Cr(Salen) Catalyzed Addition of 1,3–Dichloropropene to Aromatic Aldehydes. A Simple Access to Optically Active Vinyl Epoxides

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Supporting Information

General Procedures.

Anhydrous diethyl ether, THF and dichloromethane were supplied by Fluka in Sureseal® bottles and used as received. ^{1}H-NMR spectra were recorded on Varian 200 (200 MHz) or Varian 300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = douplet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C-NMR spectra were recorded on a Varian 200 (50 MHz) or Varian 300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240-400 mesh silica gel. Analytical gas-chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex-5 chiral (25 m) column (flow rate 15 mL/min, method: 50 °C for 2 min, ramp @ 10 °C/min to 250 °C for 15 min). Analytical high performance liquid chromatography (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190-600 nm) and using a Daicel Chiralcel^{TM} OD column (0.46 cm I.D. x 25 cm) (Daicel Inc.). HPLC grade isopropanol and *n*-hexane were used as the eluting solvents. Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. All the reactions were carried out under a nitrogen atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents. All the commercially available reagents were used without further purification ($CrCl_3$: sublimed 99%, Aldrich; Mn powder: 99.9%, -50 mesh, Aldrich).

All the aldehydes were distilled prior to use.

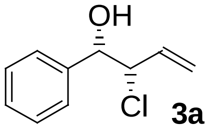
General reaction procedure for the addition of 1,3-dichloropropene to aromatic aldehydes mediated by indium.

Racemic products **3a-g** were obtained by using an indium mediated *syn* selective addition of 1,3-dichloropropene to aldehydes.[1] The reported procedure was modified as the following (the modified procedure is still *syn* selective, proved by ^{1}H-NMR analysis on the corresponding epoxides obtained from the isolated 1,2-chloridrines):

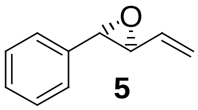
To a solution of the aromatic aldehyde (**2a-g**) (2 mmol) dissolved in a mixture 2:1 THF/H_2O (9 mL), indium (3 mmol) and 1,3-dichloropropene (2.8 mmol) were added. The mixture was stirred at room temperature until complete consumption of aldehyde (checked by TLC). The mixture was diluted with water (5 mL) then extracted with Et_2O (2 x 5 mL). The organic phases were collected, dried over Na_2SO_4 and evaporated under reduced pressure to give an oil purified by chromatography (Cyclohexane-Et_2O, 9:1-8:2).

General reaction procedure for the addition of 1,3-dichloropropene to aromatic aldehydes mediated by Cr(Salen).

$CrCl_3$ (0.016 g, 0.1 mmol) was suspended in anhydrous CH_3CN then Mn powder (0.16 g, 3 mmol) was added. The mixture was kept at room temperature without stirring[2] for 5-8min. After that, the mixture was vigorously stirred and a green-white precipitated was formed in 10-15 minutes. Then Salen (0.11 g, 0.2 mmol) and anhydrous Et_3N (0.028 mL, 0.2 mmol) were added. The resulting heterogeneous mixture was stirred at room temperature during one hour, then reagent grade 1,3-dichloropropene was added. The colour of the mixture turned out maroon-red and the resulting suspension was stirred during one hour at room temperature. After that time the aromatic aldehyde (1 mmol) and Me_3SiCl (1.5 mmol) were added to the reaction mixture. The mixture was stirred until complete consumption of the aldehyde (checked by GC, 24-48 hours). The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (5 mL) and filtered over celite®. The organic phase was separated and the aqueous phase extracted with Et_2O (2 x 4 mL). The combined organic phases were combined and evaporated under reduced pressure. The resulting brown oil was dissolved in THF (2 mL) and 2 N HCl (2 mL) was added. The reaction mixture was stirred room temperature until complete de-silylation (checked by TLC, 2-4 hours). The THF was evaporated under reduce pressure and the aqueous phase was extracted with Et_2O (2 x 4mL). The combined organic phase were dried over Na_2SO_4 and evaporated under reduced pressure to give an oil purified by chromatography (Cyclohexane-Et_2O, 9:1-8:2).

