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Engineering Polymer-Enhanced Bimetallic Cooperative Interactions in the Hydrolytic Kinetic Resolution of Epoxides

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Abstract: Through systematic variations of the length of oligo(ethylene glycol)-based linkers and the catalyst density of poly(styrene)-supported cobalt-salen catalysts, we have elucidated an optimal catalyst flexibility and density of polymeric Co-salen catalysts for the hydrolytic kinetic resolution (HKR) of racemic terminal epoxides that follows a bimetallic cooperative pathway. The optimized polymeric catalyst brings the two cooperative Co-salen units to a favorable proximity efficiently and hence displays significantly improved catalytic performance in the HKR compared with its monomeric small molecule analogue. Complex **Co(5b)**, representing the most active poly(styrene)-supported HKR catalyst known so far, can effect the resolution of a variety of epoxides to reach $\geq 98\%$ *ee* in 6–24 h with a low cobalt loading of 0.01–0.1 mol%.

Keywords: asymmetric catalysis; cobalt; hydrolytic kinetic resolution; poly(styrene); salen ligands

Introduction

The immobilization of homogeneous catalysts onto insoluble or soluble supports has been practiced intensively in the past two decades, leading to a promising avenue for the separation and recycling of oftentimes expensive transition metal-containing catalysts.[1,2] While the relationship between catalytic properties and support structures has been investigated for a spectrum of reactions involving a single catalytic site,[1,2] approaches to immobilized catalysts tailored for transformations operating *via* a bimetallic or bimolecular cooperative mechanism are largely absent in the literature. This is important since a wide variety of catalytic transformations have been found to proceed through a dual activation pathway, namely, the activation of two substrates (e.g., an electrophile and a nucleophile) simultaneously by two catalytic species in the transition state of the rate-determining step.[3,4] Besides allowing for facile removal of the usually toxic metal species as well as the possibility for recycling, immobilization of a dual activation catalyst holds the potential of providing a favorable proximity of the two cooperative catalytic species that may substantially promote the activity and/or selectivity of the resulting catalyst in comparison with its non-supported small molecule analogue.

The hydrolytic kinetic resolution (HKR) of racemic terminal epoxides with Co(III)-salen catalysts,[5,6] first studied by Jacobsen,[7] represents a pertinent example of such a dual activation pathway (Figure 1). During the catalytic transformation, one cobalt center activates an epoxide whereas the other binds to the hydroxide. A nucleophilic attack of the hydroxide to the less sterically hindered α-carbon of the epoxide affords the key bimetallic intermediate that undergoes hydrolysis to regenerate the active catalytic species. This cooperative bimetallic mechanism has been supported by the observation of a second-order dependence of the reaction rate on the Co-salen species.[8] Incorporation of Co-salen units into oligomeric,[9,10]

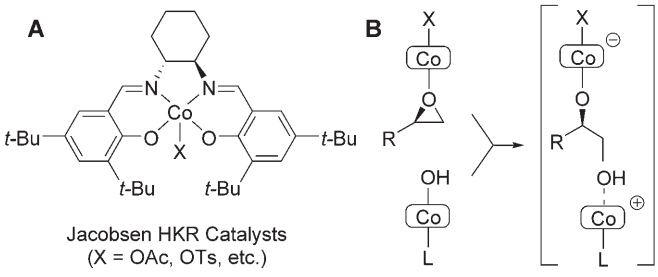


Figure 1. Jacobsen Co-salen catalysts (**A**) and key bimetallic intermediates in the HKR of epoxides (**B**).

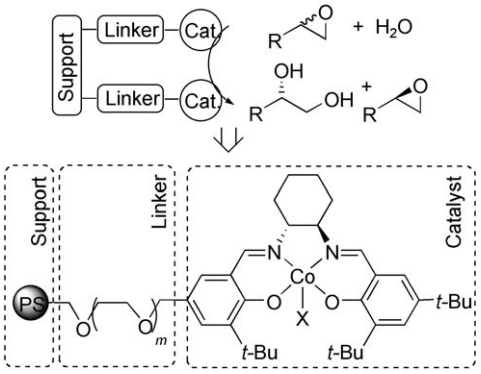


Figure 2. A working model of supported Co-salen catalysts.

polymeric,[11,12] and dendritic frameworks[13] has led to enhanced catalytic performances in terms of both activity and enantioselectivity.

