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New oligomeric catalyst for the hydrolytic kinetic resolution of terminal epoxides under solvent-free conditions

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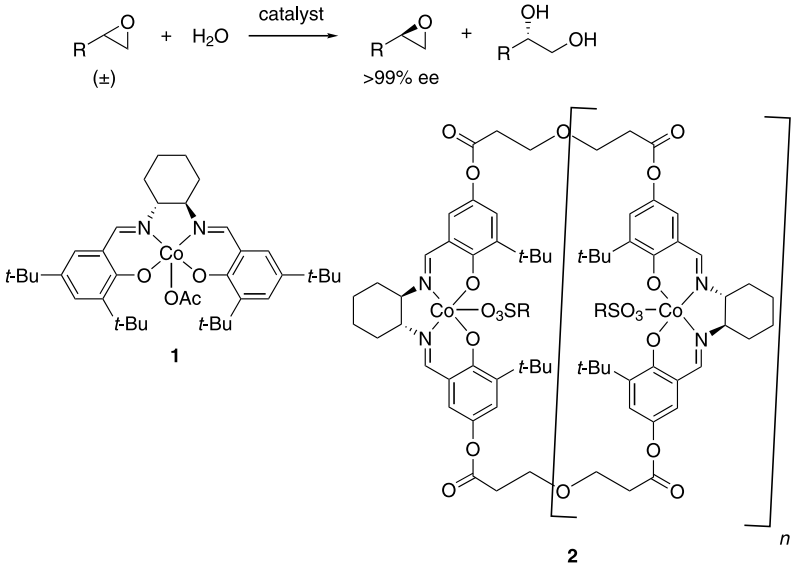
Abstract—The solvent-free hydrolytic kinetic resolution of terminal epoxides catalyzed by a new oligomeric (salen)Co complex **2** is described. Extremely low loadings of catalyst were used to provide all epoxides examined in good yields and >99% ee under ambient conditions within 24 h.

1. Introduction

The hydrolytic kinetic resolution (HKR) catalyzed by chiral (salen)Co complexes (Scheme 1) has emerged as a powerful method for the preparation of enantiopure terminal epoxides.[1,2] The attractive features of the HKR include: high selectivity factors (k_{rel} values) across a wide range of terminal epoxides, allowing access to highly enantioenriched (>99% ee) products in close to theoretical yields; a practical (and scaleable)[3] reaction protocol involving a commercially available catalyst; ready accessibility at low cost of a wide variety of terminal epoxides in racemic form; and absence of useful alternative approaches to the preparation of enantiopure terminal epoxides.[4] However, despite the relatively low catalyst loadings used in HKR reactions (0.2–2 mol%) and demonstrated catalyst recycleability with key substrates,[2,5] the principal cost determinant in



Scheme 1.

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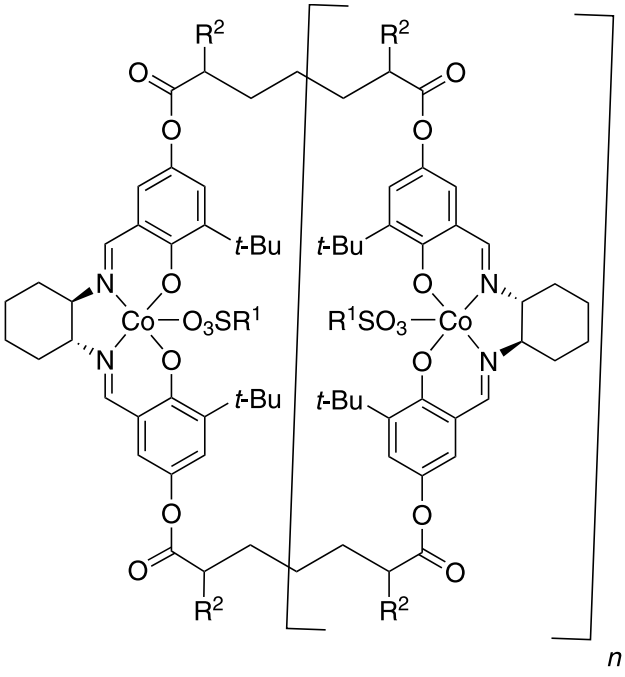
the HKR remains the catalyst.[6] Motivated at least in part by this consideration, we have directed substantial effort toward the development of catalyst systems that are more reactive and may be employed at substantially lower loadings than **1**. We describe here a new oligomeric (salen)Co catalyst system **2** that promotes the HKR of a broad range of terminal epoxides with remarkable efficiency. This new catalyst can be employed successful at extremely low catalyst loadings (down to 41 ppm by mass) under solvent-free conditions at ambient temperature, employing only a slight excess of water for the resolution.