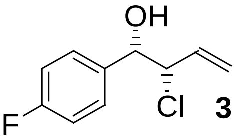

3a

3a: Elution of the column (Cyclohexane–Et_2O, 9:1) gave the product **3a** as a pure *syn* diasteroisomer. **^{1}H-NMR** (200 MHz, $CDCl_3$) and **^{13}C-NMR** (75 MHz, $CDCl_3$) spectral data were in agreement with the reported values.[3] HPLC analysis was performed by chiral HPLC column, (Chiralcel-OD); *n*-Hex:IPA 98:2 isocratic, flow 0.5 mL/min. t_r(*S*,*S*)*syn*=28.96min, t_r(*R*,*R*)*syn*=31.38 min, t_r(*R*,*S*)*anti*=29.37min, t_r(*S*,*R*)*anti*=33.95min; e.e.(*syn*)=81%; e.e.(*anti*)=44% **Anal.**: Calcd for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07. Found: C, 65.55; H, 6.19.


5

Preparation of *cis* –(1*S*,2*R*)-1,2-epoxy-1-phenyl-3-butene (5).

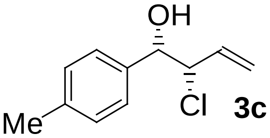
To a solution of **3a** (0.12 g, 0.65 mmol) in MeOH (3 mL), K_2CO_3 (0.18 g, 1.32 mmol) was added and the reaction mixture was stirred 3 hours at room temperature. MeOH was carefully evaporated under reduced pressure (volatile compound!) then water was added. The aqueous phase was extracted with Et_2O (2 x 3 mL) then the solvent evaporated. The crude product was sublimed then further purified by chromatography. Elution of the column (Cyclohexane-Et_2O, 97:3) gave the product as a clear oil; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H); 5.58-5.53 (m, 1H); 5.29-5.26 (m, 1H); 4.25 (d, 1H, J= 4.1Hz); 3.67 (q, 1H, J= 4.1Hz). **^{13}C-NMR** (75 MHz,$CDCl_3$) δ 135.19, 132.15, 128.53, 128.12, 127.73, 126.47, 125.54, 12.84, 59.77, 58.85. **IR** (neat) ν: 1496, 1443, 1252, 1181, 1059, 986, 927, 821, 787 cm^{-1}. $[\alpha]^D$= -89.0 (c 1, $CHCl_3$) (reported value[4]: *cis*–(1*R*,2*S*)-1,2-epoxy-1-phenyl-3-butene $[\alpha]^D$= +97.4 (c 2.65, EtOH)).


3b

3b: Elution of the column (Cyclohexane–Et_2O, 9:1) gave the product **3b** as a mixture of two diastereoisomers (*syn*:*anti* 85:15). Diastereoisomeric ratio was evaluated by ^{1}H-NMR and HPLC.

^{1}H-NMR (300, CDCl$_3$) (*anti* +*syn*): δ 7.20-7.15 (m, 2H); 7.05-7.00 (t, 2H, J= 6.9Hz); 6.00-5.80 (m, 1H, *anti*); 5.80-5.78 (m, 1H, *syn*); 5.28-5.15 (m, 2H, *anti*); 4.72 (dd, 1H, J= 8.1, 7.2Hz, *syn*); 4.51 (dd, 1H, J=7.2, 3.3Hz, *syn*); 2.83 (d, 1H, J=3.6Hz, *syn*); 2.55 (d, 1H, J= 3.3Hz, *anti*).

