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Ring-Expanding Olefin Metathesis: A Route to Highly Active Unsymmetrical Macrocyclic Oligomeric Co-Salen Catalysts for the Hydrolytic Kinetic Resolution of Epoxides

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Abstract: In the presence of the third generation Grubbs catalyst, the ring-expanding olefin metathesis of a monocyclooct-4-en-1-yl functionalized salen ligand and the corresponding Co(II)(salen) complex at low monomer concentrations results in the exclusive formation of macrocyclic oligomeric structures with the salen moieties being attached in an unsymmetrical, flexible, pendent manner. The TOF-MALDI mass spectrometry reveals that the resulting macrocyclic oligomers consist predominantly of dimeric to tetrameric species, with detectable traces of higher homologues up to a decamer. Upon activation under aerobic and acidic conditions, these Co(salen) macrocycles exhibit extremely high reactivities and selectivities in the hydrolytic kinetic resolution (HKR) of a variety of racemic terminal epoxides under neat conditions with very low catalyst loadings. The excellent catalytic properties can be explained in terms of the new catalyst's appealing structural features, namely, the flexible oligomer backbone, the unsymmetrical pendent immobilization motif of the catalytic sites, and the high local concentration of Co(salen) species resulting from the macrocyclic framework. This ring-expanding olefin metathesis is suggested to be a simple way to prepare tethered metal complexes that are endowed with key features—(i) a high local concentration of metal complexes and (ii) a flexible, single point of attachment to the support—that facilitate rapid and efficient catalysis when a bimetallic transition state is required.

Introduction

Chiral epoxides are among the most versatile building blocks for modern asymmetric organic synthesis due to the potential for the facile stereospecific attack of the strained three-membered ring unit by a wide spectrum of nucleophiles, radicals, and Lewis acids with the formation of new carbon−carbon, carbon−nitrogen, or carbon−oxygen bonds.[1,2] Among many available methods for the preparation of enantiomerically enriched epoxides, the catalytic asymmetric epoxidation[3−5] and the kinetic resolution[6−8] have been recognized as the most practical and eminent approaches. The discovery of the Sharpless epoxidation reaction has provided a straightforward access to highly enantioenriched epoxy alcohols and, thus, has been regarded as a cornerstone in the field of asymmetric catalysis.[3] The utilization of chiral Mn(III)-salen complexes[4,9] and dioxirane organo-catalysts[5] have expanded the scope of the asymmetric epoxidation to unfunctionalized olefins. As an important complementary strategy, enzymatic and microbial kinetic resolutions have been developed to yield enantioenriched glycidol and epichlorohydrin, respectively.[6,7]

More recently, the hydrolytic kinetic resolution has emerged as a general and powerful method for the generation of virtually any terminal epoxide in an enantiopure form.[8,10] Using water as the nucleophile and chiral Co(III)-salen complexes (e.g., **1**) as the catalyst, the hydrolytic kinetic resolution (HKR) features exceptionally high enantioselectivities, close-to-theoretical yields,

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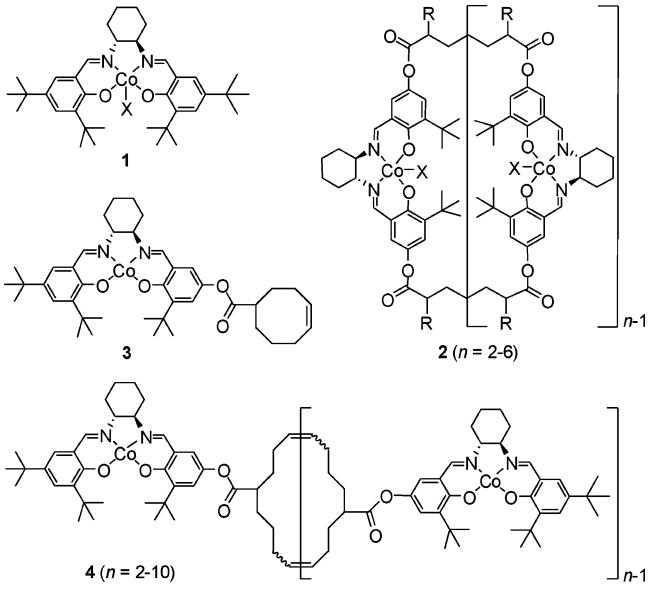
Chart 1. Monometallic and Macrocyclic Co-Salen Complexes