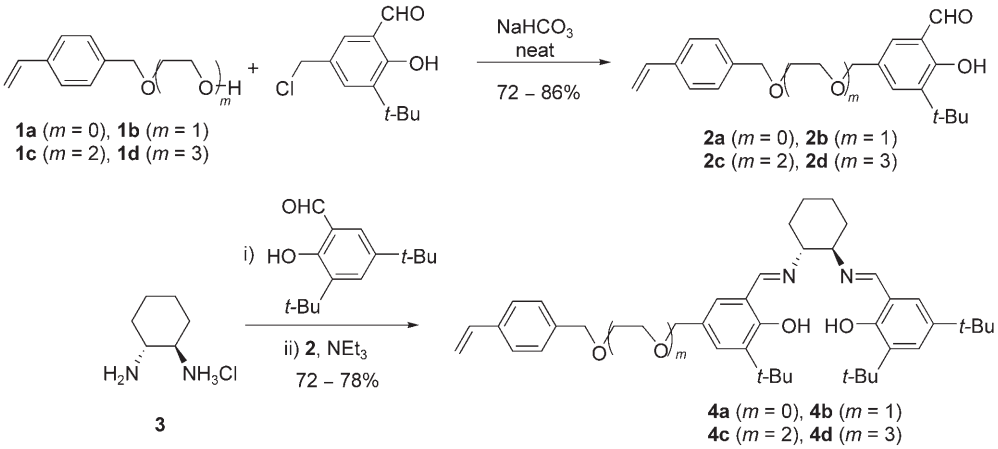
However, general design criteria that can guide the immobilization of dual activation catalysts have not been developed, limiting the rational design of supported catalysts that follow a bimetallic cooperative pathway. Whereas it is obvious that site-isolation[14] is not a key variable, the role of parameters such as linker length and flexibility as well as catalyst density remains unclear. In this contribution, we employ poly(styrene)-supported Co-salen complexes bearing different lengths of oligo(ethylene glycol) linkers as model catalysts in an approach to achieve optimal bimetallic cooperative interactions in HKR reactions (Figure 2). The goal is to establish structure-property relationships between catalysts, supports and linkers. Poly(styrene) was the support of choice for this study because it is highly stable and readily accessible.[2c] The oligo(ethylene glycol) derivatives were chosen as linkers as a result of their flexibility, stability and hydrophilicity, as well as tunable lengths of the oxyethylene repeating unit.

Results and Discussion

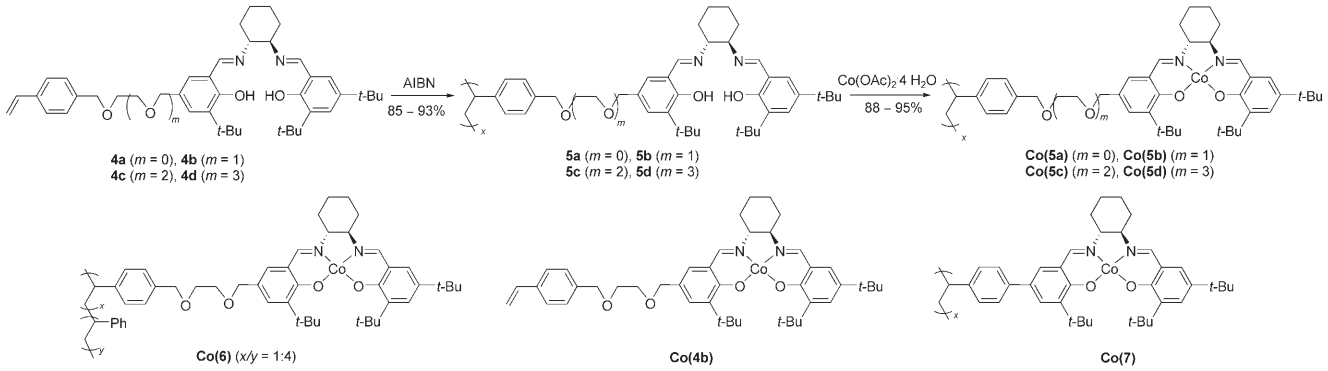
The styryl-substituted salen ligands **4a–d** were prepared from inexpensive starting materials as described in Scheme 1. Etherifications of styrene precursors **1a–d** and 3-*tert*-butyl-5-chloromethyl-2-hydroxybenzaldehyde were effected by a weak base, sodium bicarbonate, under solvent-free conditions to give oligo(ethylene glycol)-bridged styrenic salicyl aldehydes **2a–d**. A one-pot protocol, developed in our group[15] for the synthesis of unsymmetrical salen ligands, was employed to condense the HCl-protected diamine **315**[15,16] with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde and **2a–d** sequentially, affording **4a–d** with various lengths of oligo(ethylene glycol) linkers ($m = 0$–3) in 72–78% overall yields.

