High Enantioselectivities in an *E*-alkene Epoxidation by Catalytically Active Chromium Salen Complexes. Insight into the Catalytic Cycle.

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General Experimental:

Melting points were determined either on a Gallenkamp melting point block or a Reichert Thermovar and are uncorrected. Elemental analyses were carried out by the Microanalytical Laboratory, University College Dublin. Infrared spectra were obtained on a Mattson Instruments Galaxy Series FTIR 3000 spectrometer. Mass spectra were carried out by the Mass Spectrometry Service, University College Dublin. Optical rotation values were obtained using a Perkin-Elmir 241 polarimeter.

^{1}H NMR spectra were recorded at 270 MHz on a Jeol JNM-GX270 FT spectrometer and at 300 MHz on a Varian INOVA 300 spectrometer. ^{13}C NMR spectra were recorded at 67 MHz (Jeol) or 75 MHz (Varian). Chemical shifts are reported as δ-values in ppm relative to internal standard tetramethylsilane (TMS) for ^{1}H spectra.

Chiral gas-liquid chromatography (GC) was performed on a Shimadzu GC-8A gas chromatograph coupled to a Shimadzu C-R3A integrator. High-performance liquid chromatography was performed using a Waters 501 HPLC pump with a Waters 486 Tunable Absorbance detector coupled to a Shimadzu C-R5A integrator.

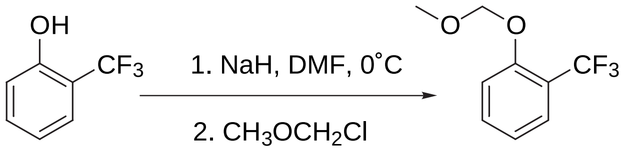
All commercially available solvents were used as supplied, unless otherwise stated. Solvents were dried according to standard procedures.[1] Oxygen-free nitrogen was obtained from BOC gases and was used without further drying.

Thin layer chromatography (TLC) was performed on Merck precoated Kieselgel $60F_{254}$ and alumina (neutral, type E) plates and realisation was by UV irradiation. Flash column chromatography was performed on Merck silica 9385, particle size 0.04-0.063 mm and aluminium oxide 90, standardised (activity II-III), particle size 0.063-0.200 mm (70-230 mesh ASTM).

2-(trifluoromethyl)phenol was obtained from Fluorochem Ltd. *Z*-ß-methylstyrene was obtained from Chemsampco Inc., 40 Enterprise Avenue , Trenton, NJ 08638, USA, Ph: +1-609-656-2440. All other chemicals were obtained from the Aldrich Chemical Company and used as received.

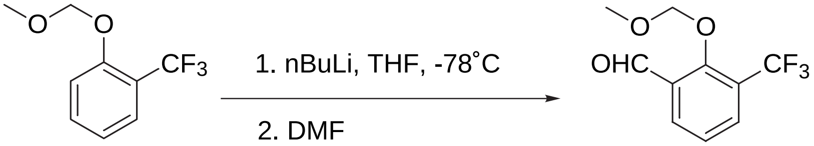
1. Synthesis of 2-Hydroxy-3-(trifluoromethyl)benzaldehyde

2-(Methoxymethoxy)-1-(trifluoromethyl)benzene.



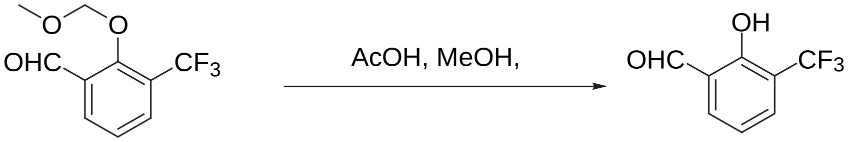
Sodium hydride (6.40 g of a 60% dispersion in mineral oil, 160 mmol) was washed with hexane and transferred to a 2-neck 250 mL round bottom flask under an atmosphere of N_2. After addition of anhydrous DMF (50 mL) the slurry was cooled with stirring to 0 ˚C. To the resulting grey suspension was added dropwise a solution of 2-(trifluoromethyl)phenol (24.00 g, 150 mmol) in anhydrous DMF (25 mL) at such a rate that the evolution of hydrogen did not become too vigorous. After complete addition the ice bath was removed and the brown reaction mixture stirred for 1 hour. Chloromethylmethyl ether (12.4 mL, 160 mmol) was added dropwise and the resulting white suspension stirred overnight. Ice/water (100 mL) was added cautiously and the mixture extracted with Et_2O (3 x 100 mL). The combined Et_2O extracts were washed with NaOH (2M, 100 mL), HCl (2M, 100 mL), and brine (100 mL). The solution was dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield a colourless liquid (28.2 g, 92%): IR (neat, cm^{-1}) 2961, 2919, 2849, 1609, 1496, 1463, 1323, 1244, 1116, 1056, 989, 758, 648; ^1H NMR (270 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1H, ArH), 7.50–7.44 (m, 1H, ArH), 7.26-7.21 (m, 1H, ArH), 7.04 (d, J = 7.9 Hz, 1H, ArH), 5.26 (s, 2H, OCH_2O), 3.49 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 133.2, 127.1, 123.7 (q, $J_{C\text{-}F}$ = 273 Hz), 121.1, 119.5 (q, $J_{C\text{-}F}$ = 31 Hz), 115.2, 94.2, 56.3; MS (EI) *m/z* (relative intensity) 206 (M^+, 2), 145 ($M\text{-}OCH_2CH_3$, 3), 127 (2), 95 (2), 63 (3), 45 (100). Anal. Calcd for $C_9H_9F_3O_2$: C, 52.43; H, 4.40; F, 27.65. Found: C, 53.05; H, 4.62; F, 27.20.

