

Electronic Supporting Information for

Manganese Catalysed Asymmetric *cis*-Dihydroxylation with H₂O₂

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Experimental

Materials. All reagents are of commercial grade (Aldrich, Acros, Fluka, Merck, NovaBiochem, Bachem) and used as received unless stated otherwise. Hydrogen peroxide: 50 w/w % (Acros) or 30 v/v % (Merck, medical grade) solution in water. D₂O₂ (Icon Isotopes): 30 % solution in D₂O, 99 atom% D. D₂O (Aldrich 99.95%) CH₃CN (Acros, extra pure). The synthesis and characterisation of complex **1** is reported elsewhere.¹

NMR Spectroscopy. ¹H (400, 300 or 200 MHz), ¹³C (100.6 or 50.3 MHz) spectra were recorded on a Varian Mercury Plus 400, Varian VXR-300, Varian Mercury Plus 200 or Varian Gemini-200. Chemical shifts are reported in ppm relative to the solvent residual peak²: ¹H NMR: CDCl₃ (7.26 ppm), dms_o-d₆ (2.50 ppm), CD₃CN (1.94 ppm), acetone-d₆ (2.05 ppm), D₂O (4.79 ppm). ¹³C NMR: CDCl₃ (77 ppm), dms_o-d₆ (39.5 ppm), acetone-d₆ (29.8 ppm). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

ESI-MS. Electrospray ionization mass spectra were recorded on a Triple Quadrupole LC/MS/MS Mass spectrometer (API 3000, Perkin-Elmer Sciex Instruments) or API-365. Mass spectra were measured in positive mode (no manganese complexes were observed in negative mode) and in the range of *m/z* 100-1500. Typical settings: ion-spray voltage (5200 V), orifice (+15 V), ring (+150 V), Q0 (-10 V).

EI-MS. Electron impact ionisation mass spectrometry was performed on a Jeol JMS-600H mass spectrometer.

CI-MS. Chemical ionisation mass spectrometry was performed on a Jeol JMS-600H mass spectrometer using NH₃ as reacting gas.

Ac-D-Phg-OH. Ac-D-Phg-OH was prepared according to a reported procedure.³ D-(-)- α -phenylglycine (2.00 g, 13.2 mmol) was suspended in H₂O (30 ml) and the resulting suspension was cooled to 0-5°C with ice-water. Subsequently, NaOH (0.53 g, 13.2 mmol) was added and a clear solution was obtained. Acetic anhydride (2.5 ml, 26.4 mmol) was added, immediately followed by a solution of NaOH (1.59 g, 39.8 mmol) in H₂O (8 ml) (giving pH 5) and the mixture was stirred at 0-5°C for an additional 15 min. The reaction mixture was then acidified to pH 1 with conc. HCl (aq.). The colourless solid was collected on a glass filter P4 and was subsequently washed with H₂O (3 x 20 ml). After recrystallisation from EtOH/H₂O (1:1) colourless needles were obtained (812 mg, 4.20 mmol, 32%). ¹H NMR (200 MHz, dmsd-d₆) δ 1.89 (s, 3H), 5.32 (d, J = 7.7 Hz, 1H), 7.27-7.39 (m, 5H), 8.60 (d, J = 7.7 Hz, 1H), in accordance with literature⁴. ¹³C NMR (50.3 MHz, dmsd-d₆) δ 22.24, 56.24, 127.63, 127.89, 128.49, 137.22, 169.07, 171.99. EI-MS *m/z* 193 [M]⁺. HRMS (calc. for C₁₀H₁₁NO₃: 193.074) found: 193.073.

Boc-Pro-Pro-OMe. Boc-Pro-OH (10.0 g, 46.4 mmol) was activated in CH₂Cl₂ (300 ml, freshly distilled from CaH₂) under N₂ with *N*-ethyl-*N'*-(3-dimethylaminopropyl)-carbodiimide (EDC) (9.76 g, 50.9 mmol) and 1-hydroxybenzotriazole hydrate (HOBt) (6.88 g, 50.9 mmol) and this mixture was stirred at r.t. for 1 h giving a clear, colourless solution (solution A).

H-Pro-OMe.HCl (7.69 g, 46.4 mmol) and *N,N*-diisopropylethylamine (24.2 ml, 139 mmol) were dissolved in CH₂Cl₂ (400 ml, freshly distilled from CaH₂) under N₂ in a three-necked flask equipped with a dropping funnel, giving a clear, colourless solution (solution B).

Solution A was transferred (under N₂) to the dropping funnel and was subsequently added slowly to solution B (ca. 90 min.) at r.t. with the reaction mixture being cooled in a water bath. When the addition was complete, the reaction mixture was heated at reflux overnight. After cooling to r.t. the organic layer was washed with brine (1 x 150 ml), 4 M NaHCO₃ (4 x 100 ml), 1 M NaHSO₄ (4 x 100 ml) and brine (1 x 200ml) and was dried over anhydrous Na₂SO₄. Evaporation of the solvents *in vacuo* yielded a pale yellow oil. Purification by column chromatography (silica, CH₂Cl₂/MeOH 98:2; TLC visualised with ninhydrin dip) yielded Boc-Pro-Pro-OMe as a pale yellow oil (13.7 g, 42.0 mmol, 91%). ¹H NMR (400 MHz, CDCl₃) δ 1.39 and 1.44 (2 x s, (CH₃)₃, 9H), 1.81-2.23 (m, 8H), 3.35-3.80 (m, 7H), 4.37-4.60 (m, 2H), mixture of rotamers (the

Boc-group shows coalescence at 60 °C in dms_o-d₆). ¹³C NMR (100.6 MHz, CDCl₃) δ 23.40, 23.89, 24.82, 24.88, 28.19, 28.35, 28.55, 28.67, 28.89, 29.83, 46.30, 46.34, 46.49, 46.68, 51.90, 51.96, 52.06, 57.53, 58.50, 79.23, 79.26, 153.56, 154.42, 170.95, 171.44, 172.49, 172.77, mixture of rotamers. EI-MS *m/z* 326 [M]⁺. HRMS (calc. for C₁₆H₂₆N₂O₅: 326.184) found: 326.185.

Boc-Pro-Pro-OH. Boc-Pro-Pro-OMe (13.7 g, 42.0 mmol) was added to 2 M aq. NaOH (250 ml) and the resulting biphasic mixture was stirred at r.t. for 2 h until all oil had dissolved and TLC (silica, CH₂Cl₂/MeOH 98:2, ninhydrin-dip) showed complete conversion. The basic aqueous layer (pH 14) was washed with CH₂Cl₂ (3x100 ml) and was then acidified (to pH 1) with concentrated HCl (30% aq.). The resulting colourless suspension was extracted with EtOAc (5x75 ml). The combined EtOAc layers were washed with brine (1x100 ml) and dried on anhydrous Na₂SO₄. The solvents were evaporated *in vacuo* yielding a very sticky foam which was dissolved in a minimum amount of CH₂Cl₂ (40 ml). Pentane (200 ml) was added and the mixture was sonicated for a few minutes until a colourless suspension was obtained. Evaporation of the solvents *in vacuo* yielded Boc-Pro-Pro-OH as a white solid (10.2 g, 32.7 mmol, 78%). ¹H NMR (300 MHz, CDCl₃) δ 1.39 and 1.45 (2 × s, 9H), 1.85-2.41 (m, 8H), 3.38-3.80 (m, 4H), 4.37-4.68 (m, 2H), mixture of rotamers. ¹³C NMR (50.3 MHz, CDCl₃) δ 23.65, 24.25, 25.04, 27.02, 27.24, 28.37, 28.44, 29.37, 30.20, 46.68, 46.92, 47.33, 57.57, 57.70, 59.91, 59.97, 79.79, 79.94, 153.48, 154.58, 172.16, 172.46, 174.38, 174.66, mixture of rotamers. EI-MS *m/z* 312 [M]⁺. HRMS (calc. for C₁₅H₂₄N₂O₅: 312.168) found: 312.170.