and excellent tolerances toward various functional groups. Detailed kinetic studies of the HKR reactions have revealed a second-order dependence of the reaction rates on the Co-salen species.[11] This finding strongly supports a cooperative bimetallic mechanism for the rate-determining epoxide ring-opening step. In this context, the incorporation of Co-salen moieties into dendritic,[12] oligomeric,[13,14] or polymeric frameworks[15−19] not only serves as a means for recycling the catalysts but also leads to catalytic systems with substantially enhanced reactivities and/or enantioselectivities in comparison with the standard monometallic catalyst **1** (Chart 1) due to the close proximity of the metal centers to each other. Catalytic reactions involving salens and/or other complexes have been shown to operate via a bimetallic or bimolecular mechanism.[20,21] Thus, methodologies to prepare catalysts with enhanced intramolecular interactions of the two cooperative catalytic sites would greatly facilitate an ever increasing variety of chemistries.

The construction of supported salen derivatives can be realized by using either symmetrical or unsymmerical salen monomers or precursors that contain identical or distinct substituents, respectively, on the two salicylidene rings.[17] The symmetrical approach introduces repeating salen units, in a bigrafted manner, along the polymer or oligomer main chain. The most successful catalytic system of this type is the cyclic oligomeric Co(salen) complexes **2** (X = OTs, etc.), presented by Jacobsen and co-workers.[13a,b] By enforcing intramolecular bimetallic interactions, **2** exhibited outstanding catalytic properties in a variety of epoxide ring-opening reactions. In comparison, the unsymmetrical approach gives salen units tethered to the support backbone via a single grafting point. This monotethered geometry allows for a higher degree of flexibility of the supported salen moieties in comparison to the symmetrical approach, making the catalytic centers potentially more accessible to substrates of different steric environments.

In our initial work, we focused on the synthesis of polymers such as poly(styrene)s and poly(norbornene)s containing unsymmetrically substituted Co-salen complexes in the side chain.[17,18,22] While these studies clearly demonstrated the advantages of the approach (the poly(styrene)-based system is among the most active and selective linear polymer supported Co-salen catalysts in the literature[17]), we still needed up to 0.5 mol % catalyst loading for the HKR of common epoxides such as epichlorohydrin. Herein we report the synthesis and the catalytic properties of the first unsymmetrical oligomeric Co-salen complex (**4**) that overcomes the need for high catalyst loadings. Complex **4** was generated via the Ru-catalyzed, sequential ring-opening and ring-closing olefin metatheses of the monocyclooct-4-en-1-yl functionalized Co(salen) monomer **3** that formally expanded a low-strained eight-membered ring to a mixture of macrocyclic oligomers. Similar phenomena of the cyclooligomerization have been known in ring-opening metathesis polymerization (ROMP)[23−25] as well as other reversible polymerization processes[26] with the cyclic oligomers usually, though not invariably,[27] as undesired byproducts. In contrast to **2** in which the Co(salen) moieties have local C_2 symmetry,[13] **4** possesses an unprecedented unsymmetrical macrocyclic structure with the Co(salen) fragments being tethered in a flexible, pendent manner. Upon activation with an appropriate acid in air, **4** exhibited exceptionally high reactivities and enantioselectivities in the HKR of a library of racemic terminal epoxides. Catalyst loadings as low as 0.01 mol % for the HKR can be employed. Catalyst **4** represents the most active unsymmetrically supported HKR catalyst.

Results and Discussion

1. Ring-Expanding Olefin Metathesis. (A) Synthesis of a Monocyclooct-4-en-1-yl Functionalized, Unsymmetrical Salen Ligand. The Co(salen) macrocycles **4** can be prepared readily

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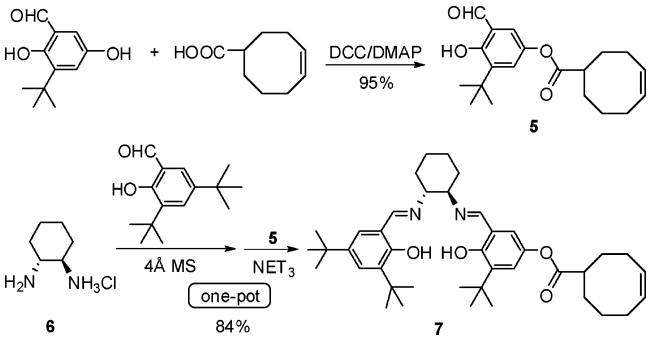
Scheme 1. Synthesis of the Cyclooct-4-en-1-yl Substituted Salen Ligand



