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A Practical Oligomeric (salen)Co Catalyst for Asymmetric Epoxide Ring Opening Reactions

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General

All ^{1}H NMR, ^{13}C NMR and spectra were recorded using Bruker DMX 500, AM 500 or AM 400 FT spectrometers at ambient temperature. IR spectra were recorded as either KBr discs or thin film between NaCl plates on a Matterson FTIR 3000. Solvents were used as received from commercial suppliers. Gas chromatographic (GC) analyses were performed on Hewlett-Packard 5890 Series II instruments equipped with FID detectors and HP 3396 integrators. HPLC analyses were performed on a Hewlett-Packard 1050 Series quaternary pump gradient instrument with a diode-array detector interfaced with HP ChemStation software for data analysis.

Materials

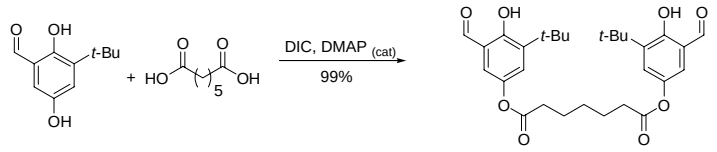
1,2-epoxyhexane was purchased from Aldrich and distilled from CaH_2 before use. Cyclohexene oxide, propylene oxide, and styrene oxide were purchased from Aldrich and used as received. Phenols and alcohols were purchased from Aldrich and used as received. 3-nitrobenzenesulfonic acid was purchased from TCI America and used as received.

Catalyst Preparation

Complex **5** is commercially available.

For preparation of complexes **6** - **8**, see the supporting information of reference 1.

Dialdehyde <u>10</u>

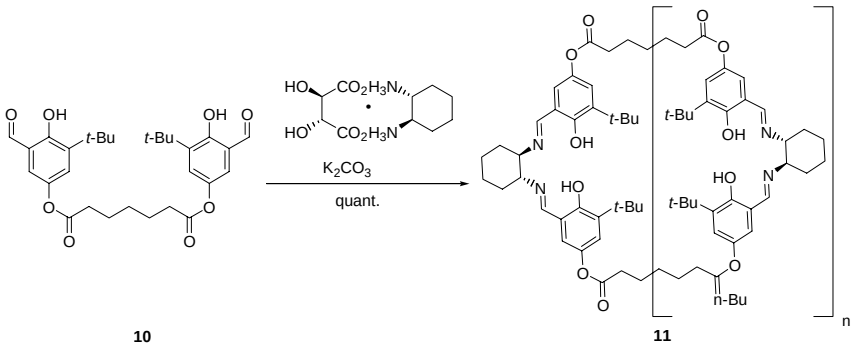


9 10

1,3 Diisopropylcarbodiimide (4.60 mL, 29.4 mmol, 2.1 equiv.) was added to a solution of 3-*tert*-Butyl-2,5-dihydroxy benzaldehyde[1] (**9**) (5.57 g, 28.7 mmol, 2.05 equiv), DMAP (0.34 g, 2.8 mmol, 0.2 equiv) and pimelic acid (2.24 g, 14 mmol, 1.00 equiv) in CH_2Cl_2 (27 mL) and DMF (2 mL) at 0 ^oC under N_2. The solution was stirred at 0 ^oC for 5 min and at rt for 2 h. The reaction solution was diluted with CH_2Cl_2 (150 mL) and extracted with 0.1 M HCl (150 mL) and brine (150 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was suspended in hexanes (200 mL), filtered through filter paper and extracted with 2% K_2CO_3 (4 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to provide 7.11 g (99%) yellow oil. . ^1H NMR ($CDCl_3$) δ = 1.40 (s, 18H), 1.52-1.63 (m,

2H), 1.83 (q, *J* = 7.6, 4H), 2.61 (t, *J* = 7.3, 4H), 7.17 (d, *J* = 2.5, 2H), 7.20 (d, *J* = 3.0, 2H), 9.79 (s, 2H), 11.7 (s). ^{13}C NMR ($CDCl_3$) δ = 24.7, 28.7, 29.2, 34.2, 35.3, 120.2, 123.4, 128.2, 140.4, 142.6, 159.2, 172.5, 196.6. IR (thin film) 1618, 1657, 1758, 2872, 2959, 3426 cm^{-1}. FAB+ MS, *m/z*: 535 $[M+Na]^+$.

Oligosalen <u>11</u>:

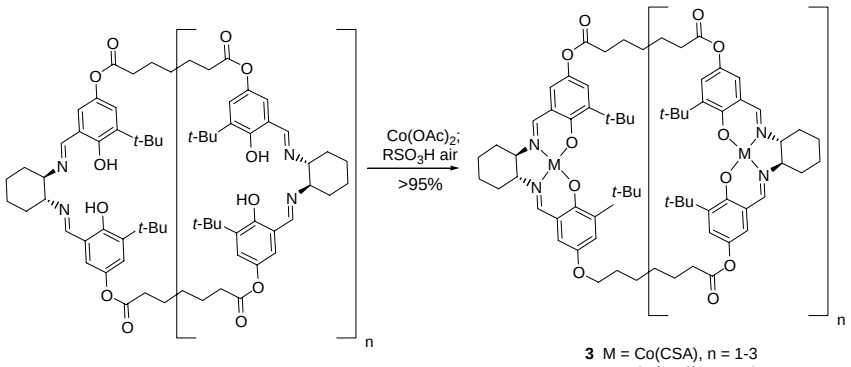


10 **11**

THF (22 mL) was added to a solution of (*R*,*R*)-1,2-diammoniumcyclohexane-mono-(+)-tartrate salt (1.75 g, 6.59 mmol) and K_2CO_3 (1.84 g, 13.32 mmol) in distilled H_2O (8.2 mL). The solution was heated to reflux and **10** (3.41 g, 6.66 mmol) was added as a solution in THF (22 mL). The reaction was stirred at reflux for 2 h, cooled to rt and diluted with EtOAc (100 mL). The organic layer was separated, extracted with brine and dried with Na_2SO_4. Solvent was removed under reduced pressure to provide 3.88 g (quantitative) yellow solid. ^{1}H NMR ($CDCl_3$) δ = 1.38 (s, 18H), 1.44-1.56 (m, 4H), 1.64-1.82 (m, 10H), 1.83-2.00 (m, 4H), 2.53 (t, *J* = 7.3, 4H), 3.26-3.36 (m, 2H) 6.77 (d, *J* = 2.9, 2H), 6.92 (d, *J* = 2.6, 2H), 8.27 (s, 2H). Approx. 5% unidentified material is evident in the ^{1}H NMR. ^{3}C NMR ($CDCl_3$) δ = 24.2, 24.6, 28.6, 29.2, 33.1, 34.1, 34.9, 72.3, 118.1, 121.4, 122.9, 138.6, 141.6, 158.1, 164.7, 172.5. IR (KBr) 1437, 1593, 1634, 1763, 2865, 2944 cm^{-1}. FAB+ MS , *m/z* (%): 590 (55) $[M]^+$ n = 0, 1180 (100) $[M]^+$ n = 1,