Free radical polymerizations of **4a–d** were performed at 80 °C for 24 h in the presence of 2.5 mol% 2,2'-azobis(isobutyronitrile) as initiator. Homopolymers **5a–d** (Scheme 2) were obtained in 85–93% isolated yields after repeated precipitations from methanol. To elucidate the effect of salen density along the poly(styrene) support on the catalytic performance, copolymerization of **4b** and styrene in a molar ratio of 1/4 was carried out to yield copolymer **6**. The copolymerization process was monitored by ^{1}H NMR spectroscopy. During the copolymerization, conversions of the two monomers were comparable, revealing a statistically randomly distributed nature of the resulting copolymer. Gel-permeation chromatography (GPC) showed that homopolymers **5a–d** have number average molecular weights (M_n) ranging from 14,100 to 18,400 whereas copolymer **6** has an M_n of 7,400 (Table 1). The GPC traces of all polymers exhibited a typical unimodal character with polydispersity indices (PDI) ranging from 2.32 to 2.80.

The salen polymers **5a–d** and **6** were metallated with cobalt(II) acetate tetrahydrate under nitrogen to give the corresponding Co(II)-(salen) complexes as



Scheme 1. Synthesis of styryl-substituted salen ligands.



Scheme 2. Synthesis of poly(styrene)-supported Co(II)-(salen) complexes.

Table 1. GPC data of salen polymers **5a–d** and **6**.

Entry	Polymer	M_n[a]	PDI[b]
1	**5a**	14,100	2.32
2	**5b**	16,700	2.38
3	**5c**	18,400	2.68
4	**5d**	18,000	2.63
5	**6**	7,400	2.80

[a] Number average molecular weight determined by GPC methods [THF, poly(styrene) standards].
[b] Polydispersity index.

brick red solids in 88–95% yields (Scheme 2). The cobalt contents were determined by ICP-MS methods to be 1.08–1.33 mmol/g, indicating that 88–96% of the salen units were loaded with cobalt. Monomeric ligand **4b** was also metallated accordingly to give **Co(4b)**, a monometallic, small metal catalyst for comparison to the supported version.

The catalytic performance of the poly(styrene)-supported Co-salen complexes was evaluated using the HKR of racemic epichlorohydrin as a model reaction. Prior to each resolution, the Co(II) precatalysts were oxidized to their Co(III) acetate species in air using an excessive amount of acetic acid. The catalyst loading was set at 0.01 mol% on the basis of cobalt (the concentration of cobalt in epichlorohydrin: 1.28 mmol/L) and 0.6 equivs. of water was used as the nucleophile. The reaction kinetics were monitored by chiral GC analysis with chlorobenzene as an internal reference.

The effect of polymerization on the HKR reaction is illustrated in Figure 3 A. When the small molecule standard **Co(4b)** was employed as the precatalyst, the resolution proceeded to an *ee* of only 14% for the remaining epichlorohydrin with 13% conversion in 10 h. In contrast, homopolymer **Co(5b)** was highly active and enantioselective under the same conditions, affording >99% *ee* in 51% conversion. The initial turnover frequency (TOF) per cobalt for the reaction time of the first hour reaches 3300 h^{-1}. This remarkable difference in activity suggested that proper catalyst designs can increase the proximity of neighboring catalytic units and hence enhance substantially the bimetallic cooperative interactions desired for the HKR. Copolymer **Co(6)** was also tested in the HKR of epichlorohydrin and gave an enantiomeric excess