2-(Methoxymethoxy)-3-(trifluoromethyl)benzaldehyde.



To a solution of 2-(methoxymethoxy)-1-(trifluoromethyl)benzene (31.9 g, 155 mmol) in anhydrous THF (200 mL) at -78 ˚C (acetone/dry ice) under an atmosphere of N_2 was added *n*-butyllithium (68.0 mL of a 2.5 M solution, 170 mmol) dropwise with stirring. After an additional hour stirring at this temperature, a solution of anhydrous DMF (13.2 mL, 170 mmol) in anhydrous THF (10 mL) was added to the green mixture and the resulting solution was allowed to warm to room temperature and stirred overnight. The yellow solution was hydrolysed by the addition of water (150 mL) and the mixture extracted with Et_2O (3 x 150 mL). The combined Et_2O extracts were then washed with 2M HCl (100 mL) and brine (100 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo* to yield a viscous yellow liquid. This was distilled *in vacuo* to yield a pale yellow liquid (29.3 g, 81%): bp 153 ˚C (0.5 mm Hg); IR (neat, cm^{-1}) 2956, 2923, 2866, 2360, 1672 (C=O), 1623, 1454, 1335, 1117, 1075, 985, 923, 757; ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.31 (s, 1H, CHO), 8.07 (dd, *J* = 1.7 Hz, 7.9 Hz, 1H, ArH), 7.90-7.87 (m, 1H, ArH), 7.38 (apparent t, *J* = 7.9 Hz, 1H, ArH), 5.13 (s, 2H, OCH_2O), 3.63 (s, 1H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6, 158.6, 132.7, 132.5, 131.5, 124.8, 123.0 (q, $J_{C\text{-}F}$ = 273 Hz), 118.4, 102.5, 58.1; MS (EI) *m/z* (relative intensity) 234 (M^+, 9), 203 (M-OCH_3, 4), 188 (3), 132 (2), 113 (3), 69 (6), 63 (5), 45 (100), 29 (47). Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.29; H, 3.87; F, 24.34. Found: C, 51.13; H, 4.03; F, 24.14.

2-Hydroxy-3-(trifluoromethyl)benzaldehyde.



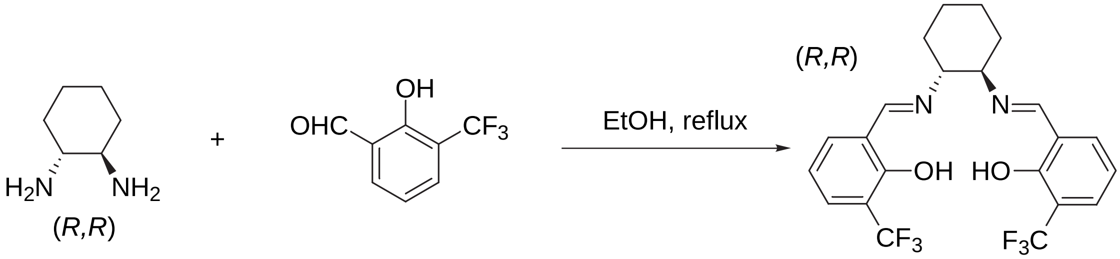
2-(Methoxymethoxy)-3-(trifluoromethyl)benzaldehyde (15.0 g, 64.0 mmol) was dissolved in MeOH (300 mL) and AcOH (0.2M, 200 mL). The mixture was heated to reflux for 8 hours, at which stage TLC analysis (silica, CH_2Cl_2) indicated the complete disappearance of starting material. After cooling overnight white needle like crystals formed in the reaction. These were filtered off, and dried in a dessicator until of constant weight (5.44 g, 45%). Drying under vacuum had to be avoided as it led to loss of material by sublimation. The filtrate was concentrated to a yield a further crop which were dried similarly (3.27 g, 27%): mp 58-59 ˚C; IR (KBr, cm^{-1}) 3103, 2867, 1680 (C=O), 1622, 1487, 1451, 1337, 1190, 1118, 747, 671, 486; ^{1}H NMR (270 MHz, $CDCl_3$) δ 11.73 (s, 1H, OH), 9.96 (s, 1H, CHO), 7.85-7.76 (m, 2H, ArH), 7.15-7.09 (m, 1H, ArH); ^{13}C NMR (67 MHz, $CDCl_3$) δ 196.3, 159.7, 137.4, 134.2, 122.9 (q, $J_{C\text{-}F}$ = 273 Hz), 121.2, 119.2, 118.9 (q, $J_{C\text{-}F}$ = 32 Hz); MS (EI) *m/z* (relative intensity) 191 (M+1, 18), 190 (M+, 100), 189 (M-1, 33), 172 (29), 171 (19), 170 (4), 169 (66), 144 (23), 143 (7), 142 (65), 141 (47), 114 (42), 63 (37), 29 (39). Anal. Calcd for $C_8H_5F_3O_2$: C, 50.54; H, 2.65; F, 29.98. Found: C, 50.21; H, 2.67; F, 30.04.

2. Synthesis of Salen Ligand

Resolution of (±)-*trans*-cyclohexane-1,2-diamine.

The resolution of (±)-*trans*-cyclohexane-1,2-diamine was carried out according to the procedure of Galsbol and co-workers[2] with only slight modification.