3: R^1 = *p*-tol, R^2 = Cl, *n* = 1-5
4a: R^1 = (1*S*)-10-camphor, R^2 = H, *n* = 1-3
4b: R^1 = 3-NO_2-C_6H_4, R^2 = H, *n* = 1-3

2. Results and discussion

As part of the ongoing development of the (salen)Co catalytic system, we reported recently the discovery of oligomeric (salen)Co complexes **3** and **4** that catalyze epoxide ring-opening reactions with improved enantioselectivities and dramatically increased reaction rates relative to the monomeric derivative **1**.[7,8] The improved reactivity is attributable to the increased effective molarity of reactive metal centers in the bimetallic ring-opening step as a result of covalent tethering of the (salen)Co units. In the context of the HKR of terminal epoxides, oligomers **3** and **4** allowed catalyst loadings to be lowered substantially relative to monomer **1**. However, the new catalysts suffered from very limited solubility, and thus a solubilizing agent such as acetonitrile was required to carry out resolutions that were possible under solvent-free conditions with catalyst **1**. This imposed significant practical limitations by necessitating involved isolation procedures, particularly for volatile substrates.

The identity of the linker unit and the cobalt counterion were identified as crucial for influencing the chemical and physical properties of the oligomeric (salen)Co complexes. Systematic variation of the counterion revealed that sulfonates afforded the most promising results, with the precise identity of the optimal derivative being dependent on the HKR substrate (see below). The identity of the linker was also explored carefully, with variations made to its length, rigidity, and functional groups. We reasoned that decreasing the hydrophobic character of the bis(ester) linker might result in a system more soluble than **4** in the complex epoxide–water–diol HKR medium, and we therefore investigated the introduction of heteroatoms into that unit. Ether derivative **2** proved to be particularly effective, and vastly superior to other analogues of **4** (e.g. the sulfide and sulfonamide analogs). The ligand for **2** was synthesized easily from commercially available 2-cyanoethyl ether utilizing the synthetic route previously developed for catalyst **4** (Scheme 2), and the corresponding Co(III) derivatives were isolated in good yield with a variety of sulfonate counterions. Characterization of these complexes (see Section 3) revealed exclusive formation of cyclic oligomeric derivatives as mixtures of predominantly dimeric and trimeric species, and these mixtures were used without further purification in all subsequent reactions.

The HKR of methyl glycidate was studied as a model reaction for the optimization of the counterion in **2**. As illustrated in Figure 1, electron deficient sulfonate derivatives demonstrated highest reactivity, with the triflate derivative **2a** emerging as the catalyst of choice based on both reactivity and cost.[†] Complete resolution (>99% ee) was achieved within 8 h using 0.03 mol% catalyst under solvent-free conditions. By comparison, resolutions with oligomeric catalyst **4b** attained only 35% ee under the same conditions as a result of the very limited solubility of this complex in the medium. Reactions with monomeric catalyst **1**[9] also proceeded to very low conversion within 8 h (8% ee of unreacted epoxide), in this case because of the inherently lower reactivity of that catalyst.