on a multigram scale from commercially available, inexpensive starting materials. The synthetic route starts with the generation of a monocyclooct-4-en-1-yl functionalized, unsymmetrical salen ligand[22,28] in which the carbon−carbon double bond is prone to the transformation of the catalytic olefin metathesis. As shown in Scheme 1, esterification of 3-*tert*-butyl-2,5-dihydroxybenzaldehyde[13a] and cyclooct-4-enecarboxylic acid[29] in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) yielded salicylaldehyde **5** in excellent yield. We have previously established a general and straightforward method for the preparation of enantiopure unsymmetrical salen ligands via a one-pot two-step condensation of two different salicylaldehydes with a protected chiral diamine.[22] This method was successfully applied to the current synthesis. The one-pot stepwise condensation of (*R*,*R*)-diaminocyclohexane mono(hydrogen chloride) salt **6** with 3,5-di-*tert*-butylsalicylaldehyde and **5** in a 1:1:1 molar ratio afforded the cyclooct-4-en-1-yl substituted unsymmetrical salen ligand **7** as a bright yellow powder in 84% yield.

(B) Ru-Catalyzed Olefin Metathesis of Monocyclooct-4-en-1-yl Functionalized Salen Derivatives. Under an inert atmosphere, salen ligand **7**, on treatment with $Co(OAc)_2 \cdot 4H_2O$ in methanol, was converted to the corresponding Co(II)(salen) complex **3** (Scheme 2). The desired product precipitated gradually from the reaction media as a brick red solid and thus could easily be separated in high yield.

Olefin metathesis reactions of these cyclooct-4-en-1-yl functionalized salen compounds can be tuned through varying monomer concentrations[23−25] to afford either low molecular weight oligomers or high molecular weight polymers. At a monomer concentration of 0.1 M in dichloromethane, ligand **7** and complex **3** underwent a ring-opening/ring-closing sequence in the presence of 2−4 mol % of the third generation Grubbs catalyst (**11**),[31] affording unsymmetrical macrocyclic oligomers **8** and **4**, respectively, in almost quantitative yields. This sequence can be regarded as an expansion of a low-strained eight-membered ring to a mixture of oligomeric macrocycles, referred to as the ring-expanding olefin metathesis in this contribution. The metathesis reaction was found to be rather fast and clean as monitored by in situ ^{1}H NMR spectroscopy. For instance, consumption of monomer **7** approaches completion in 20 min, and no side reactions were detected. This was evidenced by an upfield shift of the multiple alkenyl proton signals from 5.72 ppm for **7** to 5.42 ppm for **8**, along with a moderate line-broadening effect of almost all signals (see Supporting Information).

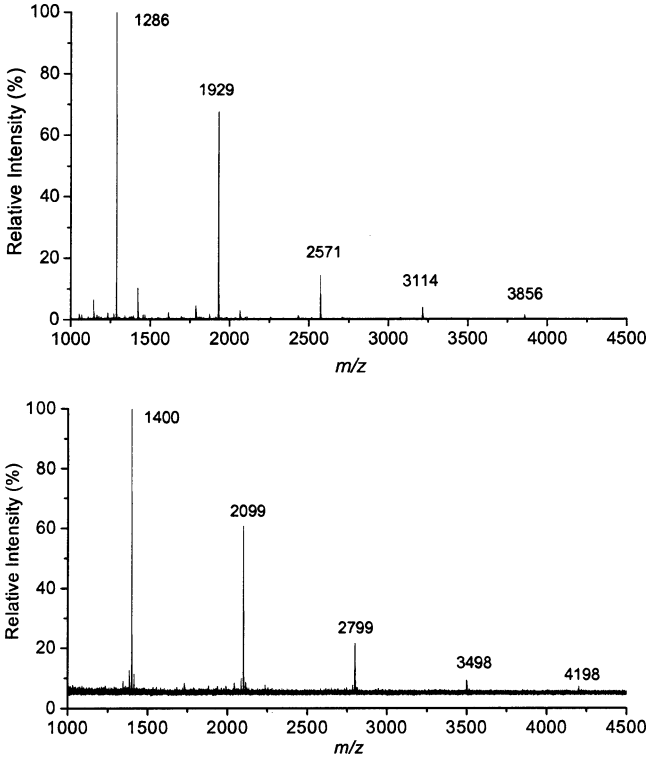


Figure 1. MALDI-TOF spectra of macrocyclic oligomeric salen ligand **8** (top) and Co(salen) complex **4** (bottom) with dithranol as the matrix.