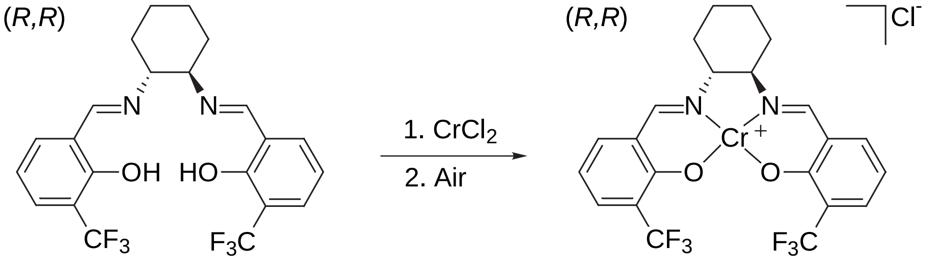
(*R*,*R*)-(-)-*N*,*N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine.



(*R*,*R*)-(-)-*trans*-Cyclohexane-1,2-diamine (2.30 g, 20.1 mmol) was dissolved in EtOH (70 mL) and 2-hydroxy-3-(trifluoromethyl)benzaldehyde (7.66 g, 40.3 mmol) added to the solution. The resulting bright yellow mixture was refluxed for 2 hours, cooled and the solvent was removed *in vacuo* to yield a solid which was recrystallised from hexane to give bright yellow needles. (8.65 g, 94%): mp 126-128 ˚C; $[\alpha]_D^{20}$ = –408˚ (c 1.1, CH_2Cl_2); IR (KBr, cm^{-1}) 2941, 2861, 1635 (C=N), 1490, 1452, 1330, 1283, 1117, 801, 758, 674, 615; ^1H NMR (270 MHz, $CDCl_3$) δ 14.52 (s, 2H, OH), 8.30 (s, 2H, N=CH), 7.54 (apparent t, *J* = 7.6 Hz, 2H, ArH), 7.34-7.26 (m, 1H, ArH), 6.84 (apparent t, *J* = 7.6 Hz, 2H, ArH), 3.37-3.33 (m, 2H, C=NCH), 2.00-1.36 (m, 8H, cyclohexyl-H); ^{13}C NMR (67 MHz, $CDCl_3$) δ 164.6, 160.3, 135.2, 129.8, 123.6 (q, $J_{C\text{-}F}$ = 273 Hz), 119.0, 118.1 (q, $J_{C\text{-}F}$ = 31 Hz), 117.5, 72.1, 32.9, 24.0; MS (EI) *m/z* (relative intensity) 458 (M^+, 12), 439 (M-F, 3), 269 (100), 190 (47), 170 (57), 155 (28), 127 (24), 81 (19). Anal. Calcd for $C_{22}H_{20}F_6N_2O_2$: C, 57.64; H, 4.40; F, 24.87; N, 6.11. Found: C, 57.61; H, 4.38; F, 24.40; N, 6.11.

3. Synthesis of (salen)Cr(III) complexes.

[(*R,R*)-(-)-*N,N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] chloride (1, R = CF_3, X = Cl).



Two methods were used to insert chromium into the salen ligand. Both methods gave complexes which exhibited identical activity in asymmetric epoxidation.

Method A: Using chromium(II) chloride generated with a zinc amalgam.

Preparation of the zinc amalgam.[3]

To a suspension of mercury(II) chloride (7.82 g, 28.8 mmol) in distilled water (78 mL), was added concentrated HCl (5.9 mL) to effect complete dissolution. Granular zinc (20 mesh, 99.8+%, 39.13 g, 599 mmol) was then added and stirring continued for two hours. Stirring should be maintained at such a rate that air does not come into contact with the solid amalgam. The zinc amalgam was filtered, washed with EtOH (10 mL) and Et_2O (10 mL) and immediately placed under an atmosphere of N_2 in a 3-neck round bottom flask, setup as described in the next section.

Reduction of chromium(III) chloride.

The zinc amalgam was placed into a 3-neck, round bottom flask, equipped with a pressure equalised dropping funnel and a nitrogen inlet and outlet, under a positive flow of nitrogen. A green solution of chromium(III) chloride hexahydrate (3.26 g, 12.2 mmol) in water (30 mL) was added with vigorous stirring. The mixture was stirred for 30 minutes or until the characteristic sky blue colour of chromium(II) chloride persisted.

Preparation of the chromium salen complex.

A solution of (*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine (5.10 g, 11.1 mmol) was prepared in acetone/MeOH (300/76 mL) in a 2-neck, round bottom flask under an atmosphere of N_2. The chromium(II) chloride solution prepared previously was transferred *via* canula to the reaction resulting in an immediate colour change to a brown solution. After stirring under an atmosphere of N_2 overnight followed by exposure to air for two hours, the reaction was concentrated *in vacuo* to yield a brown precipitate. This was collected by filtration and washed with water (5.14 g, 85% based on ligand): mp > 230 ˚C; IR (KBr, cm^{-1}) 2944, 2392, 2300, 1626 (C=N), 1555, 1448, 1351, 1306, 1110, 862, 757, 695, 646, 570; MS (Electrospray) *m/z* (relative intensity) 1206.9 (63), 1064.2 (100), 1049.2 (31), 539.6 (32), 525.4 (45), 508.3 (M-Cl, 72). Anal. Calcd for $C_{22}H_{18}ClCrF_6N_2O_2.2H_2O$: C, 45.57; H, 3.82; Cl, 6.11; F, 19.66; N, 4.83. Found: C, 45.69; H, 3.89; Cl, 5.59; F, 19.78; N, 4.42.

Method B: Using commercial chromium(II) chloride.