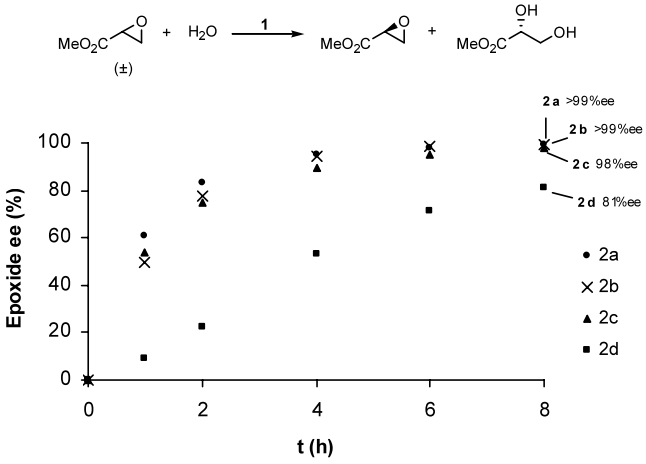
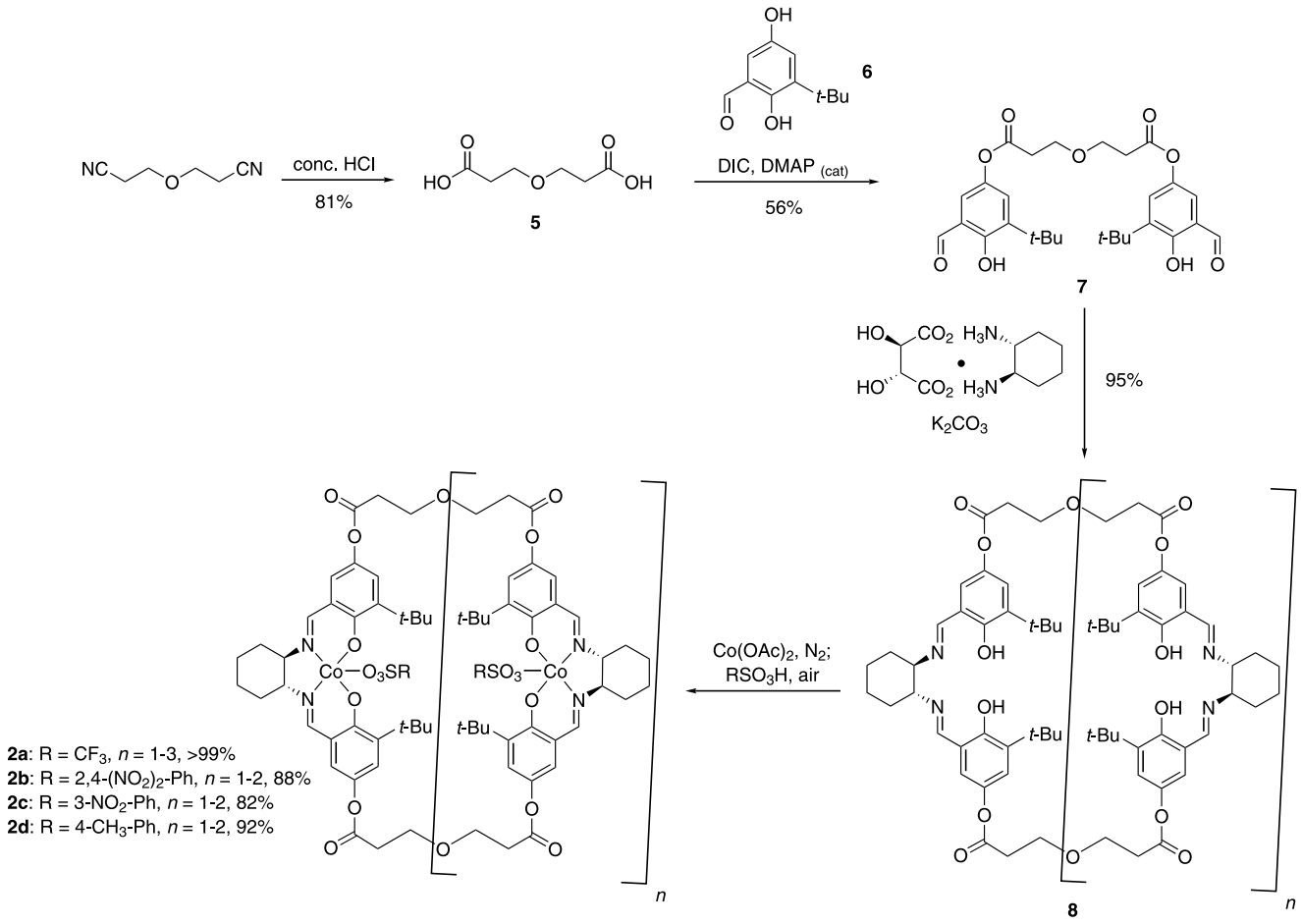