The oligomeric nature of **8** was verified by gel-permeation chromatography (GPC) that indicated a number-average molecular weight (M_n) of 1000 and a polydispersity index (PDI) of 1.23. Whereas the oligomeric nature of the sample is clear according to the GPC data, the use of linear poly(styrene) rather than structurally analogous cyclic polymers as standards tends to underestimate the molecular weight with a substantial error. Grubbs and co-workers[32] have found that cyclic polyenes possess smaller hydrodynamic volumes (i.e., eluting slower) and lower intrinsic viscosities than their linear analogues. Over a wide range of molecular weights, they have reported that the root-mean-square (rms) radius ($\langle R^2_g \rangle^{0.5}$) possesses a correlation of $\langle R^2_g \rangle_{cyclic}/\langle R^2_g \rangle_{linear}$ approaching 0.5 and the ratio of viscosities, $[\eta]_{cyclic}/[\eta]_{linear}$, approximates to 0.4.[32a]

We deduced the cyclic structure initially from the absence of end group signals in the NMR spectra. In addition, matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry provided unambiguous insight into the structures of these oligomers at a molecular level (Figure 1). The spectrum of **4** indicated the exclusive formation of oligomeric macrocycles as a mixture of predominantly dimeric to tetrameric species with observable traces of higher homologues up to a decamer (**3**: $m/z = 700$, **4**: $m/z = 1400$ (dimer),

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(30) The position of the ester functionality with respect to the macrocycles **4**, **8** or polymers **9**, **10** could be either 1,8- or 1,9-, as a result of the head-to-tail or head-to-head metathesis mode.

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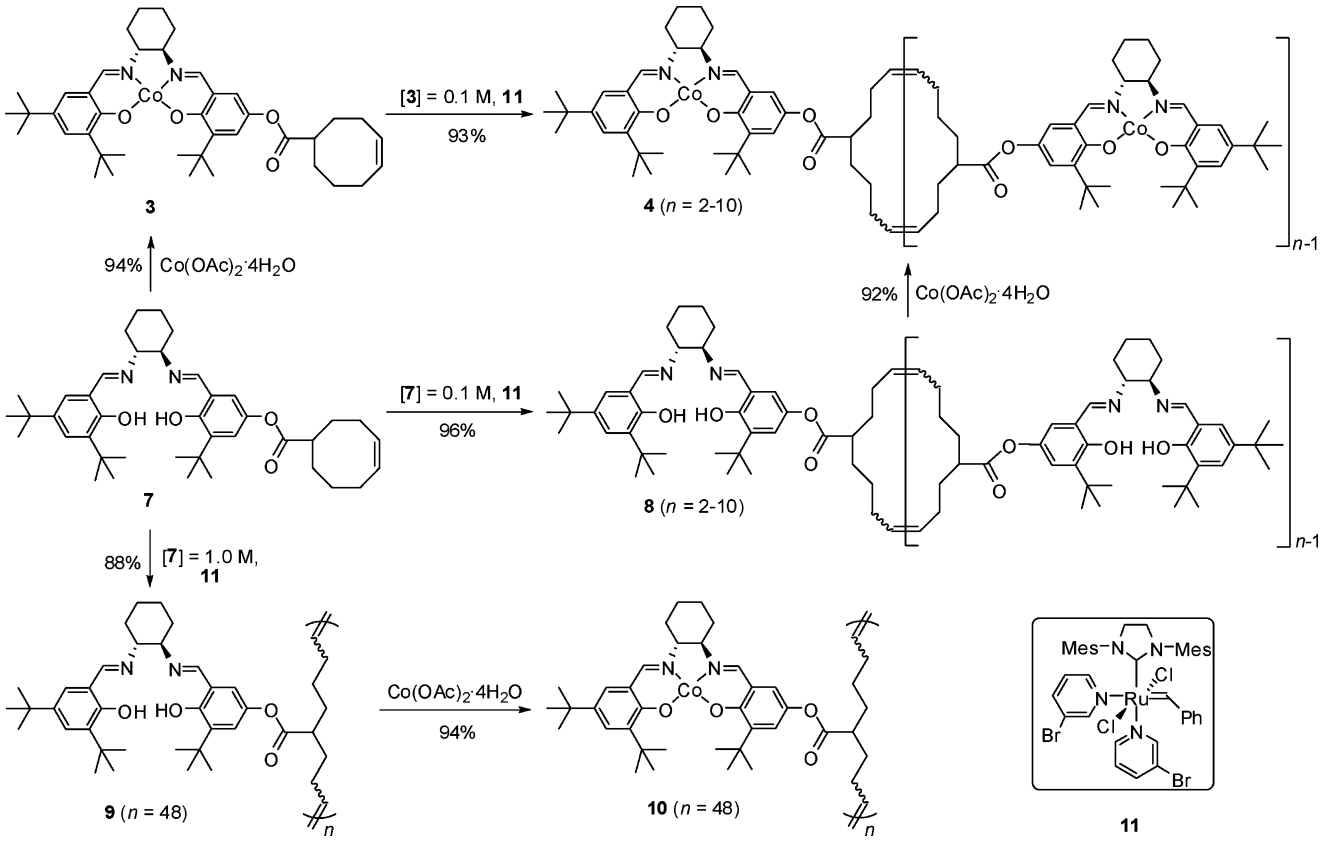
Scheme 2. Olefin Metathesis of Cyclooct-4-en-1-yl Functionalized Salen Monomers[30]