1203 (75) $[M+Na]^+$ n = 1, 1769 (30) $[M]^+$ n = 2, 1792 (25) $[M+Na]^+$ n = 2, 2350 (10) $[M]^+$ n = 3, 2373 (10) $[M+Na]^+$ n = 3.

Oligo-(salen)Co(CSA) and oligo-(salen)Co(NBS) 3 and **4**:

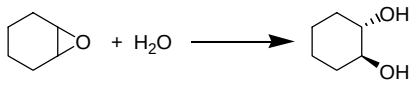


11

3 M = Co(CSA), n = 1-3
4 M = Co(NBS), n = 1-3

To a degassed solution of **11** (0.390 g, 0.66 mmol[2]) in toluene (ca. 7 mL) was added a degassed solution of $Co(OAc)_2 \bullet 2H_2O$ (0.329 g, 1.32 mmol) in MeOH (ca. 7 mL) via canula under N_2. The resulting mixture was stirred with a N_2 purge for 30 min at which time (*1S*)-10-camphorsulfonic acid (0.153 g, 0.66 mmol) or 3-nitrobenzensulfonic acid (0.146 g, 0.66 mmol) and CH_2Cl_2 (10 mL) were added. The reaction was stirred open to the air for 2h. Solvents were removed under reduced pressure and the brown residue was suspended in CH_2Cl_2. The suspension was filtered through a pad of celite to remove excess $Co(OAc)_2$ and the celite was washed with 500 mL CH_2Cl_2. Solvent was removed under reduced pressure to provide the catalyst as a paramagnetic black solid in >95 % yield. IR (KBr) (for **2**) 1547, 1567, 1605, 1641, 1746, 2868, 2947. FAB+ MS , *m/z* (%): 1294 (100) $[M]^+$ n = 1, 1317 (60) $[M+Na]^+$ n = 1, 1940 (15) $[M]^+$ n = 2, 1963 (10) $[M+Na]^+$ n = 2, 2587 (5) $[M]^+$ n = 3, 2610 (5) $[M+Na]^+$ n = 3.

(*S*)-Cyclohexane 1,2-diol (Table 2).



Entries 1, 3 and 5: Cyclohexene oxide (0.491 g, 5.00 mmol), 1:1 CH_3CN:CH_2Cl_2 (1.5 mL) and H_2O (0.11 mL, 6.0 mmol) were added to (*R,R*)-oligo-(salen)Co **1**, **3** or **4** (0.075 mmol, 0.015 equiv) at 23 ^oC. The reaction was stirred for 3 (entry 1) or 4 h (entries 3 and 5) at 23 ^oC. PPTS (0.05 g) and 1 mL 1:1 CH_3CN:CH_2Cl_2 were added, and the reaction mixture was applied to a pad of silica gel. The silica gel was washed with 600 mL EtOAc. Concentration afforded 0.551 g (with **1**), 0.561 g (98%) (with **3**) or 0.526 g (with **4**) white solid in 86 (with **1**) or 93 % ee (with **3** and **4**) by chiral GC analysis of the bis-TFA ester (formed from 2 mg product and 0.1 mL TFAA)(G-TA, 75 ^oC, t_R(minor) = 6.7 min, t_R(major) = 9.6 min). ^1H NMR ($CDCl_3$) δ = 1.20 – 1.30, (m, 4H), 1.60 – 1.75 (m, 2H), 1.90 – 2.00 (m, 2H), 2.75 – 3.15 (m, 2H), 3.30 – 3.40 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 24.5, 33.0, 75.9.

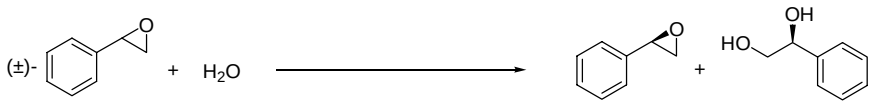
Entry 2. The same procedure as for Entry 1 was followed, except that the reaction was carried out at 4 ^oC. Reaction time: 12h. Isolated 0.568 g (98%) in 94 %ee.

Entries 4 and 6: The same procedure as for entries 3 and 5 was followed except 1 mL 1:1 CH_2Cl_2:CH_3CN and 0.025 mmol catalyst were used. Reaction time: 12 h. Yield: 0.522 g (90%) with **3**; 0.539 g (92%) with **4**. Ee: 93%.

Entries 7 and 8: The same procedure as for entries 3 and 4 was followed except that catalyst **5**[1] was used and following concentration of the filtrate, the crude reaction product was purified by chromatography on silica gel (75% EtOAc in hexanes). Reaction time:

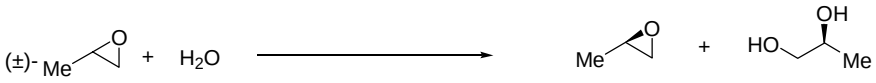
36 h (entry 7), 96 h (entry 8). Yield: 0.418 g, (72%) (entry 7), 0.093g (16%) (entry 8) . Ee: 71% (entry 7), 51% (entry 8).

(*R*)-Styrene Oxide and (*S*)-2-Phenyl-1,2-ethanediol (equation 1).