Figure 1.

[†] Much more dramatic differences between sulfonate ligands were observed for reactions such as phenolic kinetic resolution of terminal epoxides and *meso*-epoxide hydrolysis, with **2a** and **2b** consistently displaying the highest reactivity. Catalyst **2a** was deemed preferable on the basis of the practical advantages of the triflate versus the dinitrobenzenesulfonate counterion.



Scheme 2.

Encouraged by these results, we examined the utility of complex **2a** in the HKR of a variety of structurally diverse terminal epoxides under solvent-free conditions. As reflected in Table 1, high reactivity and selectivity were observed in all cases. Both methyl glycidate **9** and epichlorohydrin **11** were obtained in good yield and >99% ee with catalyst loadings orders of magnitude lower than was possible with **1**. The HKR of propylene oxide **12** was especially efficient: 1.5 mol of epoxide were resolved within 24 h using only 3.6 mg (41 ppm by mass, 3 ppm on a molar basis) of catalyst to provide 35 g of recovered enantiopure **12**. The protocol for HKR with catalyst **2a** is operationally very simple. Water is added to a solution of catalyst and epoxide, and the mixture is stirred at room temperature while the epoxide ee is monitored by removal of small aliquots and chromatographic analysis. Once >99% ee has been attained, the epoxide is isolated by vacuum transfer and dried over an appropriate desiccant. In the case of methyl glycidate **9**, considerable foaming hampered distillation of the product mixture on the laboratory scale. However, removal of the diol product by aqueous extraction prior to distillation circumvented the foaming problem, and the epoxide was thus isolated in good yield.

An important exception to the generality of **2a** was seen in the HKR of sensitive conjugated epoxides such as styrene oxide. The more Lewis acidic complexes such as **2a** promote less selective resolutions of these substrates, presumably by an S_N1 mechanism. In these cases, the less

Table 1. HKR of terminal epoxides catalyzed by oligomeric (salen)Co **2**[a]

Epoxide	Catalyst	Catalyst Loading (mol%)	Isolated Yield[b] (%)
MeO_2C **9**	**2a**	0.015	44
10	**2a**	0.0025	43
Cl **11**	**2a**	0.001	44
Me **12**	**2a**	0.0003	40
Ph **13**	**2d**	0.04	40

[a] Reactions were carried out under solvent-free conditions at ambient temperature for 15–24 h using the indicated catalyst loading and 0.6 equiv. H_2O based on racemic epoxide. HKR of epoxides **9**–**11** and **13** were carried out on 120–130 mmol scale, and HKR of **12** on 1.5 mol scale.

[b] Isolated yields based on racemic epoxide (theoretical maximum = 50%).

Lewis acidic tosylate complex **2d** afforded superior results in HKR reactions. Styrene oxide **13** underwent resolution to >99% ee and 40% yield in the presence of 0.025–0.04 mol% **2d**.‡

The combination of a soluble oligomeric framework and a highly electron-deficient sulfonate ligand has led to the development of a practical (salen)Co catalyst for the HKR resolution of terminal epoxides under solvent-free reaction conditions. The increased reactivity, high selectivity, and scope of complex **2** hold great promise for its practical application as a general catalyst for epoxide ring-opening reactions. The full scope of reactivity of this new oligomeric system and a mechanistic understanding of its enhanced efficiency are the focus of ongoing studies.