*The complexes 2 – 6 were prepared by the general routes described previously.*⁵

[Mn^{III}₂(μ-O)(μ-Boc-Phg-O⁻)₂(tmtacn)₂](PF₆)₂ (**2**). **1** (160 mg, 0.20 mmol) and Boc-Phg-OH (100.6 mg, 0.40 mmol) were mixed in 10 ml of water with the minimum of ethanol. L-ascorbic acid (36 mg, 0.02 mmol) in 1 mL of water was added resulting the the formation of a purple/red precipitate which was isolated by filtration and washed with diethylether followed by recrystallisation from acetonitrile, yielding **2** (86.1 mg, 0.068 mmol, 34%). ¹H NMR (400 MHz, CD₃CN) δ 75, 72, 68, 66, 61, 44, 40, 31, 24, 15, 10, 9, 7, -78, -80, -91, -93, -103. ESI-MS *m/z* 1113.6 [**2**(PF₆)]⁺, 484.5 [**2**]²⁺. Elemental analysis (calc. for Mn₂C₄₄H₇₄N₈O₉P₂F₁₂): C 41.64% (41.98%), H 6.05% (5.92%), N 8.80% (8.90%).

[Mn^{III}₂(μ-O)(μ-Boc-Phe-O⁻)₂(tmtacn)₂](PF₆)₂ (3). As for **2** except Boc-Phe-OH (106.1 mg, 0.40 mmol) and **1** (162 mg, 0.20 mmol) were employed, yielding **3** (64 mg, 0.050 mmol, 25%). ¹H NMR (400 MHz, CD₃CN) δ 81, 75, 69, 58, 41, 37, 33, 22, 20, 9, 8, 7.5, 7.3, 7.2, -73, -82, -90, -104. ESI-MS *m/z* 1141.6 [**3**(PF₆)]⁺, 498.3 [**3**]²⁺. Elemental analysis (calc. for Mn₂C₄₆H₇₈N₈O₉P₂F₁₂): C 43.41% (42.93%), H 6.01% (6.11%), N 8.45% (8.71%).

[Mn^{III}₂(μ-O)(μ-Boc-D-Pro-O⁻)₂(tmtacn)₂](PF₆)₂ (4). As for **2** except Boc-D-Pro-OH (86.1 mg, 0.40 mmol) and **1** (162 mg, 0.20 mmol) were employed, yielding **4** (98 mg, 0.084 mmol, 42%). ¹H NMR (400 MHz, CD₃CN) δ 88, 84, 76, 61, 50, 44, 29, 26, 12, 9, 6, 5, 4.2, 4.1, -80, -87, -98, -104. ESI-MS *m/z* 1041.6 [**4**(PF₆)]⁺, 448.5 [**4**]²⁺. Elemental analysis (calc. for Mn₂C₃₈H₇₄N₈O₉P₂F₁₂): C 36.99% (38.46%), H 6.34% (6.28%), N 9.47% (9.44%).

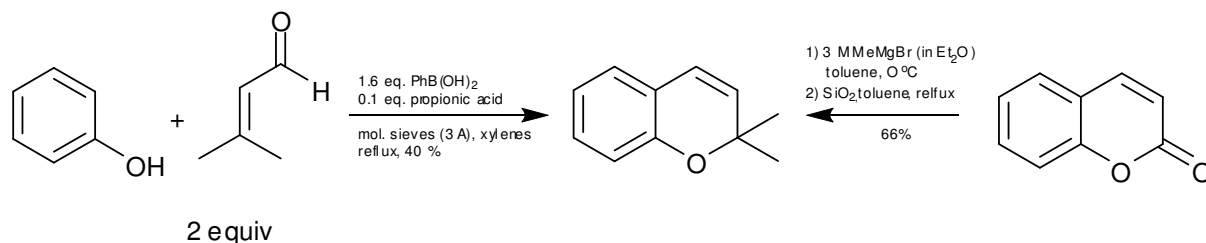
[Mn^{III}₂(μ-O)(μ-Boc-Ala-O⁻)₂(tmtacn)₂](PF₆)₂ (5). As for **2** except Boc-Ala-OH (75.7 mg, 0.40 mmol) and **1** (162 mg, 0.20 mmol) were employed, yielding **5** (41 mg, 0.036 mmol, 18%). ¹H NMR (400 MHz, CD₃CN) δ 79, 72, 61, 59, 44, 36, 22, 12, -72, -83, -87, -104. ESI-MS *m/z* 989.5 [**5**(PF₆)]⁺, 422.5 [**5**]²⁺. Elemental analysis (calc. for Mn₂C₃₄H₇₀N₈O₉P₂F₁₂): C 34.93% (35.99%), H 6.38% (6.22%), N 9.60% (9.87%).

[Mn^{III}₂(μ-O)(μ-Ac-D-Phg-O⁻)₂(tmtacn)₂](PF₆)₂ (6). As for **2** except **1** (160 mg, 0.20 mmol) and Ac-D-Phg-OH (77.3 mg, 0.40 mmol) were employed, yielding **6** (109.2 mg, 0.096 mmol, 48%). ¹H NMR (400 MHz, CD₃CN) δ 76, 68, 66, 45, 40, 32, 30, 23, 15, 11, 9, -79, -87, -96, -104. ESI-MS *m/z* 997.5 [**6**(PF₆)]⁺, 426.4 [**6**]²⁺. Elemental analysis (calc. for Mn₂C₃₈H₆₂N₈O₇P₂F₁₂): C 39.68% (39.94%), H 5.53% (5.47%), N 9.59% (9.81%).

Synthesis of 2,2-dimethylchromene

2,2-Dimethylchromene was prepared by a condensation reaction between phenol and 3-methyl-2-butenal in the presence of phenylboronic acid and propionic acid in refluxing xylenes according to the modified literature procedure for the synthesis of precocene-1 (Scheme S 1).⁶ Azeotropic removal of water, as described in the original paper, provided the product in low yield (22%). Alternatively, the use of molecular sieves (3 Å) gave higher yields (40%). Despite this improvement, the yield was still only modest and, moreover, scale up of the reaction,

resulted in decreased yields. Alternatively, 2,2-dimethylchromene was prepared in good yield (66%) via addition of excess MeMgBr to 1-benzopyran-2-one at 0 °C and subsequent ring closure in toluene at reflux (Scheme S 1).⁷



Scheme S 1 Synthesis of 2,2-dimethylchromene

The synthesis was analogous to the preparation of precocene-1.⁶ Molecular sieves (3 Å) were heated at 160°C for 2 h under several vacuum/N₂ cycles. After cooling to room temperature, xylene (200 ml) was added, together with phenol (4.28 g, 45.5 mmol), phenylboronic acid (8.9 g, 73.0 mmol), 3-methyl-2-butenal (8.8 ml, 91.2 mmol) and propionic acid (2 ml, 27 mmol). The mixture was heated at reflux under Dean-Stark conditions for 3 d. After cooling to r.t., 20% NH₄OAc (150 ml) was added. The organic phase was separated and the aqueous layer was extracted with EtOAc (3x100 ml). The combined organic layers were washed with 0.5 M aq. NaHCO₃ (3x75 ml) and brine (100 ml). After drying on anhydrous Na₂SO₄ the solvents were evaporated *in vacuo* yielding a dark brown oil. Purification by column chromatography (silica, pentane) yielded 2,2-dimethylchromene as a clear, pale yellow oil (2.95 g, 18.4 mmol, 40%).