Following the procedure described by Jacobsen and co-workers[4] a 100 mL, 2-neck, round bottom flask with a nitrogen inlet and outlet was charged with a solution of (*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine (600 mg, 1.31 mmol) in dry, degassed THF (26 mL). To the yellow solution, anhydrous chromium(II) chloride, (177 mg, 1.44 mmol) was added. The resulting brown solution was stirred for 3 hours under a blanket of nitrogen and then exposed to air for a further 3 hours. The brown solution was diluted with *tert*-butyl methyl ether (120 mL), washed with saturated ammonium chloride (80 mL) and brine (80 mL). The organic phase was dried over sodium sulphate and the solvent was removed *in vacuo* yielding a brown solid (489 mg, 69%): mp > 230 ˚C; IR (KBr, cm^{-1}) 2944, 2392, 2300, 1626 (C=N), 1555, 1448, 1351, 1306, 1110, 862, 757, 695, 646, 570. Anal. Calcd for $C_{22}H_{18}ClCrF_6N_2O_2.\frac{3}{2}H_2O.\frac{1}{2}THF$: C, 48.57; H, 4.55; Cl, 5.51; N, 4.36. Found: C, 48.28; H, 4.23; Cl, 5.91, N, 4.42.

[(***R,R***)-(-)-*N,N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] hexafluorophosphate (1, R = CF_3, X = PF_6).

[(*R,R*)-(-)-*N,N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] chloride (410 mg, 754 μmol) was dissolved in the minimum amount of MeOH (150 mL) and a solution of potassium hexafluorophosphate (210 mg, 113 mmol) in water (5mL) was added. The resulting solution was stirred overnight at room temperature and concentrated to yield a brown precipitate (375 mg, 76%): mp > 230 ˚C; IR (KBr, cm^{-1}) 3160, 2736, 1632 (C=N),1563, 1445, 1400, 1352, 1306, 1128, 1080, 836, 760, 560; MS (Electrospray) *m/z* (relative intensity) 1117.0 (57), 1064.4 (36), 1052.6 (24), 539.6 (45), 525.6 (67), 508.3 (M-PF_6, 100). Anal. Calcd for $C_{22}H_{18}CrF_{12}N_2O_2P.2H_2O$: C, 38.33; H, 3.22; Cr, 7.54; F, 33.07; N, 4.06; O, 9.28; P, 4.49. Found: C, 38.42; H, 3.24; N, 5.59; P, 3.78.

[(***R,R***)-(-)-*N,N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (1a).

[(*R,R*)-(-)-*N,N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] chloride (1.00 g, 1.84 mmol) was dissolved in the minimum amount of MeOH (100 mL) and a solution of silver nitrate (470 mg, 2.76 mmol) in water (10 mL) was added. The resulting suspension was stirred for 20 minutes and the white precipitate (of silver chloride) was filtered off. The filtrate was concentrated to yield a brown precipitate which was collected by filtration and dried under vacuum (755 mg, 72 %). A sample of this was dissolved in acetone and reprecipitated by the slow addition of Et_2O by diffusion: mp > 230 ˚C; IR (KBr, cm^{-1}) 2952, 1624 (C=N), 1560, 1440, 1380 (N-O), 1125, 861, 758, 645, 569; MS (Electrospray) *m/z* (relative intensity) 1064.3 (100), 1050.3 (30), 539.6 (40), 525.5 (60), 508.3 (M-NO_3, 89). Anal. Calcd for

$C_{22}H_{18}CrF_6N_3O_5.H_2O.CH_3OH$: C, 44.52; H, 3.90; N, 6.77. Found C, 44.68; H, 3.79; N, 6.64.

[(*R,R*)-(-)-*N,N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] trifluoromethanesulfonate (1, R = CF_3, X = OTf).

Using the procedure described for the nitrate complex above [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] chloride (200 mg, 0.368 mmol) and silver trifluoromethanesulfonate (104 mg, 0.405 mmol) were reacted to give a brown precipitate, which was collected by filtration and dried under vacuum (156 mg, 64 %). A sample of this was dissolved in CH_2Cl_2 and recrystallised by the slow addition of Et_2O by diffusion. Although none of the crystals obtained yielded a satisfactory x-ray crystal structure it was possible to see that the complex was a monomeric salen complex, with a molecule of MeOH and a molecule of water also present in the unit cell. These crystals were also used as an analytical sample: mp > 230 ˚C; IR (KBr, cm^{-1}) 2939, 2856, 1633 (C=N), 1601, 1569, 1443, 1341, 1287 (OTf), 1241, 1158, 1127, 1081, 1030 (OTf), 861, 757, 642, 570; MS (Electrospray) *m/z* (relative intensity) 1064.3 (62), 1050.1 (100), 539.7 (12), 525.5 (17), 508.3 (M - OTf, 37). Anal. Calcd for $C_{23}H_{18}CrF_9N_2O_5S.H_2O.CH_3OH$: C, 40.74; H, 3.42; N, 3.96. Found: C, 40.03; H, 3.41; N, 3.82.

[(*R,R*)-(-)-*N,N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] tetrafluoroborate (1, R = CF_3, X = BF_4).