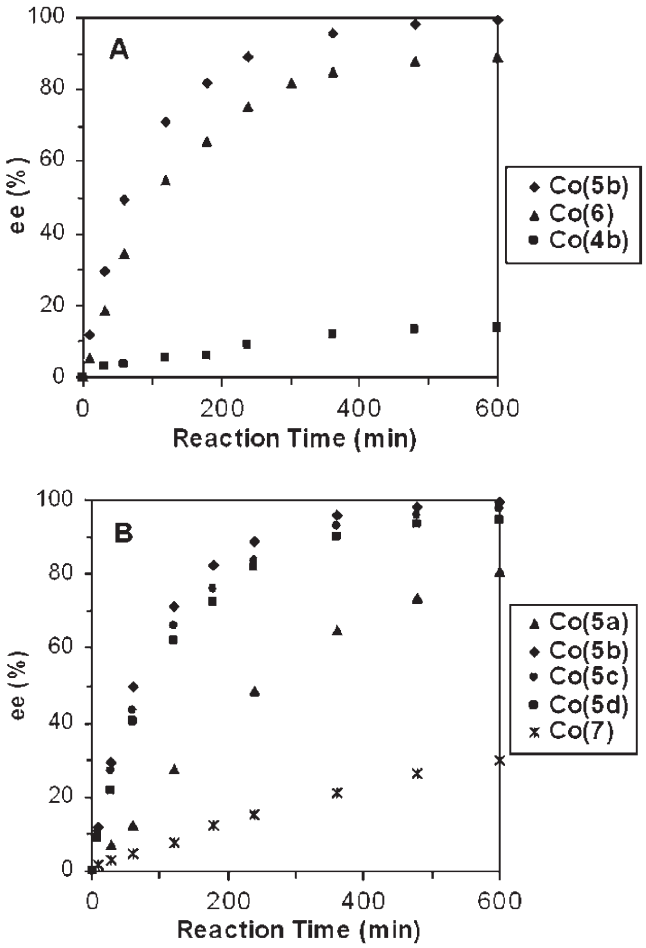


Figure 3. The HKR of epichlorohydrin (*ee vs.* reaction time plots; **A**: the effect of polymerization, **B**: the effect of the linker length).

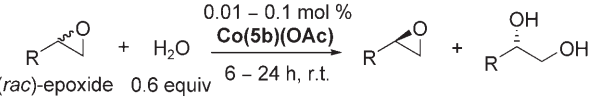
of 89% in 10 h. An *ee* of 95% was reached upon extending the reaction time to 24 h. The initial TOF for the first hour is 2500 h^{-1} which is substantially slower than that of homopolymer **Co(5b)**. This result demonstrates that the copolymerization has diluted the local concentration of Co-salen units along the polymer chain, resulting in more isolated Co-salen units, thereby making it more difficult for the bimetallic interactions to occur.

The influence of the linker length on the HKR is presented in Figure 3B. The systematic variation of the length of oligo(ethylene glycol) linkers has elucidated a clear trend. While complex **Co(5b)**, with a spacer of six carbon/oxygen atoms between the polymer backbone and the salen unit, exhibited the most desired catalytic performance, decreasing the linker atom number to three in **Co(5a)** or even zero in **Co(7)** resulted in a dramatic drop in reactivity. On the other hand, increasing the linker atom number to nine in **Co(5c)** or to twelve in **Co(5d)** also slowed the HKR reaction. Clearly, there is an optimal linker length when using oligo(ethylene glycol) linkers for this bimetallic transformation which in our case seems to be approximately six atoms.

Another variable that influences catalyst activity is the linker flexibility. We have reported previously that, in the presence of a rigid phenylene linker, homopolymeric Co-salen catalysts were less active for HKR in comparison with their copolymeric analogues due to a poor cooperative geometrical environment.[15] In comparison of this observation with the herein described catalytic data of flexibly linked catalysts, we can rationalize that the linker flexibility is also an important design motif. These results suggest that more flexible linkers are desired in enhancement of the Co-salen mediated cooperative HKR reactions.