Styrene oxide (3.00 g, 25 mmol), H_2O (0.27 mL, 15 mmol), and 1:1 CH_2Cl_2:CH_3CN (0.5 mL) were added to (*R*,*R*)-**3** (0.020 g, 0.020 mmol) and the reaction was stirred for 2.5 h at rt. Solvent and resolved epoxide were transferred under vacuum (0.2 Torr) from the reaction mixture into a cooled (-78 ^oC) receiving flask. The solution was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to provide styrene oxide (1.32 g, 44 %) in 99 % ee by chiral HPLC (*R*,*R*-Whelko, 1% IPA in hexanes, 1 mL/min, 220 nm, t_R (minor) = 7.4 min; t_R (major) = 9.1). (*S*)-2-phenyl-ethanediol was vacuum distilled (0.2 Torr, 100 ^oC) to provide 1.51 g (44%) in 97 % ee as determined by chiral GC analysis of the bistrifluoroacetate derivative (G-TA, 75 ^oC, t_R (minor) = 31.0 min; t_R (major) = 33.2).

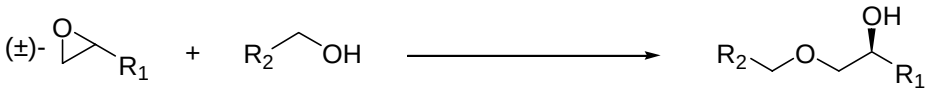
(*R*)-Proplyene oxide and (*S*) Propanediol (equation 2).



Propylene oxide (85.6 g, 103 mL, 1.475 mol) and water (15.9 mL, 0.89 mol, 0.6 equiv) were added to a stirred solution of (*R*,*R*)-**3** (5 mg, 0.0059 mmol) in CH_3CN (32.5 mL) at rt. The reaction was stirred 24 h at rt. Solvent and resolved epoxide were vacuum transferred (40 Torr) from the reaction mixture into a cooled (-78 ^oC) receiving flask.

The recovered epoxide was distilled at ambient pressure through glass helices to provide 38.56 g (45%). The ee of the recovered epoxide was determined to be >99% by chiral GC analysis of the 1-azido-2-trimethylsiloxypropane (obtained by ring opening with azidotrimethylsilane) (Cyclodex B, 55 ^{o}C, t_R (major) = 12.1 min; t_R (minor) = 12.7). The diol was distilled at 65 ^{o}C under reduced pressure (0.2 Torr) to a cooled (-78 ^{o}C) receiving flask to provide 59.1 g (51%) in 97% ee as determined by chiral GC analysis of the bistrifluoroacetate (G-TA, 60 ^{o}C, 2 min, 1^{o}/min, t_R (minor) = 3.1 min; t_R (major) = 4.61).

Synthesis of 1-alcoxy-2-alcohols (Equations 3 and 4). General Procedure

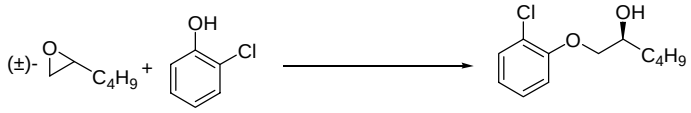


Alcohol (2.25 mmol), epoxide (5.00 mmol) and CH_3CN (0.2 mL) were added to (*R*,*R*)-**4** at 4 ^{o}C, and the solution was stirred at 4 ^{o}C until GC analysis indicated complete conversion of alcohol. The reaction was diluted with 5 mL Et_2O and filtered through a plug of silica gel. The plug of silica gel was washed with 20 mL Et_2O. The filtrate was concentrated under reduced pressure to provide the pure product.

(*R*)-1-Benzyloxy-2-hexanol:[3] **4**: 0.0048 g, 0.0056 mmol, 0.0025 equiv. Reaction time: 8 h. Isolated 0.426 g (91%) colorless oil in 99 % ee by chiral HPLC (*R*,*R*-Whelko, 2%IPA/Hexanes, t_R(minor) = 7.9 min, t_R(major) = 8.7min). ^{1}H NMR ($CDCl_3$) δ = 0.90 (t, *J* = 7.2, 3H), 1.26 – 1.35 (m, 3H), 1.35 – 1.49 (m, 3H) 2.22 (bs, 1H), 3.32 (dd, *J* – 7.9, 9.4, 1H), 3.51 (dd, *J* = 2.9, 9.5, 1H), 3.78 – 3.84 (m, 1H), 4.56 (s, 2H), 7.28, 7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ = 14.2, 22.9, 27.9, 33.0, 70.5, 73.4, 74.7, 76.8, 127.66, 127.70, 128.4, 137.9.

(*R*)-1-(2-trimethylsilyl ethoxy)-2-hexanol: **4**: (0.0019 g, 0.00225 mmol, 0.001 equiv). Reaction tine: 2 h. Recovered 0.476 g (97%). The product was formed in 99 % ee as determined by chiral GC analysis of the bis TFA ester of the deprotected diol (formed by treating 0.01g product with 0.2 mL CH_2Cl_2 and 0.2 mL 2M solution of $LiBH_4$ in CH_3CN and heating at 80 ^oC for 2h) (G-TA, 60 ^oC, 2min, 1 ^oC/min, t_R(minor) = 8.8 min, t_R(major) = 10.9min). ^1H NMR ($CDCl_3$) δ = 0.02 (s, 9H), 0.90 (t, *J* = 7.4, 3H), 0.90 – 0.97 (m, 2H), 1.28 – 1.38 (m, 3H), 1.38 – 1.45 (m, 3H), 2.26 (bs, 1H), 3.21 (dd, *J* = 8.0, 9.6, 1H) 3.42 (dd, *J* = 3.2, 9.2, 1H) 3.48 – 3.60 (m, 2H), 3.71 – 3.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ = -1.2, 14.2, 18.3, 22.9, 27.8, 33.0, 68.6, 70.4, 74.7.

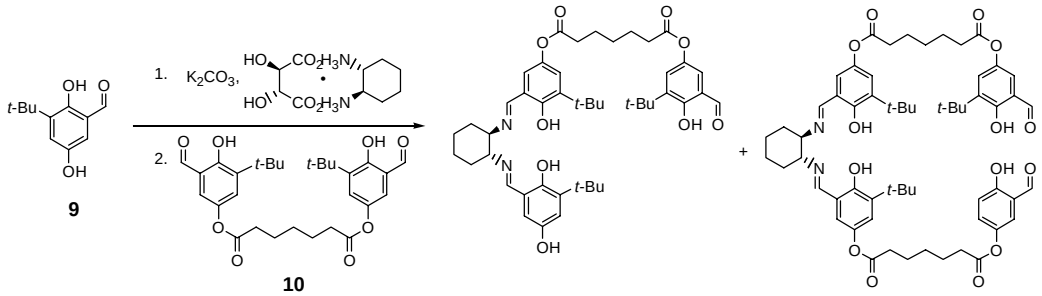
(*S*)-1-(2-chlorophenoxy)-2-hexanol (equation 5).