Using the procedure described for the nitrate complex above [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] chloride (400 mg, 0.736 mmol) and silver tetrafluoroborate (158 mg, 0.809 mmol) were reacted to give a brown precipitate, which was collected by filtration and dried under vacuum (251 mg, 57 %): mp > 230 ˚C; IR (KBr, cm^{-1}) 2943, 1633 (C=N), 1599, 1563, 1443, 1397, 1341, 1305, 1125, 1076, 861, 756, 645, 570; MS (Electrospray) *m/z* (relative intensity) 1573.9 (33), 1064.3 (100), 1052.6 (70), 539.7 (22), 525.6 (25), 508.3 (M- BF_4, 43). Anal. Calcd for $C_{22}H_{18}BCrF_{10}N_2O_2.CH_3OH$: C, 44.04; H, 3.54; N, 4.47. Found: C, 43.63; H, 3.56; N, 4.33.

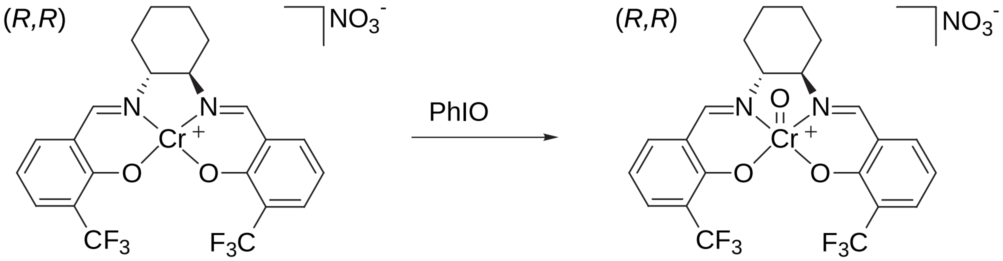
[(*R*,*R*)-(-)-*N*,*N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] BARF (1, R = CF_3, X = BARF).

Using the procedure described for the hexafluorophosphate complex above [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] chloride (224 mg, 4.12 mmol) and sodium BARF[5] (400 mg, 4.53 mmol) were reacted to give a brown oil which solidified after drying under vacuum (331 mg, 59 %): mp > 230 ˚C; IR (KBr, cm^{-1}) 2942, 2365, 1633 (C=N), 1573, 1436, 1352, 128, 1120, 887, 860, 839, 756, 713, 682, 669, 644, 570; MS (Electrospray) *m/z* (relative intensity) 722.1 (43), 706.1 (24), 621.3 (16) 539.6 (34), 525.3 (57), 508.3 (M-BARF, 100). Anal. Calcd for $C_{54}H_{30}BCrF_{30}N_2O_2.H_2O.CH_3OH$: C, 46.47; H, 2.55; N, 1.97. Found: C, 46.14; H, 2.71; N, 1.79.

4. Synthesis of (salen)Cr(V)=O complexes.

There is evidence that chromium(V)oxo complexes are carcinogenic and thus they should be handled very carefully.[6,7]

[(*R*,*R*)-(-)-*N*,*N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine oxochromium(V)] nitrate (2a).



[(*R*,*R*)-(-)-*N*,*N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate **(1a)** (248 mg, 435 μmol) was dissolved in CH_3CN and iodosylbenzene (115 mg, 522 μmol) was added. After stirring for 30 minutes, the reaction was filtered and the solvent was removed *in vacuo*. Addition of Et_2O precipitated a black solid which was collected by filtration, washed thoroughly with Et_2O, dried and stored under an atmosphere of N_2 (48 mg, 75%): mp > 230 ˚C; IR (KBr, cm^{-1}) 2942, 1629 (C=N), 1600, 1562, 1440, 1383, 1192, 1125, 1079, 861, 757, 696, 658, 645, 571, 450; MS (Electrospray) *m/z* (relative intensity) 524.3 (M–NO_3, 100). Anal. Calcd for $C_{22}H_{18}CrF_6N_3O_6.H_2O$: C, 43.72; H, 3.34; N, 6.95. Found: C, 42.86; H, 3.39; N, 5.08.

[(*R*,*R*)-(-)-*N*,*N'*-Bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine oxochromium(V)] trifluoromethanesulfonate (2, R = CF_3, X = OTf).

Using the procedure described above [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] trifluoromethanesulfonate (55 mg, 250 μmol) and iodosylbenzene (115 mg, 522 μmol) were reacted to give a black solid (84 mg, 60%): mp > 230 ˚C; IR (KBr, cm^{-1}) 2947, 1630 (C=N), 1568, 1441, 1398, 1341, 1281 (OTf), 1127, 1029(OTf), 862, 756, 696, 640, 571; Anal. Calcd for $C_{23}H_{18}CrF_9N_2O_6S.H_2O$: C, 39.95; H, 2.92; N, 4.05. Found: C, 39.53; H, 2.80; N, 4.21.

5. Asymmetric epoxidation of alkenes mediated by (salen)chromium complexes.

Procedures for analysis of epoxidation reaction product mixtures.

GC analysis (all alkenes except *E*-stilbene):

ee determination:

Typically the worked up reaction mixture (see below) was dissolved in ~1mL of Et_2O and 1 µL of this solution was injected onto a GC column. The ee of *trans*-β-methylstyrene oxide was determined with a Supelco cyclodextrin-α capillary column (alphadex 120), 30m × 0.25 mm i.d., 0.25 µm film operated at an injection temperature of 230 °C and a column temperature of 93 °C, with a column pressure of 18 psi. The column temperature was raised to 220 °C (250 °C maximum operating temperature) at regular intervals to remove any involatile material that remained. At times it was necessary to cut off a small portion (1 inch) from the top of the column, to remove solid material which had built up over regular usage. This procedure however did not affect the retention time of any compounds being analysed. The ee of *cis*-ß-methylstyrene oxide and *trans*-3-hexene oxide were determined with a Supelco cyclodextrin-ß capillary column (betadex 120), 30m × 0.25 mm i.d., 0.25 µm film. This was operated at an injection temperature of 230 °C and a column temperature of 77 °C with a column pressure of 20 psi for *cis*-ß-methylstyrene oxide and at an injection temperature of 110 ˚C, oven temperature of 46 ˚C and column pressure of 8.0 psi for *trans*-3-hexene oxide. Figure 1 shows a typical GC trace from an asymmetric epoxidation of *E*-ß-methylstyrene.