Alternatively, this compound was prepared according to another modified literature procedure.⁷ MeMgBr (68 ml, 205 mmol, 3 M in Et₂O) was added dropwise to a vigorously stirred solution of 1-benzopyran-2-one (10 g, 68.4 mmol) in toluene (500 ml) at 0°C. After the addition was complete, the reaction mixture was stirred for an additional 2 h at the same temperature. The reaction mixture was then poured onto a cold solution of 20% aq. NH₄Cl. The organic phase was concentrated *in vacuo* to remove Et₂O and MeOH. The residue (still containing toluene) was heated at reflux overnight under Dean-Stark conditions in the presence of 60 g of silica gel (activated immediately before use at 120°C). The hot reaction mixture was filtered and the residue of silica gel was washed several times with EtOAc. The combined filtrates were concentrated *in vacuo*. Purification by flash column chromatography (silica, pentane) yielded 2,2-dimethylchromene as a clear oil (7.2 g, 44.9 mmol, 66%).

^1H NMR (400 MHz, CDCl_3) δ 1.43 (s, 6H), 5.60 (d, $J = 9.9$ Hz, 1H), 6.32 (d, $J = 9.9$ Hz, 1H), 6.76-6.85 (m, 2H), 6.96-6.98 (m, 1H), 7.08-7.12 (m, 1H), in accordance with that reported in ref. [8]. ^{13}C NMR (50.3 MHz, CDCl_3) δ 27.97, 76.07, 116.27, 120.65, 121.23, 122.27, 126.24, 129.00, 130.67, 152.86. EI-MS m/z 160 $[\text{M}]^+$. HRMS (calc. for $\text{C}_{11}\text{H}_{12}\text{O}$: 160.089) found: 160.089.

***cis*-2,2-Dimethylchromane-3,4-diol (*cis*-diol) and *trans*-2,2-dimethylchromane-3,4-diol (*trans*-diol).** A mixture of $[\text{Mn}(\text{O})(\text{CCl}_3\text{CO}_2)_2(\text{tmtacn})_2](\text{PF}_6)_2$ (5.4 mg, 5 μmol), $\text{CCl}_3\text{CO}_2\text{H}$ (500 μl of a 0.1 mM stock in CH_3CN , *i.e.* 50 μmol), H_2O (110 μl) and 2,2'-dimethylchromene (400 μl , 2.5 mmol) in CH_3CN (4.5 ml) was cooled to 0°C . H_2O_2 (50% aq., 240 μl , 4.2 mmol) was added *via* syringe pump over 4 h (60 $\mu\text{l}/\text{h}$) and the reaction mixture was stirred for an additional 1 h after the addition of H_2O_2 was completed. CH_2Cl_2 (10 ml) and 0.5 M aq. NaHCO_3 (10 ml) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were washed with brine (15 ml). After drying on anhydrous Na_2SO_4 the solvents were evaporated *in vacuo*. Purification by column chromatography (silica, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97.5:2.5) afforded racemic *cis*-diol (R_f 0.30) and racemic *trans*-diol (R_f 0.27).

***cis*-diol (*rac*):** 152 mg (0.78 mmol, 31%) of a viscous, almost colourless oil which solidified upon standing. ^1H NMR (400 MHz, CDCl_3) δ 1.29 (s, 3H), 1.49 (s, 3H), 2.03 (d, $J = 8.8$ Hz, 1H), 2.61 (d, $J = 9.9$ Hz, 1H), 3.72 (dd, $J = 8.4$ and 4.4 Hz, 1H), 4.81 (dd, $J = 9.5$ and 4.0 Hz, 1H), 6.80-6.83 (m, 1H), 6.97-7.01 (m, 1H), 7.18-7.23 (m, 1H), 7.52-7.54 (m, 1H), in accordance with that reported in ref. [8]. ^{13}C NMR (50.3 MHz, CDCl_3) δ 23.30, 24.79, 65.24, 71.61, 77.70, 116.89, 121.29, 122.25, 128.83, 129.40, 151.93. EI-MS m/z 194 $[\text{M}]^+$. HRMS (calc. for $\text{C}_{11}\text{H}_{14}\text{O}_3$: 194.094) found: 194.094.

***trans*-diol (*rac*):** 8 mg (0.04 mmol, 2%) of a viscous, almost colourless oil which solidified upon standing. ^1H NMR (400 MHz, CDCl_3) δ 1.17 (s, 3H), 1.43 (s, 3H), 3.57 (d, $J = 8.8$ Hz, 1H), 3.84 (br s, 1H), 4.00 (br s, 1H), 4.54 (d, $J = 8.8$ Hz), 6.75-6.77 (m, 1H), 6.89-6.92 (m, 1H), 7.14-7.18 (m, 1H), 7.37-7.39 (m, 1H), in accordance with that reported in ref. [8]. ^{13}C NMR (50.3 MHz, CDCl_3) δ 18.64, 26.63, 69.61, 76.29, 78.38, 116.78, 120.69, 123.15, 127.34, 129.39, 152.16. EI-MS m/z 194 $[\text{M}]^+$. HRMS (calc. for $\text{C}_{11}\text{H}_{14}\text{O}_3$: 194.094) found: 194.094.

(+)-(3R,4R)-cis-2,2-dimethylchromene-3,4-diol. $[\text{Mn}^{\text{III}}_2(\mu\text{-O})(\mu\text{-Ac-D-Phg})_2(\text{tmtacn})_2](\text{PF}_6)_2$ **6** (2.9 mg, 2.5 μmol), Ac-D-Phg-OH (4.8 mg, 25 μmol) and 2,2-dimethylchromene (100 mg, 624 μmol) were dissolved in CH_3CN (2.25 ml) and water (0.25 ml). The reaction mixture was cooled to 0 °C and a stock solution of H_2O_2 (50% aq.) in CH_3CN (250 μl of a 4.2 M solution, *i.e.* 1.7 equiv. H_2O_2 w.r.t. substrate) was added slowly (63 $\mu\text{l/hr}$). After the addition was completed, the reaction mixture was stirred for another hour at 0 °C. CH_2Cl_2 (15 ml) and 0.5 M aq. NaHCO_3 (15 ml) were added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were washed with brine (15 ml) and dried over anhydrous Na_2SO_4 . The solvents were evaporated *in vacuo* and the crude sticky oil (88 mg, a mixture of *cis*- and *trans*-diol, ratio 5:1, by ^1H NMR spectroscopy) was purified by column chromatography (silica, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97.5:2.5) yielding (+)-(3R,4R)-*cis*-diol as a colorless solid (51 mg, 262 μmol , 42%, average of duplo experiment). $[\alpha]_{\text{D}}^{20} = +7^\circ$ (*c* 0.5 CHCl_3) (which corresponds to 44% *ee* lit.[10]: +16°). Determination of enantiomeric excess by HPLC (OD-H) yields the *ee* value of 41%.