3. Experimental

3.1. General

Unless otherwise stated, all reagents were purchased from Aldrich, Alfa Aesar, Pfaltz & Bauer, or Strem and used as received. Methyl glycidate was received as a generous gift from Rhodia ChiRex. Allyl glycidyl ether was distilled from CaH_2 prior to use. Aldehyde **6** was synthesized according to the published procedure.[7] CAUTION! HKR of terminal epoxides is an exothermic reaction and care should be taken to ensure adequate heat dissipation. All ^{1}H NMR and ^{13}C NMR spectra were recorded using an INOVA 600 or Bruker AM 400 FT spectrometer at ambient temperature. IR spectra were recorded as thin films on either NaCl or KBr plates on a Perkin–Elmer FTIR 1600. Optical rotations were measured using a Jasco DIP 370 digital polarimeter. Chiral GC analyses were performed on a Hewlett Packard 5890 Series II gas chromatograph using a Chiraldex G-TA column (Advanced Separation Technologies, Inc.). Chiral HPLC analyses were performed on a Hewlett-Packard 1050 HPLC instrument using either a Chiracel® OD (Daicel Chemical Industries Ltd.) or (*R*,*R*)-Whelk-O 1 column (Regis® Technologies Inc.).

3.2. Catalyst synthesis

4-Oxa-1,7-hepatanedioic acid, 5: The method of Samat et al.[10] was used. Conc. HCl (aq.) (65 mL, 780 mmol) was added to 2-cyanoethyl ether (23.78 mL, 200 mmol). The solution was transferred immediately to a heated oil bath (48–51°C) and after an initial exotherm (bath temperature reached 55°C) maintained at 48–51°C for 25 h. The mixture was then allowed to cool to rt as it was stirred for an additional 16.5 h. The mixture was concentrated under a stream of N_2 and azeotroped with benzene (3×) to remove remaining water. The residue was suspended in 1.5 L diethyl ether and filtered to remove insoluble ammonium chloride. The filtrate was dried over $MgSO_4$, and solvent removed under reduced pressure to yield **5** as a white solid (27.59g, 81%) in approximately 95 mol% purity by ^{1}H NMR. ^{1}H NMR (acetone-d_6) δ 10.60 (bs, 2H), 3.69 (t, 4H), 2.52 (t, 4H). ^{13}C NMR (acetone-d_6) δ 172.6, 67.0, 35.1. IR (thin film) ν 3435 (broad), 2932 (broad), 2636, 1719, 1400, 1195, 1110. MS (CI) m/z calcd for $C_6H_{10}O_5$ 162, found 162 (5%) $[M]^+$, calcd for $C_6H_{12}O_6$ 180, found 180 (100%) $[M+H_2O]^+$, calcd for $C_{12}H_{22}O_{11}$ 342, found 342 (3%) $[2M+H_2O]^+$.

Dialdehyde, 7: 1,3-diisolpropylcarbodiimide (1.65 mL, 10.5 mmol) was added to a suspension of **5** (0.814 g, 5.0 mmol), **6** (2.0 g, 10.3 mmol), and DMAP (0.123 g, 1.0 mmol) in anhydrous CH_2Cl_2 (9.6 mL) and anhydrous DMF (0.72 mL) at 0°C. After 5 min, the mixture was allowed to warm to rt as it was stirred for 4 h. The reaction was diluted with CH_2Cl_2 (400 mL) and washed with 0.1N HCl (1×400 mL), 2% K_2CO_3 (4×50 mL), and brine, respectively. After drying over $MgSO_4$, solvent was removed under reduced pressure. Flash chromatography on silica gel (30–50% EtOAc/hexanes, two columns) provided **7** as a pinkish-white powder (1.45 g, 56%). ^{1}H NMR ($CDCl_3$) δ 11.67 (s, 2H), 9.65 (s, 2H), 7.19 (d, J=2.8 Hz, 2H), 7.14 (d, J=2.8 Hz, 2H), 3.91 (t, J=6.2 Hz, 4H), 2.86 (t, J=6.0 Hz, 4H), 1.37 (s, 18H). ^{13}C NMR ($CDCl_3$) δ 196.3, 170.5, 158.9, 142.3, 140.1, 127.9, 123.4, 120.0, 66.4, 35.2, 35.0, 28.9. IR (thin film) ν 2960, 2911, 2873, 1760, 1656, 1434, 1315, 1223, 1158. MS (ES) m/z calcd for $C_{28}H_{36}O_{10}$ 532, found 532 (100%) $[M+H_2O]^+$, calcd for $C_{56}H_{70}O_{19}$ 1046.5, found 1046.6 (22%) $[2M+H_2O]^+$.