Yield determinations (for *E*- and *Z*-ß-methylstyrene):

1 μL of n-decane was added to the worked up reaction mixture, prior to GC analysis, for use as an internal standard. The percentage composition of the reaction mixtures were then determined by comparison of individual peak areas to the peak area due to n-decane. Authentic samples of possible products and byproducts were synthesised or purchased. GC analysis of these confirmed that the components of a typical reaction product mixture from epoxidation of *E*- or *Z*-ß-methylstyrene were: the relevant alkene and epoxide, iodobenzene (when PhIO used as oxidant), benzaldehyde and benzyl methyl ketone. The relative burn ratios of each of these were calculated by injecting a 1 μl sample of a solution, of known composition, of both the substance of interest and n-decane in Et_2O. The values determined were: *trans*-β-methylstyrene oxide, 1.41; *cis*-ß-methylstyrene oxide, 2.16; *E*-ß-methylstyrene, 1.09; *Z*-ß-methylstyrene, 1.20; benzaldehyde, 1.30; benzyl methyl ketone, 1.12. All yields were calculated using these ratios. The absolute configuration of *trans*-ß-methylstyrene oxide was assigned by comparison of a sample with the data of Witkop and Foltz[8] and of Shi and co-workers.[9] The absolute configuration of *cis*-ß-methylstyrene oxide was assigned by comparison of the GC retention times to those of a sample made according to the Jacobsen method.[10]

HPLC analysis (*E*-stilbene):

The ee of *trans*-stilbene oxide was determined by HPLC using a Chiralcel OD column, 25 cm x 0.46 cm I.D. The column was operated with a mobile phase consisting of hexane/2-propanol (99:1) and at a flow rate of 1.0 mL/min.

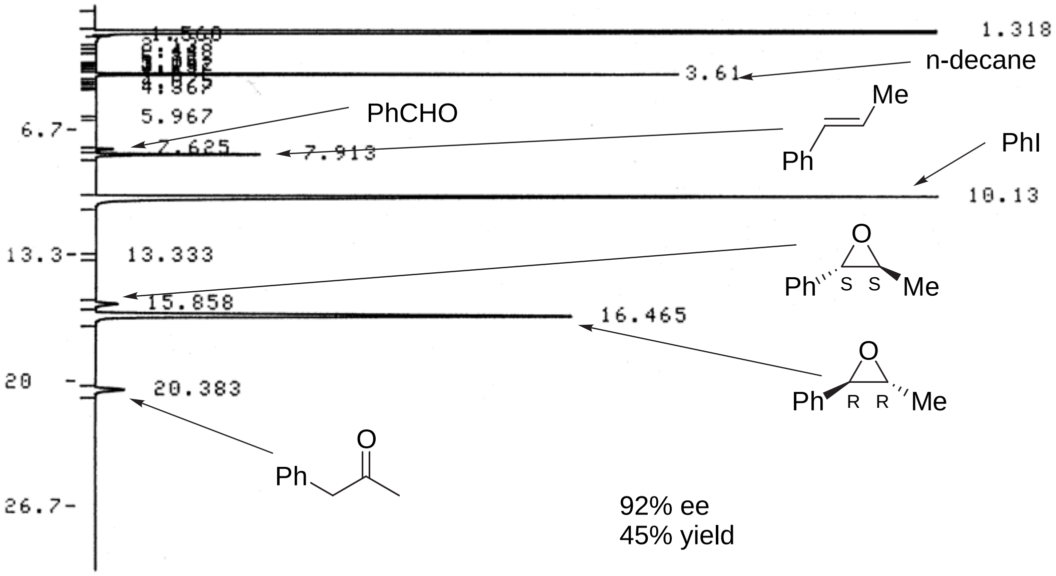
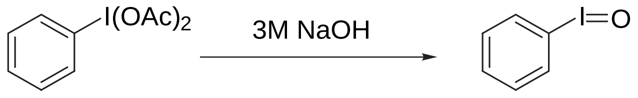


Figure 1: Typical GC trace from epoxidation of *E*-ß-methylstyrene by (salen)Cr(V)=O complex complex.

Preparation of iodosylbenzene.



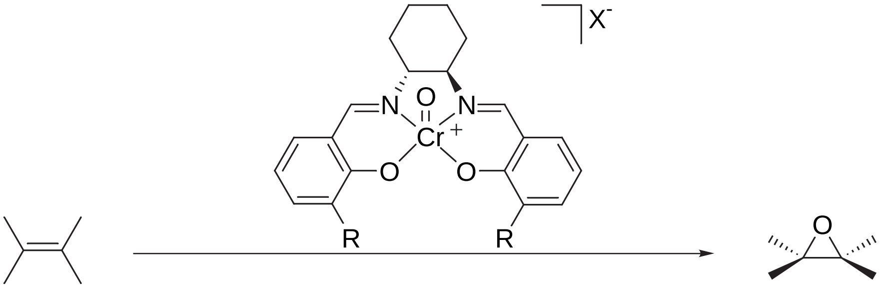
Following the procedure of Saltzman and Sharefkin,[11] NaOH (3M, 23 mL) was added to solid iodobenzene diacetate. The resulting yellow suspension was stirred for 1 hour and left stand overnight. Water (5 mL) was added, the mixture was stirred for 5 minutes, filtered and the solid was added to water (35 mL). After stirring for 15 minutes, the suspension was again filtered and the solid added to $CHCl_3$ and stirred. Filtration yielded a yellow powder which was dried under vacuum (2.63 g, 80%): Anal. Calcd for C_6H_5IO: C, 32.76; H, 2.29. Found: C, 32.46; H, 2.26.