3,4-Epoxy-2,2-dimethylchromane. A mixture of 2,2-dimethylchromene (200 mg, 1.25 mmol) in CH_2Cl_2 (12 ml) and 0.5 M aq. NaHCO_3 (5 ml) was cooled to 0°C and *m*CPBA (242 mg, 1.05 mmol) was added in small portions. After the addition was complete, the reaction mixture was stirred for an additional 30 min at 0°C and was subsequently allowed to reach room temperature. The organic layer was separated and washed with 0.5 M $\text{NaHCO}_{3(\text{aq})}$ (5 x 10 ml), H_2O (10 ml) and brine (10 ml). After drying on anhydrous Na_2SO_4 , the solvents were evaporated *in vacuo*, yielding a mixture of unreacted alkene and epoxide (215 mg, epoxide/alkene ratio: 1.7 as judged from ^1H NMR). For spectroscopic data of the epoxide, see *e.g.* ref. [8] and [9].

2,2-dimethylchroman-3-one. was prepared according to the literature procedure¹⁰ by heating *cis*-2,2-dimethylchromane-3,4-diol at reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene. ^1H NMR (400 MHz, CDCl_3) δ 1.41 (s, 6H), 3.60 (s, 2H), 6.98-7.24 (m, 4H), in accordance with that reported in ref. [10]. For the isomer 2,2-dimethylchroman-4-one, the signal due to the $-\text{CH}_2-$ protons are observed at 2.72 ppm, as reported in ref. [11].

Catalysis protocols

Procedure (A) for the catalytic oxidation of 2,2-dimethylchromene. 2,2-Dimethylchromene (100 mg, 624 μmol), 1,2-dichlorobenzene (45.9 mg, 312 μmol), the appropriate Mn_2 -dimer (2.5 μmol) and chiral carboxylic acid (typically 25 μmol) were dissolved in a mixture of CH_3CN (2.25 ml) and H_2O (0.25 ml). This mixture was cooled (typically) to 0°C . A solution of H_2O_2 (50 w/w%) in CH_3CN (250 μl of a 4.2 M solution, *i.e.* 1.7 equiv. H_2O_2 w.r.t. substrate) was added *via* syringe pump over 4 h (62.5 $\mu\text{l/h}$). The reaction mixture was stirred at 0°C for 1 h after the addition of H_2O_2 was completed, prior to sampling by GC and HPLC. All reactions were performed, at least, in duplo.

Procedure (B) for the screening of chiral carboxylic acids for the enantioselective *cis*-dihydroxylation of 2,2-dimethylchromene. H_2O_2 (7.5 μl , 132 μmol) was added at room temperature to a mixture of 1,2-dichlorobenzene (1 ml of a 312 mM stock in CH_3CN , *i.e.* 312 μmol), **1** (1 ml of a 2.5 mM stock in CH_3CN , *i.e.* 2.5 μmol), CH_3CN (0.25 ml) and chiral carboxylic acid (156 μmol). The mixture was stirred for 20 min, followed by addition of 2,2-dimethylchromene (100 μl , 100 mg, 625 μmol) and H_2O (0.25 ml). H_2O_2 (50%, 4x15 μl , 1060 μmol) was added in four portions at $t = 0, 1, 2$ and 3 h at room temperature. The reaction mixture was stirred for 1 h after the addition of H_2O_2 was completed, prior to sampling by GC.

To determine the *ee* of both the *cis*- and *trans*-diol and the *cis/trans*-diol ratio by HPLC, a small sample of the diols was isolated via preparative TLC. A small sample of the reaction mixture (25 μl) was separated on a TLC plate (5x10 cm, silica, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 97.5 : 2.5). After drying in the air (10-15 min), 0.5 cm of the TLC plate was cut off and stained with Ce/Mo-dip (the diols turn blue, $R_f \sim 0.25-0.3$). The area containing the diols was scraped off from the undeveloped TLC plate and this silica (containing the diols) was suspended in *n*-heptane/IPA (96:4). The resulting suspension was filtered on a plug of anhydrous Na_2SO_4 (1 cm) and the filtrate was collected in a sample vial (equipped with 0.3 ml glass insert) and subjected to HPLC analysis. All reactions were performed, at least, in duplo.

Analyses

GC analyses were performed on an Agilent 6890 Gas Chromatograph equipped with a HP-1 dimethyl polysiloxane column (30 m \times 0.25 mm \times 0.25 μm). Peak identification and calibration were performed using independent samples (either purchased from a commercial supplier or

independently synthesized). Conversion was determined *in duplo* employing 1,2-dichlorobenzene as internal standard. Before and after each series of catalytic runs the calibrations were checked *in duplo* with two known, independent samples (the values found were +/- 10% of their expected values).

2,2-Dimethylchromene. Column: HP-1 (30 m × 0.25 mm × 0.25 μm), oven temp.: 5 min at 100°C, 10 °C/min to 250°C, 10 min at 250°C, 25 °C/min to 100°C (inlet: 250°C, detector: 250°C). 1,2-Dichlorobenzene (internal standard, 3.93 min), 2,2-dimethylchromene (7.33 min), 2,2-dimethylchroman-3-one (not calibrated, 9.04 min), *cis*-2,2-dimethylchromane-3,4-diol (not calibrated, 12.47 min, partially decomposes to 2,2-dimethylchroman-3-one), *trans*-2,2-dimethylchromane-3,4-diol (not calibrated, 12.72 min, partially decomposes to 2,2-dimethylchroman-3-one), 3,4-epoxy-2,2-dimethylchromane (completely decomposes to 2,2-dimethylchroman-3-one).

HPLC analyses were performed on a Shimadzu LC10Advp.

2,2-dimethylchromene. Column: Chiralcel OD-H (4.6 mm × 250 mm, particle size 5 μm), *n*-heptane/^{*i*}PrOH (96:4) at 0.5 ml/min for 45 min. Monitored between 190-400 nm, *ee* determined at 210 nm. *cis*-2,2-dimethylchromane-3,4-diol (27.6 min (3R,4R) and 33.5 min (3S,4S)), *trans*-2,2-dimethylchromane-3,4-diol (25.8 and 30.0 min).

Table S 1 Catalytic *cis*-dihydroxylation of 2,2-dimethylchromene.^a

Entry	Acid	<i>ee</i> ^b <i>cis</i> -diol	<i>ee</i> ^b <i>trans</i> -diol	<i>cis/trans</i> -diol ratio ^c	Conv. (%) ^d
1	Boc-Phg-OH	28	-1	3.2	88
2	Ac-D-Phg-OH	-38	6	4.3	99
3	H-D-Phg-OH ^e	-3	-1	1.2	13
4	Fmoc-D-Phg-OH	-29	3	3.7	92
5	Cbz-Phg-OH	27	-1	3.6	80
6	Boc-Ala-OH	3	2	3.6	86
7	Boc-Val-OH	5	3	3.6	73
8	Boc-Ile-OH.½H ₂ O	5	7	4.0	69
9	Boc-Leu-OH.H ₂ O	2	5	3.4	84
10	Boc-Phe-OH	3	3	3.3	81
11	(R)-(+)-Boc-Pip-OH	6	1	1.8	80
12	Boc-Pro-OH	10	-5	3.6	68
13	Boc-Pro-Pro-OH	21	-3	3.4	27
14	(R)-(-)-2-phenylpropionic acid	-13	-7	4.1	39
15	(S)-(+)-naproxen	16	3	4.6	31
16	lactic acid (>85% in water)	-1	5	1.2	61
17	(S)-(-)-acetoxypropionic acid	-0.4	10	2.7	77
18	(R)-(+)-Mosher's acid	-20	-6	3.8	73
19	Boc-D-Phg-OH	-28	4	3.3	88
20	(R)-(-)-mandelic acid	-15	-0.2	1.0	72
21	(R)-(-)- α -acetoxyphenylacetic acid	-20	-3	3.0	82
22	(S)-(+)-2-oxo-4-phenyl-3-oxazolidineacetic acid	3	-1	1.7	75
23	(S)-(-)-2-oxo-1,5-imidazolidine-dicarboxylic acid 1-benzyl ester	5	-2	3.5	86
24	(1S)-(+)-ketopinic acid	-9	-1	7.0	53