Chlorophenol (0.290 g, 2.25 mmol), hexeneoxide (0.501 g, 5.00 mmol) and CH_3CN (0.2 mL) were added to (*R*,*R*)-4 at 4 ^oC, and the solution was stirred at 4 ^oC for 10 h. The reaction was diluted with 5 mL Et_2O, PPTS (0.015g) was added, and the solution was filtered through a pad of silica gel. The plug of silica gel was washed with 20 mL Et_2O. The filtrate was concentrated under reduced pressure to provide 0.488 g (95%) colorless oil in >99 % ee as determined by chiral HPLC analysis (Chiralpak AD, 5% EtOH in Hexanes, 270 nm, 1 mL/min t_R (minor) = 7.4 min; t_R (major) = 9.3). ^1H NMR ($CDCl_3$) δ = 0.93 (t, *J* = 7.2, 3H), 1.22 – 1.45 (m, 2H), 1.15 – 1.55 (m, 1H), 1.55 – 1.66 (m, 2H), 2.52 (bs, 1H), 3.87 (dd, *J* = 8.1, 9.9, 1H) , 4.01 – 4.08 (m, 2H), 6.89 – 6.95 (m, 2H), 7.18 – 7.23 (m, 1H), 7.34 – 7.38 (m, 1H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 22.8, 27.7, 32.7, 70.0, 73.5, 113.8, 121.7, 123.0, 127.6, 131.1, 153.9.

Synthesis of 3a - 3b.

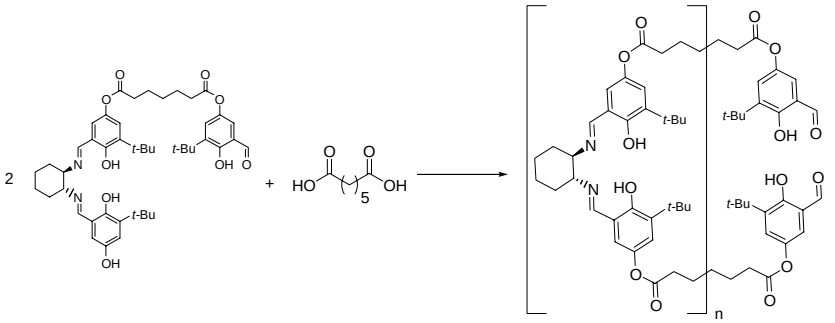
Aldehyde 12 and Dialdehyde 13a.



THF (91 mL) was added to a solution of (*R,R*)-1,2-diammoniumcyclohexane-mono-(+)-tartrate salt (4.82 g, 18.2 mmol, 10 equiv) and K_2CO_3 (5.03 g, 36.4 mmol, 20 equiv) in distilled H_2O (26 mL). The solution was heated to reflux and **9** (0.354 g, 1.82 mmol, 1 equiv) was added as a solution in THF (4.0 mL). The reaction was stirred at reflux for 2 h, cooled to rt and diluted with EtOAc (50 mL) and water (50 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated. The crude residue was dissolved in THF (9 mL) and **10** (4.67 g, 9.12 mmol, 5 equiv) was added as a solution in THF (9 mL). The reaction was stirred 4 h at room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel (20% EtOAc/hexanes) to provide 0.480 g **12** (34%) as a yellow foam in 95% purity. ^{1}H NMR ($CDCl_3$) δ = 1.38 (s, 18H) 1.40 (s, 9H), 1.41-1.57 (m, 4H), 1.66-2.02 (m, 10H), 2.55 (t, *J* = 7.2, 2H), 2.60 (t, *J* = 7.5, 2H), 3.25-3.34 (m, 2H), 6.44 (s, 1H), 6.71 (d, *J* = 2.6, 1H), 6.82 (d, *J* = 2.9, 1H), 6.92 (d, *J* = 2.6, 1H), 7.16 (d, *J* = 2.6, 1H), 7.20 (d, *J* = 2.5, 1H), 8.14 (s, 1H), 8.16 (s, 1H), 9.77 (s, 1H), 11.7 (s, 1H). ^{13}C NMR ($CDCl_3$) δ = 24.4, 24.7, 28.7, 29.2, 29.3, 29.5, 29.9, 33.1, 33.2, 34.2, 35.0, 35.1, 35.3, 72.2, 72.4, 114.8, 118.26, 118.30, 120.2, 121.5, 123.1, 123.5, 128.3, 138.7, 138.9, 140.3, 141.7, 142.6, 147.1, 154.6, 158.4, 159.2, 165.1, 165.4, 172.6, 172.9, 196.68, 196.70. IR (KBr) 1150, 14.7, 1597,

1633.8, 1655, 1757, 2864, 2949, 3447 cm^{-1}. MS (ES+) *m/z* (%): 785.4 (100) $[M+H]^+$. Dialdehyde **13a** (0.58 g) was also isolated from the reaction mixture. ^1H NMR ($CDCl_3$) δ = 1.46, (s, 18H), 1.49 (s, 18H), 1.52-1.68 (m, 6H), 1.76-2.06, (m, 14H), 2.64 (t, *J* = 7.5, 4H), 2.69 (t, *J* = 7.5, 4H), 3.36-3.44 (m, 2H), 6.86 (d, *J* = 2.6, 2H), 7.02 (d, *J* = 2.9, 2H), 7.26 (d, *J* = 2.9, 2H), 7.29 (d, *J* = 2.6, 2H), 8.31 (s, 2H), 9.88 (s, 2H), 11.79 (s, 2H). ^{13}C NMR ($CDCl_3$) δ = 24.2, 24.50, 24.53, 28.5, 29.0, 29.2, 33.1, 34.0, 34.9, 35.1, 72.3, 118.1, 120.0, 121.4, 122.9, 123.3, 128.1, 138.7, 140.1, 141.6, 142.4, 158.1, 159.0, 164.7, 172.3, 172.5, 196.5. IR (KBr) 1437, 1597, 1633, 1657, 1759, 2866, 2951 cm^{-1}. MS (ES+) m/z (%): 1103.8 (100%), $[M+H]^+$, 1125.8. (60) $[M+Na]^+$. Unreacted dialdehyde **10** (2.50 g, 54%) was recovered from the reaction mixture.