The most active catalyst **Co(5b)** was used in the resolution of a variety of terminal epoxides (Table 2). The majority of epoxides can be resolved with a cobalt loading of merely 0.01 mol%. For instance, the HKR of 1,2-epoxyhexane afforded the (*R*)-enantiomer in 44% isolated yields with >99% *ee* (entry 1). Racemic allyl glycidyl ether and glycidyl phenyl ether were resolved in 10 h and 24 h, respectively, with greater than 99% *ee*. Even the HKR of styrene oxide was complete in 24 h with a 0.1 mol% catalyst loading.

Table 2. The HKR of various racemic terminal epoxides.



Entry	R	Loading [mol%][a]	Time [h][b]	*ee* [%][c]	Yield [%][d]
1	*n*-Bu	0.01	6	>99	44
2	CH_2Cl	0.01	8 (10)	>99	45 (49)
3	$CH_2OAllyl$	0.01	10	>99	46
4[e]	CH_2OPh	0.01	24	>99	43
5	Ph	0.1	24	98	45

[a] Catalyst loadings based on cobalt.
[b] Reaction times with (in parenthesis) or without an internal reference (0.5 mL chlorobenzene).
[c] Determined by chiral GC or HPLC methods.
[d] Isolated yields or GC yields (in parenthesis) based on *rac*-epoxides; theoretical maximum yield = 50%.
[e] HKR was performed at room temperature for 4 h and at 35 °C for 20 h.

Conclusions

In conclusion, we have employed poly(styrene)-supported Co-salen complexes bearing different lengths of oligo(ethylene glycol) linkers as model catalysts to investigate the HKR of epoxides operating via a bimetallic cooperative mechanism. The systematic variation of the linker length and the catalyst density within this series of catalysts elucidated clearly the following trends: (i) Using poly(styrene) as the supporting matrix and oligo(ethylene glycol) as the linker, a linker of approximately six atoms represents the optimal length for promoting bimetallic cooperative interactions in the HKR. (ii) In the presence of a flexible linker, the homopolymer-supported Co-salen catalysts are more active than their copolymer analogues. (iii) By means of proper linker and polymer designs, the polymer-supported catalysts can significantly enhance the activity in the HKR obtained with the monometallic Jacobsen-type catalysts. Currently, the aforementioned findings are being used to guide the design and synthesis of insoluble solid-supported dual activation catalysts.

Experimental Section

General Remarks

Reagents were purchased from Aldrich, Acros, or Alfa, and used as received unless noted below. Dichloromethane and THF were dried by passing through columns of activated copper and alumina successively. Chlorobenzene was distilled over calcium dihydride and stored in a Schelenk flask under argon. (4-Vinylphenyl)methanol (**1a**),[17] 2-(4-vinylbenzyloxy)ethanol (**1b**),[18] 2-[2-(4-vinylbenzyloxy)ethoxy]ethanol (**1c**),[19] 2-{2-[2-(4-vinylbenzyloxy)ethoxy]ethoxy}ethanol (**1d**),[20] (1*R*,2*R*)-1,2-diaminocyclohexane mono(hydrogen chloride) (**3**),[15,16] 3-*tert*-butyl-5-(chloromethyl)-2-hydroxybenzaldehyde,[21] and poly(styrene)-supported Co(salen) complex **Co(7)** (cobalt loading: 1.37 mmol/g, degree of polymerization: $x = 24$)[12a] were prepared according to published procedures. NMR spectra were acquired with a

Varian Mercury 400 (^{1}H, 400.0 MHz; ^{13}C, 100.6 MHz) or a Varian Mercury 300 (^{1}H, 300.0 MHz; ^{13}C, 75.5 MHz) spectrometer. Chemical shifts are reported in ppm and referenced to the residual nuclei in the corresponding deuterated solvents. IR and UV-vis spectra were recorded with a Shimadzu FTIR-8400S and a Shimadzu UV-2401PC spectrometer, respectively. Mass spectra were recorded with a VG 7070 EQ-HF hybrid tandem mass spectrometer or an Applied Biosystems 4700 spectrometer. Gel-permeation chromatography (GPC) analyses were performed with American Polymer Standards columns (100, 1,000, 100,000 Å linear mixed bed) equipped with a Waters 510 or a Shimadzu LC-10 AD pump and a UV detector. Poly(styrene)s (M_n ranging from 580 to 7,500,000) were employed as standards for calibration and THF was used as a mobile phase (flow rate at 1.0 mL min^{-1}). Enantiomeric excesses (*ee*) were determined by capillary gas-phase chromatography (GC) analysis or by high performance liquid-phase chromatography (HPLC). The chiral GC analysis was performed on a Shimadzu GC 14 A instrument equipped with an FID detector as well as a Chiraldex γ-TA column (40 m × 0.25 mm × 0.25 μm film thickness, Advanced Separation Technologies, Inc.) with helium as the carrier gas. The chiral HPLC analysis was carried out with a Chiracel OD column (24 cm × 0.46 mm, Chiral Technologies, Inc.; flow rate = 1 mL min^{-1}) using a UV detector.