a) See procedure B. b) Determined by HPLC. c) Estimated from HPLC, assuming equal molar absorptivities for the *cis*- and *trans*-diol at 210 nm. d) Determined after 4 h by GC. e) It should be noted that the solubility of H-D-Phg-OH is very low in CH₃CN/H₂O.

Colour code:

<i>ee</i>	< 2 %	2-10 %	11-25 %	25-35 %	>35 %
<i>cis/trans</i> -diol ratio	< 2	2-5	> 5		
conversion	< 50 %	50-75 %	> 75 %		

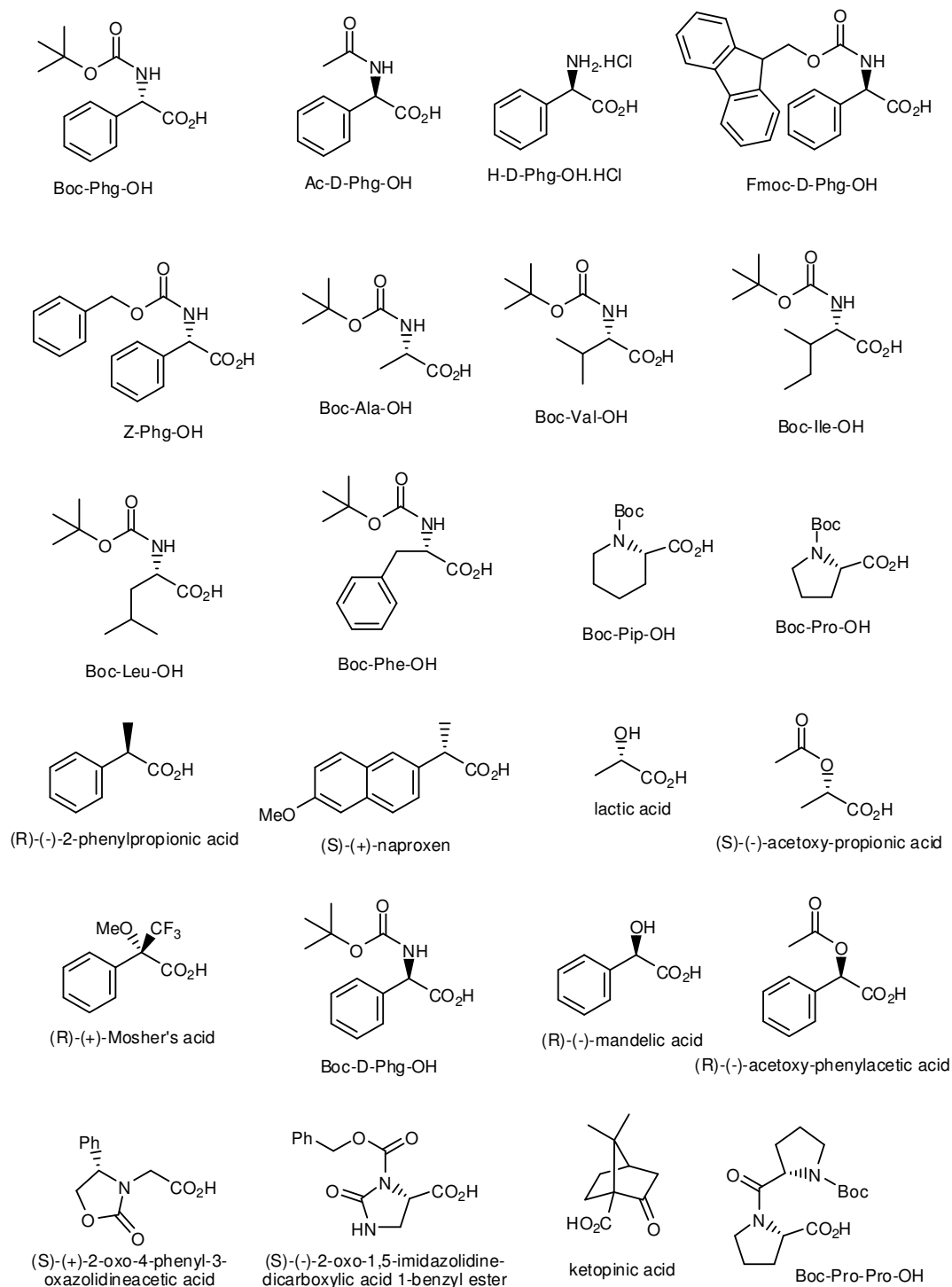


Figure S 1 Chiral carboxylic acids employed in the screening for enantioselective *cis*-dihydroxylation of 2,2-dimethylchromene.

¹H NMR Spectra of reaction mixture

A typical reaction was followed by ¹H NMR spectroscopy using CD₃CN and D₂O₂/D₂O. Conversion and *ee* were determined by GC and HPLC also.