Dialdehyde 13b.

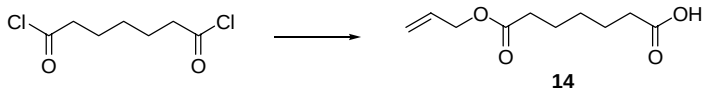


12 **13b**: n = 2

1,3-diisopropylcarbodiimide (0.023 mL, 0.15 mmol, 2.2 equiv) was added to a solution of **12** (0.11 g, 0.14 mmol, 2 equiv), pimelic acid (0.011g, 0.069 mmol, 1 equiv) and DMAP (0.002 g, 0.016 mmol, 0.2 equiv) in CH_2Cl_2 (0.18 mL) and DMF (0.02 mL) at 0 ^oC. The reaction was stirred at 0 ^oC for 5 min, then rt for 24 h. The reaction was diluted with CH_2Cl_2 (5 mL), extracted with 0.1 M HCl (5 mL), saturated $NaHCO_3$ (5 mL) and brine. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (gradient elution, 20 to

25% EtOAc/hexanes) to provide 0.065 g (56%) **13b** as a yellow foam. ^{1}H NMR ($CDCl_3$) δ = 1.37 (s, 18H), 1.38 (s, 18H), 1.40 (s, 18H), 1.42-1.58 (m, 10H), 1.64-1.84 (m, 16H), 1.84-1.97 (m, 8H), 2.53 (t, *J* = 8.0, 4H), 2.55 (t, *J* = 7.7, 4H), 2.6 (t, *J* = 7.5, 4H), 3.28-3.35 (m, 4H), 6.77 (d, *J* = 3.0, 4H), 7.17 (d, *J* = 2.9, 2H), 7.20 (d, *J* = 2.9, 2H), 8.22 (s, 2H), 8.23 (s, 2H), 9.79 (s, 2H), 11.71 (s, 2H). ^{13}C NMR ($CDCl_3$) δ = 24.2, 24.49, 24.52, 24.6, 28.5, 28.6, 29.0, 29.2, 33.1, 34.0, 34.1, 36.9, 35.1, 72.2, 72.3, 118.1, 120.0, 121.39, 121.4, 122.9, 123.3, 128.1, 138.6, 138.7, 140.1, 141.56, 141.58, 142.4, 158.06, 158.09, 159.8, 164.7, 164.8, 172.3, 172.47, 172.50, 196.5. IR (KBr) 1437, 1595, 1634, 1655, 1757, 2865, 2947 cm^{-1}. MS (ES+) *m/z* (%): 848 (100) $[M+2H]^{+2}$, 1693 (20%) $[M+H]^{+}$.

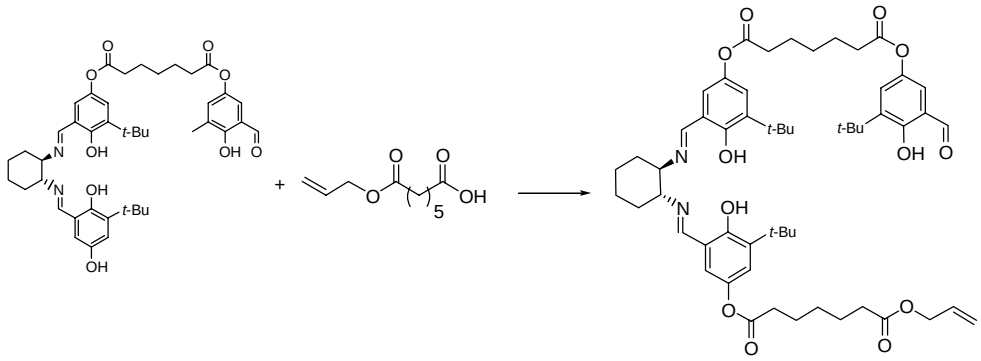
Pimelic Acid monoallyl ester (14)



14

Pimeloyl dichloride (2.45 mL, 15 mmol, 6 equiv) was added to a solution of allyl alcohol (0.17 mL, 0.145 g, 2.5 mmol, 1 equiv), DMAP (0.031 g, 0.25 mmol, 0.1 equiv) and Et_3N (0.42 mL, 3 mmol, 1.2 equiv) in CH_2Cl_2 (5 mL). The reaction was stirred 18 h at room temperature, at which time the reaction was diluted with CH_2Cl_2 and carefully quenched with 1M HCl (50 mL). The organic layer was separated, extracted with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (gradient elution 30 to 40% EtOAc/0.1% AcOH/hexanes) to provide 0.382 g (76%) **14** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.33-1.43 (m, 2H), 1.59-1.70 (m, 4H), 2.30-2.38 (m, 4H), 4.57 (ddt, *J* = 1.2, 1.2, 5.5, 2H), 5.23 (dd, *J* = 0.9, 10.5, 1H), 5.29-5.34 (m, 1H), 5.84-5.96 (m, 1H). ^{13}C NMR ($CDCl_3$) δ = 24.3, 24.6, 28.5, 33.8, 34.0, 65.1, 118.3, 132.3, 173.3, 179.6. IR (thin film) 1710, 1738, 2943 cm^{-1}. MS (CI+) *m/z* (%): 218 (100) $[M+NH_4]^{+}$.

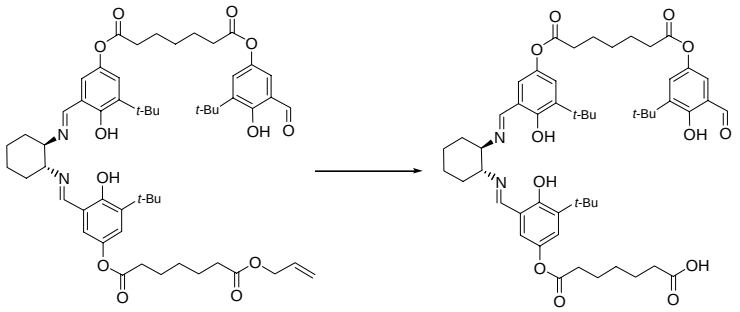
Allyl ester <u>15</u>.