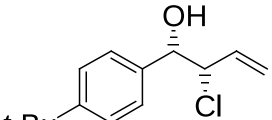
^{13}C-NMR (50, CDCl$_3$): δ 165.30, 134.30, 129.04, 128.80, 115.30, 112.20, 76.90 (*syn*), 72.80 (*anti*), 69.40 (*anti*), 67.50 (*syn*). **IR** (neat) ν: 3423, 1639, 1513, 1414, 1222, 1062, 930, 830 cm^{-1}. HPLC analysis was performed with a chiral column, (Chiracel-OD); *n*-Hex:IPA 90:10 isocratic, flow 0.5 mL/min. t_r(*S*,*S*)*syn*=28.19 min, t_r(*R*,*R*)*syn* =28.98 min, t_r(*R*,*S*)*anti*=30.24 min, t_r(*S*,*R*)*anti* =30.48 min; e.e.(*syn*) = 83%; e.e.(*anti*)= 30%. **Anal**.: Calcd for $C_{10}H_{11}ClFO$: C, 59.86; H, 5.02. Found: C, 59.94; H, 4.96.



3c

3c: Elution of the column (Cyclohexane-Et$_2$O, 85:15) gave the product **3c** as a mixture of two diastereoisomer (*syn*:*anti* 86:14). Diastereoisomeric ratio was evaluated by ^{13}C-NMR and HPLC.

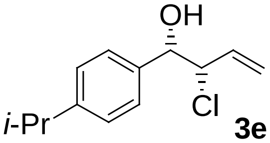
^{1}H-NMR (300, CDCl$_3$) (*anti*+*syn*): δ 7.30-7.24 (m, 2H), 7.20-7.15 (m, 2H) 6.00-5.92 (m, 1H, *anti*); 5.90-5.78 (m, 1H, *syn*); 5.40-5.20 (m, 2H, *anti*); 5.28-5.10 (m, 2H, *syn*); 4.90 (br, 1H, *anti*); 4.80 (br, 1H, anti); 4.70 (dd, 1H, J= 7.2, 3.3Hz, *syn*), 4.56 (dd, 1H, J=8.1, 7.2Hz, *syn*); 2.73 (d, 1H, J= 3.3Hz); 2.49 (d, 1H, J= 3.5Hz, *anti*); 2.32 (s, 3H). **^{13}C-NMR** (75, CDCl$_3$): δ 138.00 (*anti*), 136.07 (*anti*), 134.27 (*syn*), 133.47 (*anti*), 128.29 (*syn*), 128.81 (*anti*), 126.73 (*syn*), 125.65 (*anti*), 119.71 (*anti*), 119.13 (*syn*), 77.09 (*syn*), 76.62 (*anti*), 69.15 (*syn*), 67.02 (*anti*), 43.65 (*anti*), 21.50 (*syn*). **IR** (neat) ν: 3423, 2925, 1619, 1507, 1434, 1195, 1062, 923, 824 cm^{-1}. HPLC analysis was performed with chiral column, (Chiracel-OD); *n*-Hex:IPA 99:1 isocratic, flow 0.5 mL/min. t_r(*S*,*S*)*syn*=32.28 min, t_r(*R*,*R*)*syn* =34.36 min; e.e.(*syn*)=71%. **Anal**.: Calcd for $C_{11}H_{13}ClO$: C, 67.18; H, 6.66. Found: C, 67.28; H, 6.59.



3d

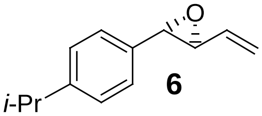
3d: Elution of the column (Cyclohexane-Et$_2$O, 85:15) gave the product **3d** as a mixture of two diastereoisomers (*syn*:*anti* 77**:**14). Diastereoisomeric ratio was evaluated by ^{13}C-NMR and HPLC.