Oligomeric salen ligand, 8: THF (3.7 mL) was added to a solution of (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate (290 mg, 1.1 mmol) and K_2CO_3 (307 mg, 2.2 mmol) in H_2O (1.4 mL). The mixture was brought to reflux, and **7** (571 mg, 1.1 mmol) was added as a solution in THF (2.7 mL) via cannula, washing with additional THF (1 mL). After 2 h at reflux, the reaction was cooled to rt and diluted with EtOAc (50 mL). The organic layer was separated, washed with brine, and dried over Na_2SO_4. Solvent was removed under reduced pressure to give **8** as a yellow powder (663 mg, 96%) in approximately 95% purity by mass. ^{1}H NMR ($CDCl_3$) (major oligomeric species) δ 8.14 (s, 2H), 6.92 (d, J=3.0 Hz, 2H), 6.77 (d, J=2.4 Hz, 2H), 3.84 (t, J=6.9 Hz), 3.30–3.22 (m, 2H), 2.78 (t, J=6.6 Hz, 2H), 1.92–1.80 (m, 4H), 1.74–1.60 (m, 2H), 1.46–1.40 (m, 2H), 1.36 (s, 18H). A second minor oligomeric species (ca. 13 mol%) was also observed by ^{1}H NMR as well as small baseline impurities. ^{13}C NMR ($CDCl_3$) δ 170.5, 164.6, 158.1, 141.4, 138.6, 122.9, 121.5, 118.1, 72.1, 66.4, 35.1, 34.9, 32.9, 29.1, 24.1. IR (thin film) ν 2939, 2865, 1759, 1632, 1437, 1163. MS (FAB) m/z calcd for $C_{68}H_{88}N_4O_{14}$ 1185, found 1185 (100%) [n=1, $M]^+$, calcd for $C_{102}H_{132}N_6O_{21}$ 1777, found 1777 (30%) [n=2, $M]^+$, calcd for $C_{136}H_{177}N_8O_{28}$ 2370, found 2370 (12%) [n=3, $M+H]^+$.

‡ Commercially available styrene oxide is contaminated with varying amounts of phenylacetaldehyde, and this was found to induce catalyst reduction to the inactive Co(II) state. This problem may be circumvented by careful purification of the epoxide prior to the HKR, or more simply by use of slightly higher catalyst loadings (up to 0.04 mol%).

Oligomeric (salen)Co Complexes, 2: Typical procedure: deoxygenated toluene (ca. 11.6 mL) was added to **8** (649 mg, 1.1 mmol) under N_2, and deoxygenated MeOH (ca. 11.6 mL) to $Co(OAc)_2{\cdot}4H_2O$ (545 mg, 2.2 mmol) under N_2. N_2 was bubbled through the resulting solutions for 20 min to ensure complete deoxygenation. The solution of $Co(OAc)_2{\cdot}4H_2O$ in MeOH (purple) was added via cannula under N_2 to the solution of **8** in toluene (yellow) to give a deep red solution. The resulting mixture was stirred for 30 min under an N_2 purge. Trifluoromethanesulfonic acid (97 μL, 1.1 mmol) and CH_2Cl_2 (16.6 mL) were added, and the resulting black solution stirred for an additional 2 h under an air atmosphere with vigorous stirring. Solvent was removed under reduced pressure, and the residue dissolved in minimal CH_2Cl_2. Excess insoluble $Co(OAc)_2{\cdot}4H_2O$ was removed via filtration through a Celite® pad, washing with CH_2Cl_2 (200 mL). Removal of solvent under reduced pressure provided complex **1a** as a paramagnetic black solid (892 mg, >99%). IR (thin film) ν 3476 (broad), 2947, 2869, 1750, 1644, 1610, 1547, 1417, 1340, 1258, 1231, 1171, 1030. MS (FAB) m/z calcd for $C_{68}H_{85}Co_2N_4O_{14}$ 1299, found 1299 (100%) [$n=1$, M+H]$^+$, calcd for $C_{102}H_{126}Co_3N_6O_{21}$ 1948, found 1948 (54%) [$n=2$, M]$^+$, calcd for $C_{136}H_{168}Co_4N_8O_{28}$ 2597, found 2597 (14%) [$n=3$, M]$^+$.