Preparation of tetrabutylammonium persulphate ($(nBu)_4NHSO_5$).[12]

To a solution of Oxone (6.8 g, 22.4 mmol of $KHSO_5$) in water (70 mL) was added nBu_4NHSO_4 (6.8 g, 20 mmol). The solution was stirred for 30 minutes and then extracted with CH_2Cl_2 (70 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The crude product was washed with n-hexane (20 ml) and dried *in vacuo* to produce a white powder (4.91 g, 69%).

Stoichiometric epoxidation procedures:

Using Iodosylbenzene as oxidant.



Iodosylbenzene (1-2 eqv.) was added to a stirred solution of the appropriate (salen)Cr(III) complex (30 mg, 1 eqv.) in CH_3CN (5 mL). A deep blue/black colour appeared almost immediately. After stirring for 30 minutes this solution was filtered and the filtrate cooled to 0 ˚C using an ice/water bath. The donor ligand (L) (1 eqv.) was added followed 5 minutes later by the alkene substrate (1 eqv.). The reaction mixture was stirred at 0 ˚C until the brown colour of the (salen)Cr(III) complex returned completely (~1.5 hours). The solvent was removed *in vacuo* and the residue treated with Et_2O. The Et_2O washings were flushed through a short alumina column using Et_2O as eluant. The eluant was concentrated *in vacuo* to a small volume (~1 mL) and this sample was analysed by GC as described previously.

Using NaOCl as oxidant:

Following the procedure of Jacobsen[10] (salen)Cr(III) complex (1 eqv.) was dissolved in CH_2Cl_2 (1 mL) and alkene (1 eqv., 50 μmol) and donor ligand (1 eqv.) were added. After stirring at 0 ˚C for 10 minutes, NaOCl (4 eqv. of a 0.55M solution in 0.05M Na_2HPO_4) was added. After vigorous stirring for 3 hours at 0 ˚C the reaction was diluted with water and CH_2Cl_2. The layers were separated and the organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to a small volume (~1 mL) and this sample was analysed by GC as described previously.

Using Hydrogen Peroxide as oxidant:

A modification of Katsuki and coworkers' method[13] was used. H_2O_2 (877 μmol, 99 μL of a 30% solution) was added dropwise over 5 minutes to a solution of *N*-methylimidazole (7.2 mg, 87.6 μmol), [(*R*,*R*)-(-)-*N*,*N*'-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (50 mg, 87.6 μmol) and *E*-ß-methylstyrene (11.4 μL, 8,76 μmol) in CH_3CN (5 mL) at 0 ˚C. No colour change was observed. After stirring for three hours the reaction mixture was worked up as described previously.

Using tetrabutylammonium persulphate as oxidant:

Pietikäinen's method was used.[12] nBu_4HSO_5 (28 mg, 78.9 μmol) was added in two portions over 20 minutes to a solution of Ph_3PO (15 mg, 52.6 μmol), [(*R*,*R*)-(-)-*N*,*N*'-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (30 mg, 52.6 μmol) and *E*-ß-methylstyrene (6.8 μL, 52.6 μmol) in CH_3CN (5 mL). No colour change was observed. After stirring for three hours the reaction was quenched by adding dimethyl sulfide (9.7 μL, 13.2 μmol). Excess solid K_2CO_3 was added, the mixture was allowed to reach room temperature and then filtered. The filtrate was worked up as described previously.

Miscellaneous stoichiometric experiments

Investigation of effect of reaction time.

Epoxidation of *E*-ß-methylstyrene using iodosylbenzene was carried out according to the method above using [(*R*,*R*)-(-)-*N,N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate and Ph_3PO as donor, however the reaction was left to stir overnight at room temperature despite the brown Cr(III) colour having returned after 1.5 hours. The ee and yield were determined to be 90% and 19% respectively. 8% *E*-ß-methylstyrene remained.

Kinetic resolution investigation.

Using (salen)Cr(V)=O complex:

Iodosylbenzene (8 mg, 38 μmol) was added to a stirred solution of [(*R*,*R*)-(-)-*N,N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (21 mg, 38 μmol) in CH_3CN (5 mL). A deep blue/black colour appeared almost immediately. After stirring for 30 minutes this solution was filtered. Ph_3PO (10 mg, 38 μmol) was added to the filtrate followed 5 minutes later by *trans*-ß-methylstyrene oxide (10 mg, 75 μmol). The reaction was stirred overnight and the resulting black solution was worked up as in Method A. GC analysis indicated that 85% epoxide was recovered and this had an ee of 0%. No peaks due to epoxide decomposition products were present in the GC trace.

Using (salen)Cr(III) complex:

Ph_3PO (10 mg, 35 μmol) was added to a stirred solution of [(*R*,*R*)-(-)-*N,N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (21 mg, 53 µmol) in CH_3CN (5 mL). After 5 minutes *trans*-ß-methylstyrene oxide (10 mg, 75 µmol) was added. The reaction was stirred overnight and the resulting black solution was worked up as in Method A. GC analysis indicated that 89% epoxide was recovered and this had an ee of 1%. No peaks due to epoxide decomposition products were present in the GC trace.