^{1}H-NMR (200 MHz, CDCl$_3$) (*anti*+*syn*) δ 7.40-7.20 (m, 4H); 6.00-5.85 (m, 1H, *anti*); 5.90-5.70 (m, 1H, *syn*); 5.34-5.20 (m, 2H, *anti*); 5.29-5.10 (m, 2H, *syn*); 4.90 (br, 1H, *anti*); 4.70 (dd, 1H, J=7.2, 3.3Hz); 4.55 (dd, 1H, J= 8.1, 7.2Hz); 2.75 (d, 1H, J= 3.3Hz); 2.47 (d, 1H, J= 3.4Hz, *anti*); 1.30 (s, 9H). **^{13}C-NMR** (75 MHz, $CDCl_3$) (*anti*+*syn*) δ 151.19 (*anti*), 136.39 (*anti*), 134.64 (*syn*), 133.88 (*anti*), 126.89 (*syn*), 126.74 (*anti*), 125.54 (*syn*), 125.41 (*anti*), 120.08 (*anti*), 119.45 (*syn*), 77.39 (*syn*), 73.43 (*anti*), 69.36 (*syn*), 67.54 (*anti*), 31.63 (*syn*). **IR** (neat) ν: 3409, 2959, 1613, 1507, 1407, 1252, 1202, 1059, 917, 830 cm^{-1} . HPLC analysis was performed with a chiral column, (Chiracel-OD); *n*-Hex:IPA 99.5:1 isocratic, flow 0.5 mL/min. t_r(*S*,*S*)*syn*=34.35 min, t_r(*R*,*R*)*syn* =35.11 min. e.e.(*syn*)=73%. **Anal**: Calcd for $C_{14}H_{19}ClO$: C, 70.43; H, 8.02. Found: C, 70.50; H, 7.95



3e

3e: Elution of the column (Cyclohexane-Et_2O, 99.5:0.5) gave the product **3e** as a mixture of two diastereoisomers (*syn*:*anti* 87**:**13). Diastereoisomeric ratio was evaluated by ^{13}C-NMR and HPLC. **^{1}H-NMR** (200 MHz, $CDCl_3$) (*anti*+*syn*) δ 7.40-7.20 (m, 4H); 6.00-5.80 (m, 1H, *anti*); 5.90-5.70 (m, 1H, *syn*); 5.40-5.15 (m, 2H, *anti*); 5.30-5.10 (m, 2H, *syn*); 4.90(br, 1H, *anti*); 4.72 (dd, 1H, J=7.3, 3.5Hz); 4.55 (dd, 1H, J= 7.7, 7.3Hz); 2.90 (sept, 1H, H= 6.9Hz); 2.75 (d, 1H, J= 3.6Hz, *syn*); 2.47 (d, 1H, J= 3.4Hz, *anti*); 1.25 (d, 6H, J= 6.9Hz). **^{13}C-NMR** (75 MHz, $CDCl_3$) (*anti*+*syn*) δ 136.71 (*anti*), 134.60 (*syn*), 133.79 (*anti*), 127.13 (*syn*), 126.96 (*anti*), 126.69 (*syn*), 126.57 (*anti*), 120.13 (*anti*), 119.49 (*syn*), 77.50 (*syn*), 77.04 (*anti*), 69.49 (*syn*), 67.51 (*anti*), 34.12, 24.24. **IR** (neat) ν: 3416, 2972, 1626, 1513, 1420, 1125, 1056, 937, 824, cm^{-1}. **Anal**.: Calcd for $C_{13}H_{17}ClO$: C, 69.48; H, 7.62. Found: C, 69.40; H, 7.56.



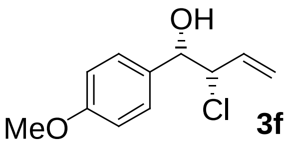
6

Preparation of the epoxide 6.