2b: The reaction was carried out on a 0.7 mmol scale with respect to ligand to provide complex **1b** as a paramagnetic black solid (552 mg, 88%). IR (thin film) ν 3387 (broad), 2950, 2869, 1754, 1651, 1644, 1606, 1548, 1538, 1417, 1347, 1229, 1183, 1164, 1027. MS (FAB) m/z calcd for $C_{68}H_{84}Co_2N_4O_{14}$ 1298, found 1298 (100%) [$n=1$, M]$^+$, calcd for $C_{102}H_{126}Co_3N_6O_{21}$ 1948, found 1948 (12%) [$n=2$, M]$^+$.

2c: The reaction was carried out on a 0.42 mmol scale with respect to ligand to provide complex **1c** as a paramagnetic black solid (296 mg, 82%). IR (thin film) ν 3456 (broad), 2945, 2917, 2867, 1751, 1644, 1608, 1417, 1340, 1228, 1182, 1164. MS (FAB) m/z calcd for $C_{68}H_{84}Co_2N_4O_{14}$ 1298, found 1298 (100%) [$n=1$, M]$^+$, calcd for $C_{102}H_{126}Co_3N_6O_{21}$ 1948, found 1948 (15%) [$n=2$, M]$^+$.

2d: The reaction was carried out on a 0.48 mmol scale with respect to ligand to provide complex **1d** as a paramagnetic black solid (361 mg, 92%). IR (thin film) ν 3439 (broad), 2947, 2868, 1754, 1644, 1609, 1538, 1532, 1417, 1350, 1228, 1182, 1167. MS (FAB) m/z calcd for $C_{68}H_{85}Co_2N_4O_{14}$ 1299, found 1299 (100%) [$n=1$, M+H]$^+$, calcd for $C_{102}H_{127}Co_3N_6O_{21}$ 1949, found 1949 (16%) [$n=2$, M+H]$^+$.

3.3. Resolution of terminal epoxides, 9–13

(*S*)-Methyl glycidate, 9: To a mixture of (±)-methyl glycidate (12.28 g, 120 mmol) and **1a** (14.4 mg, 0.018 mmol) in a rt water bath was added H_2O (1.3 mL, 72 mmol) in one portion. After stirring 16 h at rt, the reaction was diluted with H_2O (18 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure (51 mm). Resolved epoxide was then purified by vacuum distillation (bp 64°C/25 mmHg) to give a clear liquid (5.46 g, 44%) in >99% ee as determined by chiral GC analysis (γ-TA, 100°C, isothermal, t_R (minor) = 1.8 min; t_R (major) = 2.4 min). $[\alpha]_D^{31} = -9.8$ (c 1.01, MeOH); lit.[11] $[\alpha]_D^{20} = +10.4$ (c 3.6, MeOH, *R* enantiomer).