1,3-diisopropylcarbodiimide (0.036 mL, 0.23 mmol, 1.2 equiv) was added to a solution of **12** (0.150 g, 0.19 mmol, 1 equiv), **14** (0.040g, 0.20 mmol, 1.05 equiv) and DMAP (0.002 g, 0.016 mmol, 0.1 equiv) in CH_2Cl_2 (0.27 mL) and DMF (0.03 mL) at 0 ^oC. The reaction was stirred at 0 ^oC for 5 min, then rt for 24 h. The reaction was diluted with CH_2Cl_2 (10 mL), extracted with 0.1 M HCl (10 mL), saturated $NaHCO_3$ (10 mL) and brine. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc/hexanes) to provide 0.121 g (66%) **15** as a yellow glass. ^1H NMR ($CDCl_3$) δ = 1.37 (s, 9H), 1.38 (s, 9H), 1.40 (s, 9H), 1.42-1.58 (m, 6H), 1.64-1.84 (m, 10H), 1.84-1.98 (m, 4H), 2.36 (t, *J* = 7.5, 2H), 2.51 (t, *J* = 7.5, 2H), 2.55 (t, *J* = 7.5, 2H), 2.60 (t, *J* = 7.5, 2H), 3.25-3.37 (m, 2H), 4.58 (dm, *J* = 5.9, 2H), 5.23 (dd, *J* = 10.4, 1.3, 1H), 5.31 (dd, *J* = 17.0, 1.6, 1H), 5.86-5.97 (m, 1H), 6.77 (d, *J* = 2.5, 2H), 6.92 (t, *J* = 2.4, 2H), 7.17 (d, *J* = 2.9, 1H), 7.20, (d, *J* = 2.8, 1H), 8.22 (s, 1H), 8.24 (s, 1H), 9.79 (s, 1H), 11.7 (s, 1H). ^{13}C NMR ($CDCl_3$) δ = 24.2, 24.50, 24.52, 24.56, 24.59, 28.5, 28.6, 29.0, 29.2, 29.8, 33.1, 34.0, 34.1, 34.9, 35.1, 65.1, 72.2, 94.5, 118.1, 118.3, 120.0, 121.39, 121.42, 123.0, 123.3, 128.1, 132.3, 138.69, 138.73, 140.1, 141.6, 142.4, 158.07, 158.11, 159.0, 164.8, 172.3, 172.49, 172.54, 173.2,

196.5. IR (KBr) 1437, 1595, 1633, 1657, 1757, 2864, 2945 cm^{-1}. MS (ES+) *m/z* (%): 484 (15%) $[M+2H]^{+2}$, 968 (100%) $[M+H]^{+}$, 990 (25) $[M+Na]^{+}$.

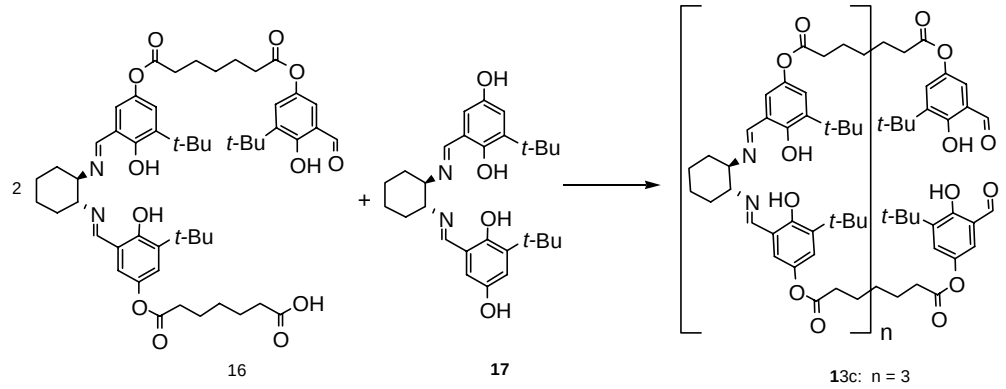
Acid <u>16</u>.



15 16

Under air-free conditions, morpholine (0.065 mL, 0.66 mmol, 6 equiv) was added to a solution of **15** (0.103 g, 0.11 mmol, 1equiv) and $Pd(PPh_3)_4$ (0.013g, 0.01 mmol, 0.1 equiv) in THF (2.8 mL). The reaction was stirred for 2 h at rt, diluted with CH_2Cl_2, extracted with 0.1 M HCl (20 mL) and brine (20 mL). The combined organic layers were dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography on silica gel (gradient elution, 20 to 30% EtOAc/0.2% AcOH/hexanes) to provide 0.064 g (63%) **16** in 95 % purity. ^{1}H NMR ($CDCl_3$) δ = 1.37 (s, 9H), 1.38 (s, 9H), 1.40 (s, 9H), 1.41-1.59 (m, 6H), 1.64-1.84 (m, 10H), 1.84-2.00 (m, 4H), 2.38 (t, *J* = 7.5, 2H), 2.51 (t, *J* = 7.5, 2H), 2.55 (t, *J* = 7.5, 2H), 2.60 (t, *J* = 7.5, 2H), 3.30-3.35 (m, 2H), 6.76 (d, *J* = 2.6, 2H), 6.91-6.93 (m, 2H), 7.17 (d, *J* = 2.6, 1H), 7.19 (d, *J* = 3.0, 1H), 8.21 (s, 1H), 8.24 (s, 1H), 9.79 (s, 1H), 11.7 (s, 1H). ^{13}C NMR ($CDCl_3$) δ = 22.8, 24.2, 24.3, 24.50, 24.53, 58.5, 29.0, 29.2, 33.1, 33.6, 34.1, 34.9, 35.1, 72.27, 72.31, 118.1, 120.0, 121.4, 122.9, 123.3, 128.1, 138.6, 138.7, 140.1, 141.5, 141.6, 142.4, 158.09, 158.12, 159.0, 164.7, 164.8, 172.4, 172.5, 196.5. IR (KBr) 1437, 1597, 1634, 1655, 1711, 1757 cm^{-1}. MS (ES+) *m/z* (%): 926 (100) $[M+H]^{+}$.