General Procedure A: Synthesis of Styryl-Substituted Salicyl Aldehydes 2a–d

3-*tert*-Butyl-5-(chloromethyl)-2-hydroxybenzaldehyde (1.13 g, 5.0 mmol), styryl-substituted alcohol **1** (1.5 equivs., 7.5 mmol), and a fine powder of anhydrous sodium bicarbonate (4.0 equivs., 1.68 g, 20 mmol) were charged into a Schlenk tube connected to a bubbler. The reaction mixture was stirred as a slurry at 90 °C for 2 h till not further carbon dioxide evolved from the system. Chromatography of the reaction residue on silica gel with a mixture of ethyl acetate and hexanes gave the desired salicyl aldehyde **2** in 70–-77 % yields.

3-*tert*-Butyl-2-hydroxy-5-((4-vinylbenzyloxy)methyl)benzaldehyde (2a): Colorless oil in 77 % yield after chromatography on silica gel with 5/95–15/85 (v/v) ethyl acetate/hexanes.

3-*tert*-Butyl-2-hydroxy-5-[6-(4-vinylphenyl)-2,5-dioxahexyl]benzaldehyde (2b): Colorless solid in 70 % yield after chromatography on silica gel with 10/90–20/80 (v/v) ethyl acetate/hexanes.

3-*tert*-Butyl-2-hydroxy-5-[9-(4-vinylphenyl)-2,5,8-trioxanonyl]benzaldehyde (2c): Pale yellow oil in 75 % yield after chromatography on silica gel with 15/85–25/75 (v/v) ethyl acetate/hexanes.

3-*tert*-Butyl-2-hydroxy-5-[12-(4-vinylphenyl)-2,5,8,11-tetraoxadodecyl]benzaldehyde (2d): Pale yellow oil in 72 % yield after chromatography on silica gel with 30/70 (v/v) ethyl acetate/hexanes.

General Procedure B: Synthesis of Styryl-Substituted Salen Ligands 4a–d

To a solution of (1*R*,2*R*)-1,2-diaminocyclohexane mono(hydrogen chloride) (**3**, 226 mg, 1.5 mmol) in anhydrous methanol (15 mL) was added 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (352 mg, 1.5 mmol) and activated 4 Å molecular sieve (0.75 g). The reaction mixture was stirred at ambient temperature for 3 h till the salicyl aldehyde was completely consumed according to TLC analysis. A solution of styryl-substituted salicyl aldehyde **2** (1.5 mmol) in anhydrous dichloromethane (15 mL) was added to the reaction system, followed by the slow addition of triethylamine (2 equiv, 3.0 mmol). After the reaction mixture was stirred at room temperature for an additional 3 h, all solvents and the excessive triethylamine were removed under vacuum. Chromatography of the residue on silica gel with a mixture of ethyl acetate and hexanes gave the desired product **4** in 72–84 % yields.

(*R,R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-{3-*tert*-Butyl-5-[(4-vinylbenzyloxy)methyl]-salicylidene}-1,2-cyclohexanediamine (4a): Bright yellow solid in 84 % yield after chromatography on silica gel with 2/98 (v/v) ethyl acetate/hexanes.

(*R,R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-{3-*tert*-Butyl-5-[6-(4-vinylphenyl)-2,5-dioxahexyl]salicylidene}-1,2-cyclohexanediamine (4b): Bright yellow solid in 72 % yield after chromatography on silica gel with 5/95 (v/v) ethyl acetate/hexanes.