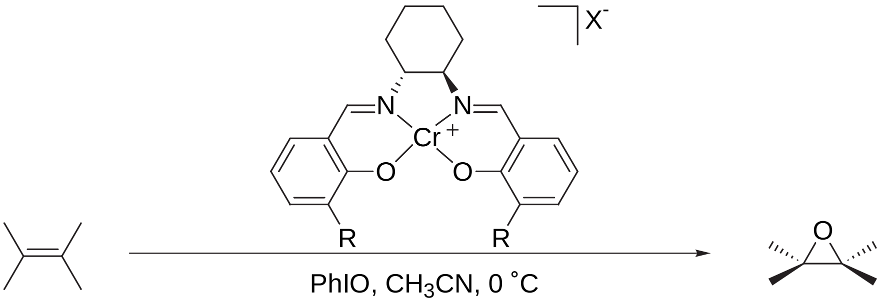
Use of recycled complex.

Epoxidation of *E*-ß-methylstyrene using iodosylbenzene was carried out according to the method above using [(*R*,*R*)-(-)-*N,N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (70 mg, 123 µmol) and Ph_3PO as donor ligand. *trans*-ß-Methylstyrene oxide was obtained in 88% ee and 34% yield. The residue from treating the crude reaction mixture with Et_2O was recovered as a brown powder (84 mg). Electrospray mass spectroscopy showed this to be a 56:44 mixture of the starting complex and the starting complex with Ph_3PO bound to it. Therefore 84 mg represents 97% recovery. The recovered mixture of complexes was halved. One half was used in an epoxidation of *E*-ß-methylstyrene according to method B with Ph_3PO as donor yielding *trans*-ß-methylstyrene oxide in 87% ee and 33% yield. The other half was used in an epoxidation of *E*-ß-methylstyrene according to method B with no donor ligand yielding *trans*-ß-methylstyrene oxide in 87% ee and 39% yield.

The effect of slow addition of (salen)Cr(V)=O complex.

Iodosylbenzene (14 mg, 63 µmol) was added to a stirred solution of [(*R*,*R*)-(-)-*N,N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate**)** (30 mg, 53 µmol) in CH_3CN (2 mL). A deep blue/black colour appeared almost immediately. After stirring for 30 minutes this solution was filtered and the filtrate cooled to 0 ˚C using an ice water bath. Ph_3PO (15 mg, 53 µmol) was added and the resulting solution added dropwise over 1.5 hours to a solution of *E*-ß-methylstyrene in CH_3CN (3 mL) at 0 ˚C. After stirring for a further 30 minutes the reaction was worked up as described by method A to yield *E*-ß-methylstyrene oxide in 10% yield and 89% ee. 14% *E*-ß-methylstyrene remained.

Catalytic epoxidation procedure.



Iodosylbenzene (2 eqv.) was added to a solution of Ph_3PO (5 or 10 mol %), the appropriate (salen)Cr(III) complex (5 or 10 mol%) and alkene (1 eqv., 50 µmol) in CH_3CN (5 mL) at 0 ˚C. The reaction was stirred and was worked up after 24 hours as described previously.

Investigation of variation of ee and yield with time in a catalytic experiment.

An epoxidation of *E*-ß-methylstyrene was carried out using [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (0.1 eqv.) according to the procedure above (2 eqv. PhIO, L = Ph_3PO, 20 ˚C). 1 µL aliquots were removed from the reaction at intervals and analysed by GC. The yield was calculated using the ratio of volume removed to reaction volume.

Time (minutes)	**ee (%)**	**Yield (%)**	**Unreacted alkene (%)**
15	69	31	32
45	72	42	19
75	72	53	13
105	73	69	10
1080	72	70	10
after work up	72	62	8

6. Miscellaneous Experiments.

Reaction of (salen)Cr(III) complex with (salen)Cr(V)=O complex.

Iodosylbenzene (9.0 mg, 42 µmol) was added to a solution of [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (20 mg, 35 µmol) in CH_3CN (5 mL). After stirring for 30 minutes the mixture was filtered and divided in half. To one half was added [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (10 mg, 17 µmol) and stirring continued. The other half was left stir without interference. The solution to which the (salen)Cr(III) complex was added returned to a brown colour noticeably more quickly (1.5 hours v. 3 hours) than the control solution.

The effect of excess (salen)Cr(III) complex on an epoxidation reaction.

E-ß-methylstyrene was epoxidised using [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate and iodosylbenzene according to the stoichiometric procedure described earlier. However, a second portion of [(*R*,*R*)-(-)-*N*,*N'*-bis(3-trifluoromethylsalicylidene)-*trans*-cyclohexane-1,2-diamine chromium(III)] nitrate (1 eqv.) was added to the (salen)Cr(V)=O solution at the same time as the alkene. *trans*-ß-Methylstyrene oxide was produced in 91% ee and 22% yield. 8% unreacted *E*-ß-methylstyrene remained. This compares to 91% ee, 29% yield and 11% unreacted *E*-ß-methylstyrene in a parallel reaction run without addition of the excess (salen)Cr(III) complex.

Control reaction to investigate background oxidation.

Iodosylbenzene (14 mg, 63 µmol) was added to a solution of *E*-ß-methylstyrene (6.8 µL, 53 µmol) in CH_3CN (5 mL). This mixture was stirred for 3 days and worked up as per the method described earlier for epoxidations, to yield *trans*-ß-methylstyrene oxide in 2% yield and 0% ee. 90% unreacted alkene remained.

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