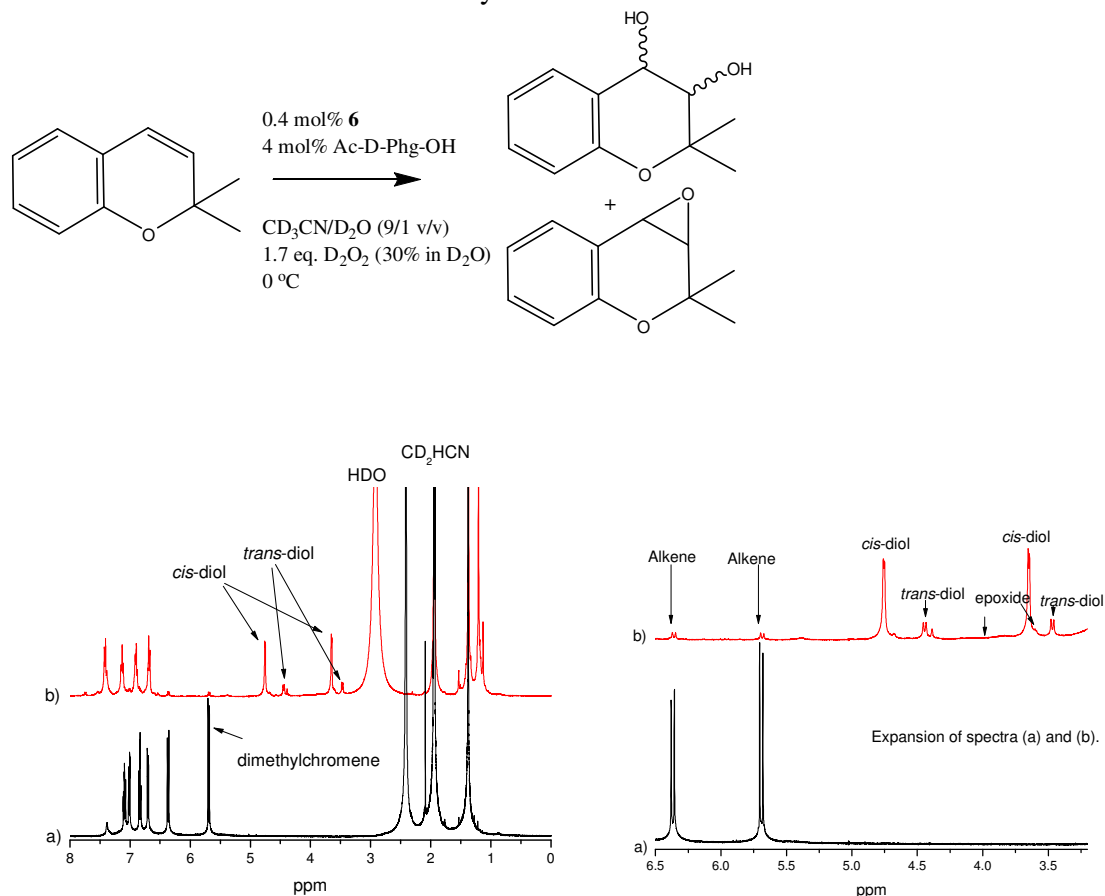


Figure S 2 (a) Before addition of D₂O₂/D₂O to the reaction mixture: 100 μL of the reaction mixture was diluted in 400 μL of CD₃CN before the spectra were recorded. (b) After 4 h: 300 μL of the reaction mixture was diluted in 300 μL of CD₃CN before the spectra were recorded.

	HPLC	¹ H NMR spectroscopy
<i>cis/trans</i> ratio	4.9	4.7
<i>ee cis</i> -diol	50.8% (3R4R)	-
<i>ee trans</i> -diol	12.1 %	-

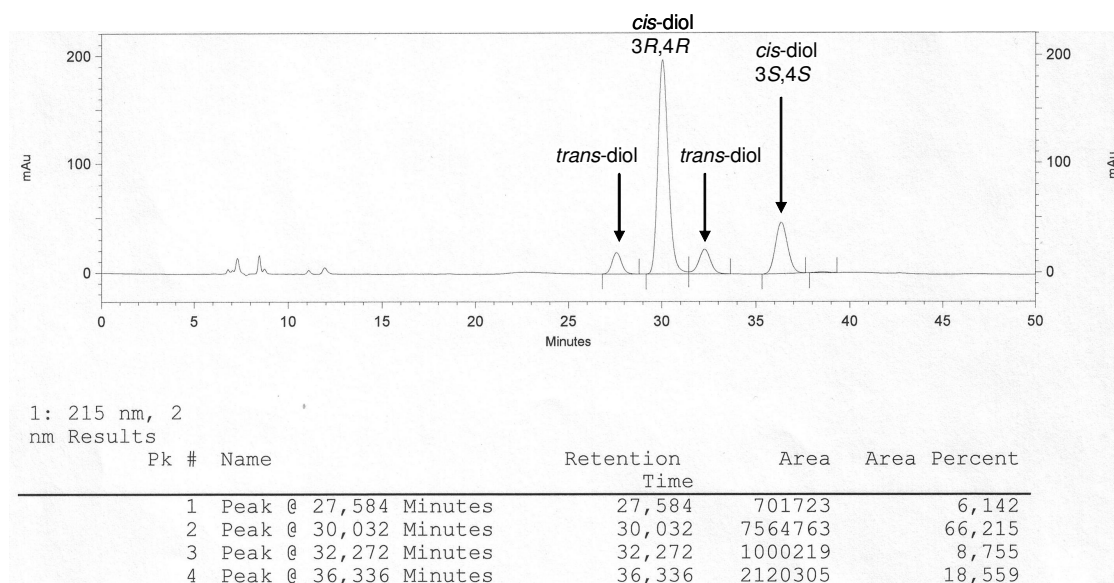


Figure S 3 Chiral HPLC chromatographic analysis. Oxidation of 2,2'-dimethylchromene (0.624 M) in CH₃CN/H₂O (95:5) with 1.7 eq. H₂O_{2(aq)} (50%) at -20 °C, catalyzed by [Mn₂O(Ac-D-PhgO)₂(tmtacn)₂]²⁺ (0.4 mol%)/Ac-D-Phg-OH (4 mol%) with 1,2-dichlorobenzene as internal standard. Conversion (by GC) 55%, *cis/trans* diol ratio 5.2, *ee* (3*R*,4*R*) 54 %.

Validation of Methods.

A series of control experiments were employed in order to validate the method used in the screening of chiral carboxylic acids (Table S1) with respect to conversion and enantioselectivity with respect to the alternate procedures employed. As can be seen from Table S2, the conversions and enantioselectivities obtained under different conditions (*i.e.* concentration of the carboxylic acid employed, temperature and manner of addition of H₂O₂) show similar trends.

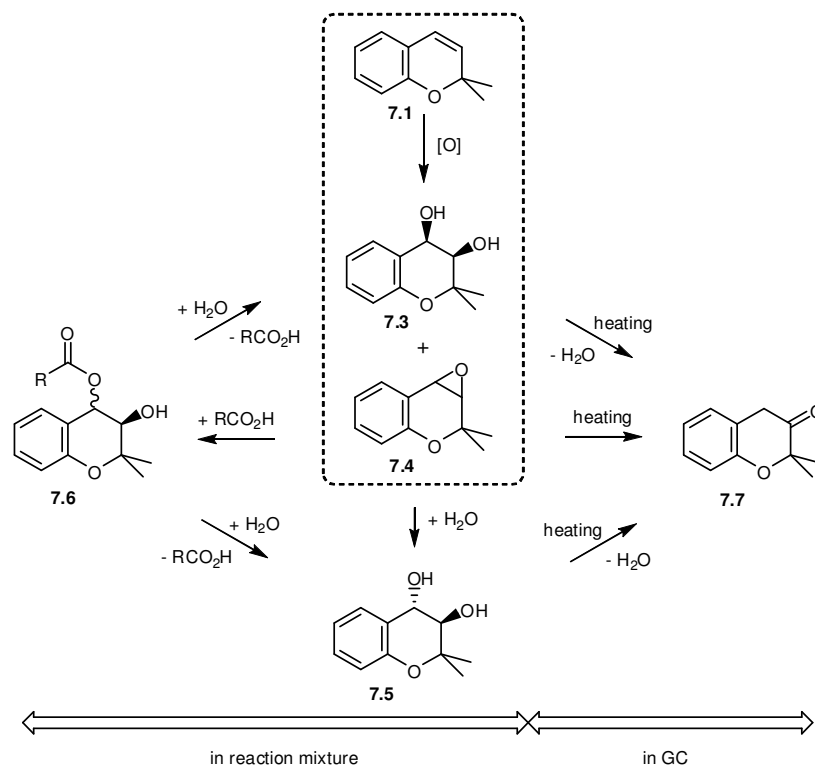
Table S2 Comparison ‘screening’ and ‘standard’ conditions.^a

Entry	Carboxylic acid	Screening conditions		Standard conditions	
		Conv. (%) ^b	<i>ee</i> (%)	Conv. (%) ^c	<i>ee</i> (%)
1	Boc-Phg-OH	89	29	85	36
2	Boc-Phe-OH	82	2	80	3
3	Boc-Pro-OH	71	9	50 ^d	-12 ^d
4	Boc-Ala-OH	90	2	75	5

a) Enantioselective *cis*-dihydroxylation of 2,2-dimethylchromene in CH₃CN/H₂O (9:1). b) **1** (1 mM, 0.4 mol%) and chiral carboxylic acid (62.5 mM, 25 mol%) at r.t. and batchwise addition of H₂O₂, single run (see general procedure B). c) Respective Mn^{III}₂ complex (*i.e.* **2-6**, 1 mM, 0.4 mol%) and chiral carboxylic acid (10 mM, 4 mol%) at 0 °C and continuous addition of H₂O₂, *in duplo* (see general procedure A). d) [Mn₂(O)(Boc-D-Pro-O⁻)₂(tmtacn)₂](PF₆)₂ (**4**) used.