(*R,R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-{3-*tert*-Butyl-5-[6-(4-vinylphenyl)-2,5-dioxahexyl]salicylidene}-1,2-cyclohexanediamine (4c): Viscous yellow oil in 78 % yield after chromatography on silica gel with 10/90 (v/v) ethyl acetate/hexanes.

(*R,R*)-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-{3-*tert*-Butyl-2-hydroxy-5-[12-(4-vinylphenyl)-2,5,8,11-tetraoxadodecyl]salicylidene}-1,2-cyclohexanediamine (4d): Viscous yellow oil in 72 % yield after chromatography on silica gel with 20/80 (v/v) ethyl acetate/hexanes.

General Procedure C: Synthesis of Polymeric Salen Ligands 5a–d and 6 *via* Free Radical Polymerizations

A Schlenk tube equipped with a Teflon screw cap was charged with salen monomer **4** (0.4 mmol on the basis of salen units) and free radical initiator AIBN (2.5 mol %, 1.6 mg, 10 μmol). The system was purged with argon three times. Degassed chlorobenzene (1.0 mL) was injected and the sealed reaction mixture was stirred at 80 °C for 24 h. The mixture was slowly poured into methanol (10 mL) to precipitate the crude polymer. The suspension was stirred for 60 min and the powder was collected by centrifuge. The resulting solid was dissolved in dichloromethane (0.5 mL) and reprecipitated from methanol (10 mL). The precipitation procedure was repeated till signals of the salen monomer were no longer detectible in the ^{1}H NMR spectrum. The desired polymer was obtained as a yellow powder in 81–93 % yields.

General Procedure D: Synthesis of Polyermic Co(II)(salen) Complexes Co(5a-d) and Co(6)

In a glove box under nitrogen, a solution of $Co(OAc)_2 \cdot 4H_2O$ (1.2 equivs., 90 mg, 0.36 mmol,) in methanol (3.0 mL) was added slowly to a solution of the polymeric salen **5** or **6** (0.30 mmol) in dichloromethane (3.0 mL). A red slurry formed in seconds and the reaction mixture was stirred at ambient temperature for 20 h. Methanol (10 mL) was added

to precipitate more solid and the resulting suspension was stirred for an additional 4 h. The solid was collected by filtration, washed sequentially with 1/10 (v/v) degassed dichloromethane/methanol (10 mL) and methanol (2×10 mL), and dried under vacuum to give the desired Co(II)-(salen) complex in 88–95% yields.

Synthesis of Complex Co(4b)

In a glove box under nitrogen, a mixture of salen ligand **4b** (272 mg, 0.40 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (125 mg, 0.50 mmol) in methanol (4.0 mL) was stirred at room temperature for 4 h. A red powder precipitated from the reaction mixture and was collected by filtration. The solid was washed with methanol (2×10 mL) and dried under vacuum to give the desired **Co(4b)** as a brick red powder; yield: 275 mg (93%).

General Procedure E: Hydrolytic Kinetic Resolutions of Epoxide

The Co(II)-(salen) precatalyst (5.0 μmol, 0.01 mol% on the basis of cobalt) was dissolved in dichloromethane (0.5 mL) in a 25-mL flask. Glacial acetic acid (50 μL) was added to the solution and the mixture was stirred in the open air for 30 min, during which time the color changed from deep red to dark brown. After the solvent and the excessive amount of acetic acid were roughly removed by rotary evaporation, the residue was pumped under vacuum for 5 min to give Co(III)(salen)(OAc) catalyst as a dark brown solid. The activated catalyst was dissolved in the racemic epoxide (50 mmol) (in the cases of kinetic studies, 0.5 mL chlorobenzene was added as an internal reference for the GC analysis). Deionized water (0.54 mL, 30 mmol, 0.60 equiv.) was added to the system at room temperature to start the reaction and the process of the HKR was monitored by chiral GC or HPLC method till an *ee* of >98% was reached. The remaining enantiopure epoxide, together with the unreacted water, was vacuum-distilled into a receiving flask pre-cooled at −78 °C. Water was removed by passing the recovered epoxide through a plug of dry silica gel packed in a Pasteur pipet.

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