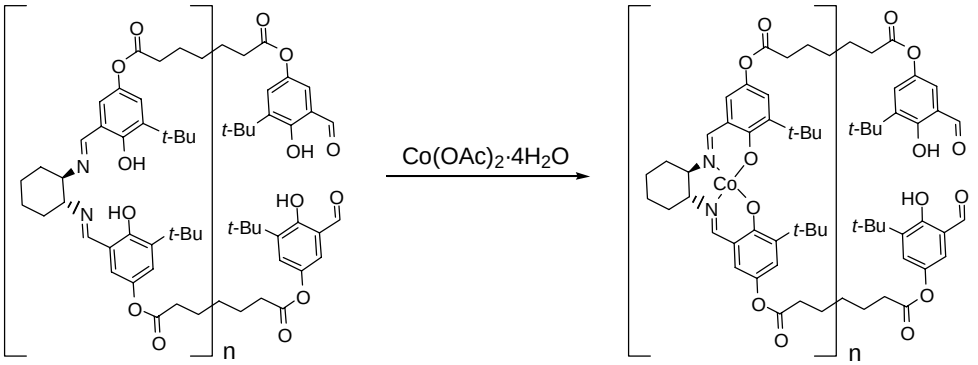
Dialdehyde 13c.



16 17 **13**c: n = 3

1,3-diisopropylcarbodiimide (0.013 mL, 0.083 mmol, 2.5 equiv) was added to a solution of **16** (0.064 g, 0.069 mmol, 2.1 equiv), **17**[1] (0.015g, 0.033 mmol, 1 equiv) and DMAP (0.001 g, 0.008 mmol, 0.2 equiv) in CH_2Cl_2 (0.07 mL) and DMF (0.007 mL) at 0 ^oC. The reaction was stirred at 0 ^oC for 5 min, then rt for 2 h. The reaction was diluted with CH_2Cl_2 (10 mL), extracted with 0.1 M HCl (10 mL), saturated $NaHCO_3$ (10 mL) and brine. The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (25% EtOAc/hexanes) to provide 0.031 g (41%) **13c** as a yellow foam. ^1H NMR ($CDCl_3$) δ = 1.38 (s, 54 H), 1.40 (s, 18 H), 1.42-1.48 (m, 16H), 1.66-1.84 (m, 24H), 1.84-1.97 (m, 8H), 2.53 (t, *J* = 7.9, 8H), 2.55 (t, *J* = 7.9, 4H), 2.60 (t, *J* = 7.6, 4H), 3.30-3.36 (m, 6H), 6.77 (d, *J* = 2.6, 6H), 6.92 (d, *J* = 2.9, 6H), 7.17 (d, *J* = 2.9, 2H), 7.20 (d, *J* = 2.5, 2H), 8.22 (s, 2H), 8.23 (s, 4H), 9.79 (s, 2H), 11.7 (s). ^{13}C NMR ($CDCl_3$) δ = 24.4, 24.69, 24.72, 24.8, 28.7, 28.8, 29.2, 29.4, 29.9, 33.3, 34.2, 34.3, 351, 35.3, 72.4, 72.46, 72.52, 118.3, 120.2, 121.58, 121.61, 123.1, 123.5, 128.3, 138.80, 138.81, 138.9, 140.3, 141.7, 141.8, 142.6, 158.26. 158.09, 164.90, 164.95, 172.5, 172.68, 172.70, 196.6. IR (KBr) 1595, 1634, 1656, 1758, 1865, 1946 cm^{-1}. MS (ES+) *m/z* (%): 926 (100) $[M+2H]^{+2}$.

Dialdehyde 13.



13a n = 1
13b n = 2
13c n = 3

12a n = 1
12b n = 2
12c n = 3

A degassed solution of $Co(OAc)_2 \bullet H_2O$ (2 equiv relative to available metal binding sites) in MeOH (0.2 M) was added to a degassed solution of **13** in toluene (0.025 M). The reaction was stirred under N_2 for 30 min at which time MeOH (3 x reaction vol) was added and the reaction was cooled in an ice bath. The product was collected as a red solid by vacuum filtration.

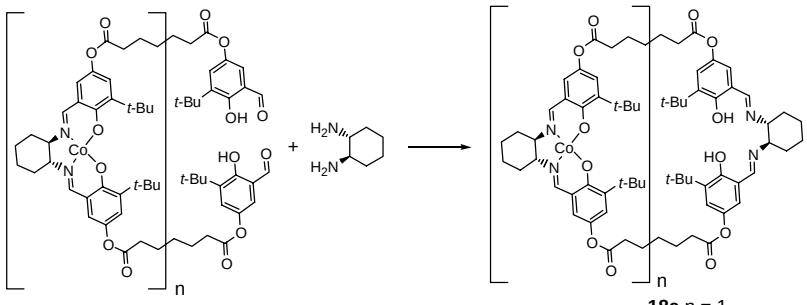
12a. Isolated 0.508 g, (80%). The aromatic, immine and aldehyde resonances of complex **12a** were resolved in the ^{1}H NMR spectrum of its paramagnetic acetate complex (formed from treatment with HOAc in CH_2Cl_2 in air for 30 min). ^{1}H NMR (DMSO-d_6) δ = 6.6-7.9 (m), 8.5-8.6 (bs), 9.9-10.0 (m). IR (KBr) 1537, 1604, 1655, 1755, 2868, 2949 cm^{-1}. MS (FAB+) *m/z* (%): 1159 (100) $[M]^+$, 1182 (85) $[M+Na]^+$.

12b. Isolated 0.043 g, (47%). The aromatic, immine and aldehyde resonances of complex **12b** were resolved in the ^{1}H NMR spectrum of its paramagnetic acetate complex (formed from treatment with HOAc in CH_2Cl_2 in air for 30 min). ^{1}H NMR (DMSO-d_6) δ

= 6.5-7.6 (m), 8.5-8.6 (bs), 9.8-9.9 (m). IR (KBr) 1537, 1605, 1651, 1657, 1755 cm^{-1}. MS (FAB+) *m/z* (%): 1806 (95) $[M]^+$, 1828 (100) $[M+Na]^+$.

12c. Isolated 0.01 g (45%). The aromatic, immine and aldehyde resonances of complex **12c** were resolved in the ^1H NMR spectrum of its paramagnetic acetate complex (formed from treatment with HOAc in CH_2Cl_2 in air for 30 min). ^1H NMR (DMSO-d_6) δ = 6.5-8.0 (m), 8.5-8.7 (bs), 9.9-10.0 (s). IR (KBr) 1411, 1535, 1610, 1635 (shoulder), 1753, 2861, 2943. MS (FAB+) *m/z* (%): 2452 (40) $[M]^+$, 2475 (55) $[M+Na]^+$.