The stability of 3,4-epoxy-2,2-dimethylchromane in CH₃CN in the presence of carboxylic acid and/or H₂O was tested. While in CH₃CN solution 3,4-epoxy-2,2-dimethylchromane is stable, in the presence of 2,6-dichlorobenzoic acid (10 mM) the 2,6-dichlorobenzoate ester is detected by CI-MS ([M+NH₄]⁺ *m/z* 384), however, in the presence of H₂O (*i.e.* CH₃CN/H₂O 9:1) part of these esters are hydrolysed to the corresponding diols. Indeed, it is known that opening of 3,4-epoxy-2,2-dimethylchromane by a carboxylic acid gives both the *trans*- and *cis*-ester in a 6:1 ratio.¹⁰ Similarly, hydrolysis of the epoxide in aqueous dioxane buffer in the presence of HClO₄ (pH 2.5) yields the *trans*- and *cis*-diol in the same ratio (*trans:cis* 6:1).⁸ Thus the *cis*-diol product can be formed via two different pathways (Figure S3): i) via direct *cis*-dihydroxylation of the alkene by the dinuclear manganese catalyst, or ii) via opening of the epoxide intermediate. Overall, it is apparent that the *cis*-diol product is enantiomerically enriched. However, the question remains whether this is due to direct enantioselective *cis*-dihydroxylation of the alkene

by the manganese catalyst or whether the observed *ee* of the *cis*-diol is due to opening of the enantiomerically enriched epoxide and/or enantioselective opening of the epoxide intermediate.



Scheme S2 Processes occurring in the reaction mixture during the catalytic oxidation of 2,2-dimethylchromene and inside the GC injection port. The dehydration of both the *cis*- and *trans*-diol occurs only partially (ca. 20-35%).

Isolation of the racemic *cis*-diol and epoxide product via catalytic oxidation of 2,2-dimethylchromene employing **2a**/ $\text{CCl}_3\text{CO}_2\text{H}$ was attempted, however, only the (racemic) *cis*- and *trans*-diols could be isolated. The intrinsic reactivity of the Mn^{III}_2 bis(carboxylato) complexes results in the formation of both the *cis*-diol and epoxide products. However, the epoxide formed is not stable under reaction conditions in the presence of a slight excess of carboxylic acid and ring-opening and hydrolysis gives both the corresponding *trans*- and *cis*-diol products (ratio *trans/cis* 6:1, as reported in literature,^{8,10} *vide supra*). As a consequence, a minor part of the *cis*-diol is not formed directly by catalysed *cis*-dihydroxylation of the alkene, but

originates either from hydrolysis of the epoxide or from hydrolysis of the *cis*-ester, which in turn is the result of ring-opening by the carboxylic acid of the epoxide formed initially.

The occurrence of (partial) rearrangements of the epoxide and *cis*- and *trans*-diol products inside the gas chromatograph further complicates the analysis of the products formed during the catalytic oxidation of 2,2-dimethylchromene by 1/carboxylic acid with respect to the determination of turnover numbers and product selectivity. While the GC trace of pure 3,4-epoxy-2,2-dimethylchromane (isolated by preparative TLC) showed a single compound, the same compound was observed in the GC trace of pure (>97% by ¹H NMR spectroscopy) *cis*-2,2-dimethylchromane-3,4-diol and in the GC trace of pure (>97% by ¹H NMR spectroscopy) *trans*-2,2-dimethylchromane-3,4-diol. That the epoxide, *cis*-diol and *trans*-diol showed a common species in their respective GC traces is judged from the identical retention times and mass spectra (obtained by GC-MS(EI), *m/z* 176) of this common species, which was identified to be 2,2-dimethylchroman-3-one,^{10,12} based on comparison with a sample synthesised independently. This 2,2-dimethylchroman-3-one is formed via rearrangement from the epoxideⁱ and via dehydration¹⁰ of the diols inside the gas chromatograph.

Both conversion of the alkene and the turnover numbers for both *cis*-dihydroxylation and epoxidation for all substrates in our earlier report¹³ were determined by GC (using an internal standard). However, for the substrate 2,2-dimethylchromene the determination of the turnover numbers for the epoxide, *cis*-diol and *trans*-diol product was not possible with GC (the conversion of the alkene substrate, however, was determined by GC using an internal standard).

ⁱ Similarly, phenylacetaldehyde has been observed in the GC traces of styrene oxide. These rearrangements of the epoxide take place inside the liner, which is part of the injection port of the GC. Using a deactivated liner, instead of a non-deactivated liner, and/or reduction of the temperature of the injection port suppresses these rearrangements partly, but not completely.

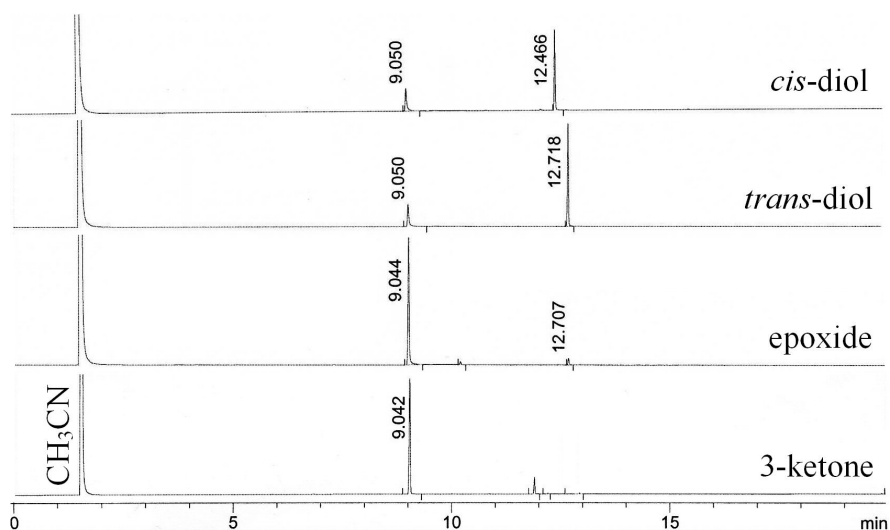


Figure S 4 GC traces of *cis*-2,2-dimethylchromane-3,4-diol, *trans*-2,2-dimethylchromane-3,4-diol, 3,4-epoxy-2,2-dimethylchromane) and 2,2-dimethylchroman-3-one (top to bottom). See above for conditions.