Enantiomeric excess of **3e** was evaluated by the transformation of **3e** in the corresponding epoxide **6**. Elution of the column (petroleum ether-Et_2O, 95:5) gave the product as a clear oil;

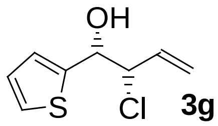
^{1}H-NMR (200 MHz, $CDCl_3$) (*trans*+*cis*) δ 7.40-7.20 (m, 4H); 5.80-5.72 (m, 1H); 5.70-5.58 (m, 1H); 4.22 (d, 1H, J= 4.4Hz, *cis*); 3.75 (d, 1H, J= 2.2Hz, *trans*); 3.40 (dd, 1H, J=7.2, 2.2Hz, *trans*); 3.64 (dd, 1H, J=7.2, 4.4Hz); 2.45 (sept, 1H, J= 7.4Hz); 1.12 (d, 6H, J=7.4Hz). **^{13}C-NMR** (75 MHz,$CDCl_3$) (*trans*+*cis*) δ 148.28, 135.11 (*trans*), 132.21 (*cis*), 126.51 (*trans*), 126.31 (*cis*), 126.14 (*cis*), 125.44 (*trans*), 121.75 (*cis*), 119.36 (*trans*), 65.85 (*trans*), 62.87 (*trans*), 59.88 (*cis*), 58.86

(*cis*), 33.87, 24.00. Chiral GC analysis was performed with a Megadex-5 chiral column, 115°C isotherm, t_r(*S,S*)*cis*=30.42 min, t_r(*R,R*)*cis* =31.63 min. e.e. (*cis*)=82%.



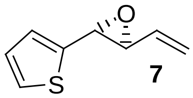
3f

3f: Elution of the column (Cyclohexane-Et_2O, 80:20) gave the product **3f** as a mixture of two diastereoisomers (*syn*:*anti* 76:24). Diastereoisomeric ratio was evaluated by ^{13}C-NMR and HPLC. **^{1}H-NMR** (200 MHz, $CDCl_3$) (*anti*+*syn*) δ 7.30-7.20 (m, 2H); 6.90-6.80 (m, 2H), 6.00-5.80 (m, 1H, *anti*); 5.84-5.70 (m, 1H, *syn*); 5.30-5.20 (m, 2H, *anti*); 5.22-5.11 (m, 2H, *syn*); 4.90 (br, 1H, *anti*); 4.70-4.50 (m, 1H, *syn*); 4.54 (dd, 1H, 8.1, 7.5Hz, *syn*); 3.90 (s, 3H, *anti*); 3.88 (d, 1H, J= 3.3Hz, *anti*), 3.8 (s, 3H, *syn*); 3.79 (d, 1H, J= 3.3Hz, *syn*). **^{13}C-NMR** (75 MHz, $CDCl_3$) (*anti*+*syn*) δ 134.25 (*syn*), 131.92 (*anti*), 131.11 (*anti*), 128.11 (*syn*), 127.90 (*anti*), 119.87 (*anti*), 119.26 (*syn*), 114.24 (*syn*), 113.70 (*anti*), 77.00 (*syn*), 76.46 (*anti*), 69.38 (*syn*), 67.38 (*anti*), 55.57 (*anti*), 55.23 (*syn*). **IR** (neat) ν: 3443, 2952, 1606, 1507, 1467, 1507, 1248, 1023, 937, 837 cm^{-1}. HPLC analysis was performed with a chiral column, (Chiralcel-OD); *n*-Hex:IPA 99:1 isocratic, flow 0.5 mL/min. t_r(*S,S*)*syn*=54.72 min, t_r(R,R)*syn* =62.07 min; t_r(*S,R*)*anti*=64.96 min, t_r(*S,R*)*anti* =68.87 min; e.e. (*syn*)=61%; e.e. (*anti*)= 48%. **Anal**: Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 62.21; H, 6.13.