(*S*)-Allyl glycidyl ether, 10: To a mixture of (±)-allyl glycidyl ether (15.4 mL, 130 mmol) and **1a** (2.6 mg, 0.0033 mmol) in a rt water bath was added H_2O (1.4 mL, 78 mmol) in one portion. After stirring 24 h at rt, resolved epoxide and excess H_2O were vacuum transferred (0.45 mmHg, reaction pot: rt–52°C) to a −78°C receiving flask. H_2O was separated and the epoxide dried over $MgSO_4$. Filtration through a sand plug gave a clear liquid (6.41 g, 43%) in >99% ee as determined by chiral GC analysis (γ-TA, 60°C, isothermal, t_R (minor) = 6.1 min; t_R (major) = 8.5 min). $[\alpha]_D^{31} = +11.6$ (c 1.00, MeOH); lit.[12] $[\alpha]_D^{25} = +9.6$ (c 0.94, EtOH).

(*S*)-Epichlorohydrin, 11: To a mixture of (±)-epichlorohydrin (10.3 mL, 130 mmol) and **1a** (1.0 mg, 0.0013 mmol) in a rt water bath was added H_2O (1.4 mL, 78 mmol) in one portion. After stirring 15 h at rt, resolved epoxide and excess H_2O were vacuum transferred (0.45 mmHg, reaction pot: rt) to a −78°C receiving flask. The epoxide was then separated and dried by filtration through neutral Brockmann Activity Grade I alumina to give a clear liquid (5.27 g, 44%) in >99% ee as determined by chiral GC analysis (γ-TA, 40°C, isothermal, t_R (major) = 6.9 min; t_R (minor) = 8.6 min). $[\alpha]_D^{31} = +32.9$ (c 0.998, MeOH); lit.[13] $[\alpha]_D^{25} = +34.5$ (c 1.20, MeOH).

(*R*)-Propylene oxide, 12: To a mixture of (±)-propylene oxide (105 mL, 1.5 mol) and **1a** (3.6 mg, 0.0045 mmol) in a rt water bath was added H_2O (16.2 mL, 0.90 mol) in one portion. The reaction vessel was sealed to prevent substrate evaporation. (CAUTION! An initial pressure buildup is observed due to the volatility of the epoxide under the exothermic reaction conditions. Care should be taken to use equipment adequate for elevated pressures). After stirring 24 h at rt, resolved epoxide and excess H_2O were vacuum transferred (51 mmHg, reaction pot: rt) to a −78°C receiving flask. The epoxide was dried over $MgSO_4$ and filtered through a sand plug to give a clear liquid (35.2 g, 40%) in >99% ee as determined by chiral HPLC analysis of the 2-napthylsulfide derivative (obtained by ring opening with 0.8 equiv. 2-napthalenethiol and 0.8 equiv. Et_3N in MeOH at 4°C and subsequent purification of the terminal addition product by preparative TLC, Chiracel® OD, 4% EtOH/Hexanes, 1 mL/min, 220 nm, t_R (minor) = 13.2 min; t_R (major) = 15.6 min). $[\alpha]_D^{31} = +13.8$ (neat); lit.[14] $[\alpha]_D^{25} = +13.9$ (neat).

(*R*)-Styrene oxide, 13: To a mixture of (±)-styrene oxide (14.8 mL, 130 mmol) and **1d** (42.8 mg, 0.052 mmol) in a rt water bath was added H_2O (1.4 mL, 78 mmol) in one portion, and the reaction stirred at rt for 19 h. Between 18 and 18.75 h, the diol product was observed to precipitate from solution. At 19 h, resolved epoxide

and excess H_2O were vacuum transferred (0.45 mmHg, reaction pot: rt–70°C) to a −78°C receiving flask. The epoxide was then separated and dried by filtration through a $MgSO_4$ plug to give a clear liquid (6.16 g, 40%) in >99% ee as determined by chiral HPLC analysis ((*R*,*R*)-Whelk-O 1, 1% EtOH/hexanes, 1 mL/min, 220 nm, t_R (minor) = 6.8 min; t_R (major) = 8.1 min). $[\alpha]_D^{31} = -23.7$ (*c* 1.01, $CHCl_3$); lit.[15] $[\alpha]_D^{26} = -23$ (*c* 0.8, $CHCl_3$).

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