The quantitative contributions of the indirect routes to the *cis*-diol product (*i.e.* via the epoxide intermediate) are complex. Especially since the *ee* of the epoxide intermediate and the relative contributions and enantioselectivities of these processes (*i.e.* opening of the epoxide by H₂O and epoxide opening by the chiral carboxylic acid with subsequent ester hydrolysis) are unknown. Furthermore, a detailed and very complicated kinetic analysis of these parallel processes would be required.

However, in order to answer the most pertinent question, whether the dinuclear manganese complexes engage in direct enantioselective *cis*-dihydroxylation of the alkene, it is sufficient to calculate the two extremes for the contribution to the observed *ee* of the portion of the *cis*-diol product formed indirectly via the epoxide intermediate. The *cis*-diol product (*cis*-diol_{observed}) is formed via direct *cis*-dihydroxylation of the alkene (*cis*-diol_{direct}) and via opening of the epoxide intermediate (either directly by H₂O or via hydrolysis of an ester intermediate, Figure S2). The latter are taken together as *cis*-diol_{indirect}.

$$cis\text{-diol}_{\text{observed}} = cis\text{-diol}_{\text{direct}} + cis\text{-diol}_{\text{indirect}}$$

As discussed above, it has been reported previously⁸ that the acid catalysed ring-opening of the epoxide results in formation of the *trans*- and *cis*-diol products with a ratio of 6:1. Ring-opening

of the epoxide by a carboxylic acid yields the *trans*- and *cis*-esters with a *trans/cis* ratio of 6:1 also. It is thus fair to assume that $cis\text{-diol}_{\text{indirect}}$ can be calculated from the amount of *trans*-diol observed ($trans\text{-diol}_{\text{observed}}$) taking into consideration this *trans/cis*-ratio of 6:1, *i.e.*

$$cis\text{-diol}_{\text{indirect}} = 1/6 * trans\text{-diol}_{\text{observed}}$$

The *cis*-diol product observed ($cis\text{-diol}_{\text{observed}}$) consists of a mixture of its two enantiomers ($cis_{\text{enantiomer1}}$ and $cis_{\text{enantiomer2}}$). The *cis*-diol formed via the indirect pathways ($cis\text{-diol}_{\text{indirect}}$) can have a maximum *ee* of 100%. That is, it can in principle consist of only one of the two *cis*-diol enantiomers. In the one extreme case, $cis\text{-diol}_{\text{indirect}}$ consists of only a single $cis_{\text{enantiomer1}}$, in the other extreme case, $cis\text{-diol}_{\text{indirect}}$ consists of only $cis_{\text{enantiomer2}}$. Subtracting these (extreme) contributions of the $cis\text{-diol}_{\text{indirect}}$ from $cis\text{-diol}_{\text{observed}}$ affords the minimum and maximum enantioselectivity achieved by direct formation of *cis*-diol by the dinuclear Mn^{III}_2 catalysts, respectively (Figure S4).

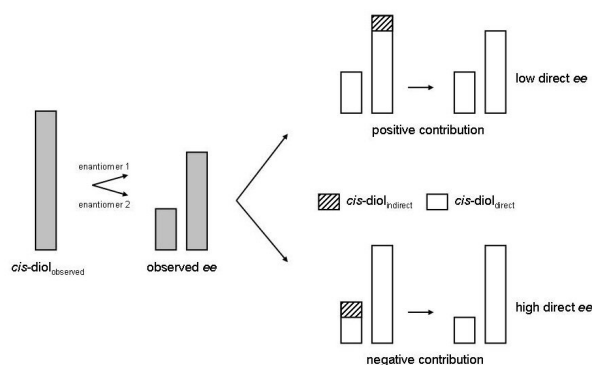


Figure S 5 Effect of *ee* of the *cis*-diol formed indirectly on the enantioselectivity of *cis*-dihydroxylation catalysed by the dinuclear Mn^{III}_2 -complex.

These two extreme cases have been calculated for all carboxylic acids used in the screening (Table S3). For Ac-D-Phg-OH, the carboxylic acid which affords the highest (observed) *ee* for the *cis*-diol product (-38%, entry 2), even in the worst case scenario, when all of the $cis\text{-diol}_{\text{indirect}}$ contributes positively to the *ee* of the $cis\text{-diol}_{\text{observed}}$, the intrinsic enantioselectivity of the direct *cis*-dihydroxylation of the alkene by the dinuclear Mn^{III}_2 -catalyst is still -35%. In the other extreme case, *i.e.* when $cis\text{-diol}_{\text{indirect}}$ contributes negatively to the *ee* of the $cis\text{-diol}_{\text{observed}}$, the intrinsic enantioselectivity of the dinuclear Mn^{III}_2 -catalyst would be -43%.

It should be noted that even in these extreme cases the *ee* achieved by the catalyst is close to the *ee* observed. Furthermore, it is important to note that the assumption that the sum of the indirect pathways (*i.e.* formation of the *cis*-diol product via the epoxide intermediate) would afford 100% selectivity for only one of the *cis*-diol enantiomers is highly unlikely. In fact, the low *ee* observed for the *trans*-diol product, which is being formed via these ‘indirect’ pathways from epoxide intermediate also, suggests strongly that the *ee* of *cis*-diol_{indirect} is low as well (0-10%, Table 7.4). The latter would mean that the intrinsic *ee* of the Mn-catalyst is even closer to the observed *ee* than suggested by the limit values for the intrinsic enantioselectivity of the Mn^{III}₂-catalyst as summarized in Table S3. Thus it can be concluded confidently that this catalyst system is truly a catalyst for enantioselective *cis*-dihydroxylation.

Table S3 Observed, maximum and minimum direct *ees* for the *cis*-dihydroxylation of 2,2-dimethylchromene.

Entry	Acid	Observed <i>ee</i>	Direct <i>ee</i> max.	Direct <i>ee</i> min.
1	Boc-Phg-OH	28	35	24
2	Ac-D-Phg-OH	-38	-43	-35
3	H-D-Phg-OH	-3	-20	14
4	Fmoc-D-Phg-OH	-29	-35	-25
5	CBZ-Phg-OH	27	33	24
6	Boc-Ala-OH	3	8	-2
7	Boc-Val-OH	5	10	1
8	Boc-Ile-OH.0.5H ₂ O	5	9	0
9	Boc-Leu-OH.H ₂ O	2	7	-3
10	Boc-Phe-OH	3	9	-2
11	(R)-(+)-Boc-Pip-OH	6	18	-5
12	Boc-Pro-OH	10	15	6
13	Boc-Pro-Pro-OH	21	27	17
14	(R)-(-)-2-phenylpropionic acid	-13	-18	-10
15	(S)-(+)-naproxen	16	20	12
16	lactic acid (>85% in water)	-1	-17	15
17	(S)-(-)-acetoxypipionic acid	-0,4	6	-7
18	(R)-(+)-Mosher's acid	-20	-25	-16
19	Boc-D-Phg-OH	-28	-35	-24
20	(R)-(-)-mandelic acid	-15	-38	2
21	(R)-(-)- α -acetoxypipionic acid	-20	-27	-15
22	(S)-(+)-2-oxo-4-phenyl-3-oxazolidineacetic acid	3	15	-7
23	(S)-(-)-2-oxo-1,5-imidazolidine-dicarboxylic acid 1-benzyl ester	5	10	0
24	(1S)-(+)-ketopinic acid	-9	-12	-7

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