3g

3g: Elution of the column (Cyclohexane-Et_2O, 80:20) gave the product **3g** as a mixture of two diastereoisomer (*syn:anti* 71**:**29). Diastereoisomeric ratio was evaluated by ^{13}C-NMR and HPLC. **^{1}H-NMR** (200 MHz, $CDCl_3$): (*anti*+*syn*) δ 7.10-7.09 (m, 1H); 7.08-6.90 (m, 2H); 6.00-6.85 (m, 1H, *anti*); 5.90-5.80 (m, 1H, *syn*); 5.40-5.20 (m, 2H, *anti*); 5.30-5.20 (m, 2H, *syn*); 5.02 (d, 1H, J= 6.9Hz, *syn*); 5.11 (br, 1H, *anti*); 4.65-4.60 (m, 2H, *anti*); 4.60 (dt, 1H, J= 7.8, 6.9Hz, *syn*); 2.6 (br, 1H). **^{13}C-NMR** (75 MHz,$CDCl_3$) (*anti*+*syn*) δ 142.23 (*anti*), 133.92 (*syn*), 133.24 (*anti*), 126.58 (*syn*), 125.71 (*syn*), 125.57 (*syn*), 124.53 (*anti*), 120.48 (*syn*), 119.79 (*anti*), 118.83 (*anti*), 77.00 (*syn*), 73.50 (*anti*), 68.62 (*syn*), 67.03 (*anti*). **IR** (neat) ν: 3423, 1653, 1427, 1222, 1049, 923 cm^{-1}. **Anal**: Calcd for C_8H_9ClOS : C, 50.93; H, 4.81. Found: C, 50.80; H, 4.94.


7

Preparation of the epoxide 7.

Enantiomeric excess of **3g** was evaluated by the transformation of **3g** in the corresponding epoxide **7**. Elution of the column (Cyclohexane-Et_2O, 95.5) gave the product as a pale yellow oil. **^{1}H-NMR** (200 MHz, $CDCl_3$) (*cis*+*trans*) δ 7.27 (d, 1H, J= 1.5, 1Hz, *trans*); 7.25 (d, 1H, J= 1.2Hz, *cis*); 7.12 (dd, 1H, J= 1.5, 0.8Hz, *trans*); 7.01 (dd, 1H, J= 1.2, 0.9Hz, *cis*); 5.70-5.50 (m, 2H); 5.4-5.35 (m, 1H); 4.39 (dd, 1H, J= 4.2, 0.3Hz, *cis*); 4.02 (d, 1H, J= 2.1Hz, *trans*); 3.70 (dd, 1H, J= 6.9, 4.2Hz, *cis*); 3.56 (dd, 1H, J=.6.9, 2.1Hz, *trans*). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 140.92 (*trans*), 138.39 (*cis*), 134.52 (*trans*), 131.93 (*cis*), 127.14 (*cis*), 126.95 (*trans*), 126.09 (*cis*), 126.05 (*trans*), 125.23 (*cis*), 125,15 (*trans*), 122.31 (*cis*), 120.08 (*trans*), 63.62 (*trans*), 60.62 (*cis*), 57.19 (*trans*), 56.15 (*cis*). **IR** (neat) ν: 3409, 2959, 1613, 1507, 1407, 1252, 1202, 1059, 917, 830 cm^{-1}. Chiral GC analysis was performed with a Megadex-5 chiral column, 60 °C, 5 min then 130 °C 4 °C/min., t_r(*R*,*R*)*cis*=18.83 min, t_r(*S*,*S*)*cis* =19.78 min; e.e. (*cis*) = 74%.

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[1] Hirashita, T.; Kamei, T.; Horie, T.; Yamamura, H.; Kawai, M.; Araki, S. *J. Org. Chem.* **1999**, *64*, 172.

[2] The reduction of $CrCl_3$ by Mn is a critical point. We recommend to not stir the reaction mixture until the purple colour of the $CrCl_3$ completely disappeared. Stirring the reaction mixture immediately upon the addition of the two reagents furnished disappointing results.

[3] Julia, M.; Verpeaux, J.N.; Zanheisen, T. *Bull. Soc. Chim. Fr.* **1994**, *131*, 539.

[4] Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513.