Cyclic salen complexes <u>18</u>



12a n = 1
12b n = 2
12c n = 3

18a n = 1
18b n = 2
18c n = 3

(*R*,*R*)-1,2-diaminocyclohexane (1.2 equiv) and **12** (1 equiv) were dissolved in equal volumes degassed THF and EtOH (final concentration of **12** = 0.01 M) under N_2. The solution was stirred under N_2 for 18 h. The solvent was removed under reduced pressure without exposing the reaction mixture to the atmosphere. The crude product was used without purification.

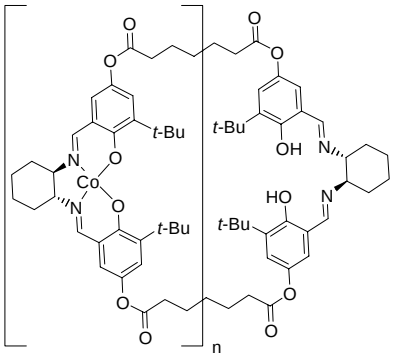
18a: The aromatic and immine resonances of complex **18a** were resolved in the ^1H NMR spectrum of its paramagnetic acetate complex (formed from treatment with HOAc in CH_2Cl_2 in air for 30 min). No aldehyde resonance was evident. ^1H NMR (DMSO-d_6) δ

= 6.5-7.3 (m, 8H), 7.4-7.9 (m, 2H), 8.2-8.6 (m, 2H). IR (KBr) 1437, 1604, 1632, 1755, 1864, 1944. MS (FAB+) *m/z* (%): 1238 (60) $[M]^+$.

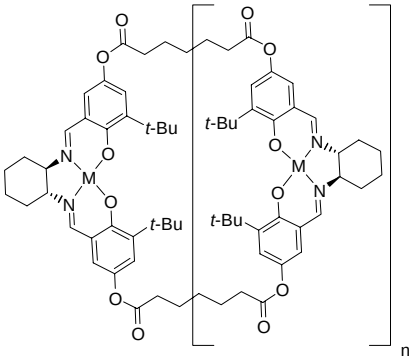
18b: The aromatic and immine resonances of complex **18b** were resolved in the ^1H NMR spectrum of its paramagnetic acetate complex (formed from treatment with HOAc in CH_2Cl_2 in air for 30 min). No aldehyde resonance was evident. ^1H NMR (DMSO-d_6) δ = 6.8-7.4 (m), 7.6-7.9 (m, 4H), 8.2-8.3 (m, 2H). MS (ES+) *m/z* (%): 1828 (20) $[M-Co]^+$, 1911 (70) $[M+Na]^+$, 1995 (100) $[M+5Na]^+$.

18c was used without characterization.

Cyclic (salen)Co(CSA) complexes 3.



18a: n = 1
18b: n = 2
18c: n = 3



3a M = Co(+CSA), n = 1
3b M = Co(+CSA), n = 2
3c M = Co(+CSA), n = 3

A degassed solution of $Co(OAc)_2 \cdot 2H_2O$ (2 equiv) in MeOH (0.2M) was added via canula to a degassed solution of **18** (1 equiv) in toluene (0.04 M). The solution was stirred for 1 h, at which time the reaction was exposed to air; (+)-10-camphorsulfonic acid (1 equiv) and CH_2Cl_2 (equal volume as toluene) were added. The reaction was stirred open to air for 1h. Solvent was removed under reduced pressure and the residue was suspended in CH_2Cl_2 and filtered through celite. The celite was washed with CH_2Cl_2 and the combined filtrates were concentrated under reduced pressure to provide **3** as

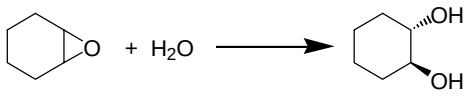
paramagnetic black solids. The aromatic and immine resonances could be resolved in the ^{1}H NMR and are reported below.

3a. Recovered 0.072 g (77%). ^{1}H NMR (DMSO-d_6) δ = 7.1 (bs, 4H), 7.3 (bs, 4H), 7.9 (bs, 4H). IR (KBr) 1541, 1611, 1641, 1745, 2865, 2946 cm^{-1}. MS (FAB+) *m/z* (%): 1292 (100) $[M]^+$.

3b. Recovered 0.056 g (quantitative). ^{1}H NMR (DMSO-d_6) δ = 6.6-7.4 (m), 7.6-7.9 (m). IR (KBr) 1541, 1617, 1637, 1745, 2866, 1945 cm^{-1}. MS (FAB+) *m/z* (%): 1941 (100) $[M]^+$, 1964 (90) $[M+Na]^+$.

3c. Recovered 0.030 g (quantitative). ^{1}H NMR (DMSO-d_6) δ = 7.0-7.2 (bs), 7.3-7.4 (bs), 7.8-7.9 (bs). IR (KBr) 1541, 1618, 1636, 1745, 2866, 1944. MS (ES+) *m/z* (%): 1307 (25) $[M+Na]^{+2}$, 1340 (100) $[M+4Na]^{+2}$.

Hydrolysis of Cyclohexene Oxide (Figure 3).



Water (0.011 mL, 0.6 mmol, 1.2 equiv) was added to a solution of catalyst **3a-3c** (0.011g, 0.0125 mmol, 0.025 equiv), cyclohexene oxide (0.050 mL, 0.5 mmol, 1 equiv), bromobenzene (internal standard) (0.002 mL) and 1:1 CH_2Cl_2:CH_3CN (0.05 mL) at 22 ^oC. Conversion of cyclohexene oxide was measured by GC relative to an internal standard.

	% Conversion			
time (min)	mixture (**3**)	**3a**	**3b**	**3c**
7.5	28	53	28	
15	44	78	39	3
30	64	98	52	36
45	81	100	66	41
60	92		78	50
90	99		92	
120			97	64

Table S1. Conversion and ee data for the asymmetric hydrolysis of cyclohexene oxide.

[1] J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687-2688.

[2] The molecular weights per metal binding site (**7**) or per Co (**2** or **3**) are independent of n.

[3] Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *56*, 6206.