977, 951 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.2-7.4 (m, 5 H), 4.52 (ddd, *J* = 11.4, 4.8, 3.9 Hz, 1H), 4.4 (ddd, *J* = 11.4, 10.4, 3.7 Hz, 1H), 3.24 (m, 1H), 2.93 (ddd, *J* = 16.7, 5.9, 1.7 Hz, 1H), 2.64 (dd, *J* = 17.7, 10.7 Hz, 1H), 2.18 (m, 1H), 2.05 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.64, 142.7, 128.95, 127.19, 126.42, 68.64, 37.48, 37.41, 30.26.

Part 3. X-ray Crystallographic Data

Data were collected using a Bruker SMART CCD (charge coupled device) based diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at 193 K. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were measured using omega scans of 0.3 ° per frame for 30 seconds, such that a hemisphere was collected. A total of 1271 frames were collected with a maximum resolution of 0.75 Å. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART[9] software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software[10] which corrects for Lp and decay. Absorption corrections were applied using SADABS[14] supplied by George Sheldrick. The structures are solved by the direct method using the SHELXS-97[11] program and refined by least squares method on F^2, SHELXL-97,[12] incorporated in SHELXTL-PC V 5.10.[13]

The structure was solved in the space group $P4_22_12$ (# 94) by analysis of systematic absences. All non-hydrogen atoms are refined anisotropically. Hydrogens were calculated by geometrical methods and refined as a riding model. The crystal used for the diffraction study showed no decomposition during data collection. All drawing are done at 50% ellipsoids. There appears to be two voids in the cell of approximately 1089 cubic angstroms, that we could not find any residual electron density in to assign as solvent. Previous structure contained THF molecule, this was re-crystallized without THF present.

Acknowledgement. The CCD based x-ray diffractometer at Harvard University was purchased through NIH grant (1S10RR11937-01).

References:

1. W. R. Roush, M. L. Reily, K. Koyama, B. B. Bradley, *J. Org. Chem.* **1997**, *62*, 8708. The crude aldehyde was purified on deactivated silica gel according to the following procedure: SiO_2 deactivated by washing with 5% diethylmethylamine in pentane (3 column volumes) then rinsing with 3 column volumes before loading the aldehyde on the column (10% EtOAc/ Hexanes)
2. J. Kang, J. Geun, S. K. Yoon, M. Y. Kim, *J. Org. Chem.* **1995**, *58*, 4465. The crude aldehyde was purified on deactivated silica gel according to reference 1.
3. T. V. Protopopova, A. P. Skoldinov, *Zh. Obshch. Khim.* **1958**, *28*, 240. It is essential that this aldehyde be purified immediately before use by the recrystalization procedure provided in the paper.
4. T. Veysoglu, L. A. Mitscher, J. K. Swayze, *Synthesis*, **1980**, 807.
5. S. J. Danishefsky, M. Bednarski, *Tetrahedron Lett.*, **1984**, *25*, 721-724.
6. D. P. Steinhuebel, J. J. Fleming, J. Du Bois, *Org. Lett.* **2002**, *4*, 293.
7. R. S. McKelvey, V. Kawada, T. Sugawara, H. Iwagara, *J. Org. Chem.* **1981**, *46*, 4948.
8. J. B. Jones, A. J. Irwin, *J Am. Chem. Soc.* **1977**, *99*, 556; D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635-1649.
9. SMART V 5.050 (NT) *Software for the CCD Detector System*; Bruker Analytical X-ray Systems, Madison, WI (1998).
10. SAINT V 5.01 (NT) *Software for the CCD Detector System* Bruker Analytical X-ray Systems, Madison, WI (1998).
11. Sheldrick, G. M. SHELXS-90, *Program for the Solution of Crystal Structure*, University of Göttingen, Germany, 1990.
12. Sheldrick, G. M. SHELXL-97, *Program for the Refinement of Crystal Structure,* University of Göttingen, Germany, 1997.
13. SHELXTL 5.10 (PC-Version), *Program library for Structure Solution and Molecular Graphics*; Bruker Analytical X-ray Systems, Madison, WI (1998).
14. SADABS. *Program for absorption corrections using Siemens CCD based on the method of Robert Blessing*; Blessing, R.H. Acta Cryst. A51 (1995) 33-38.