2099 (trimer), 2799 (tetramer), 3498 (pentamer), and so forth). From the mass spectrometry data, M_n was estimated to be 2460 with a PDI of 1.3. A similar ionization pattern was observed in the mass spectrum of oligomeric salen ligand **8** with $M_n = 2050$ and PDI = 1.3 (**7**: $m/z = 643$, **8**: $m/z = 1286$ (dimer), 1929 (trimer), 2571 (tetramer), 3114 (pentamer), and so forth). Based on these data, the average degree of oligomerization was estimated to be 3.2−3.5. As an alternative preparative pathway, macrocycles **4** can be prepared from the metalation of oligomeric ligand **8** with $Co(OAc)_2 \cdot 4H_2O$ in methanol. The complex obtained via this route has a stoichiometric cobalt content according to elemental analysis (calcd: 8.42%, found: 8.35%) and exhibits an almost identical mass spectrum to that generated from the olefin metathesis of **3**.

At a higher monomer concentration of 1.0 M in dichloromethane, the metathesis reaction of salen ligand **7** was allowed to proceed for 30 min and then quenched with ethyl vinyl ether to give polymer **9**, contaminated with ca. 5% oligomeric species, in 88% yield after repeated precipitations from methanol. The GPC characterization indicated a number-average molecular weight of 33 500, corresponding to an average degree of polymerization of 48 and a PDI of 2.84. Unfortunately, the solubility of the Co(salen) monomer **3** is not as high in common organic solvents, and thus, it was not used to generate the corresponding polymer. Instead, the metalation of polymeric ligand **9** with $Co(OAc)_2 \cdot 4H_2O$ in methanol and dichloromethane afforded the polymeric Co(salen) complex **10**. The elemental analysis of **10** gave a cobalt loading of 7.60% (w/w), indicating that 90.3% of the salen centers were bound with the metal.

(C) Mechanistic Considerations of the Ring-Expanding Olefin Metathesis. It is well-known that the ring strain and bulkiness of the chosen cyclic monomers play a key role in ROMP.[23,33] Whereas the ROMP of highly strained, norbornene-based monomers is essentially enthalpy-driven and often can be performed in a controlled manner,[34] the polymerization of medium-sized, low-strain rings such as cyclooctene-based monomers is not "living" and can result in polymers with higher PDIs.[35] The high flexibility of the main chain in the latter case would significantly increase the possibility of the intramolecular chain transfer with the elimination of cyclic oligomers. Since olefin metathesis reactions are reversible in principle and the resulting cyclic oligomers are involved in the polymerization process, a ring−chain equilibrium can be established depending on concentrations.[33−35] It is also notable that ring-closing metathesis (RCM) has been well documented in the literature as a powerful method for the synthesis of macrocyclic compounds with the elimination of a small olefin such as ethylene.[36] To avoid undesired cross-metathesis reactions, RCM reactions have usually been carried out in high dilution. Using the second generation Grubbs catalyst, the ring expansion of cyclic

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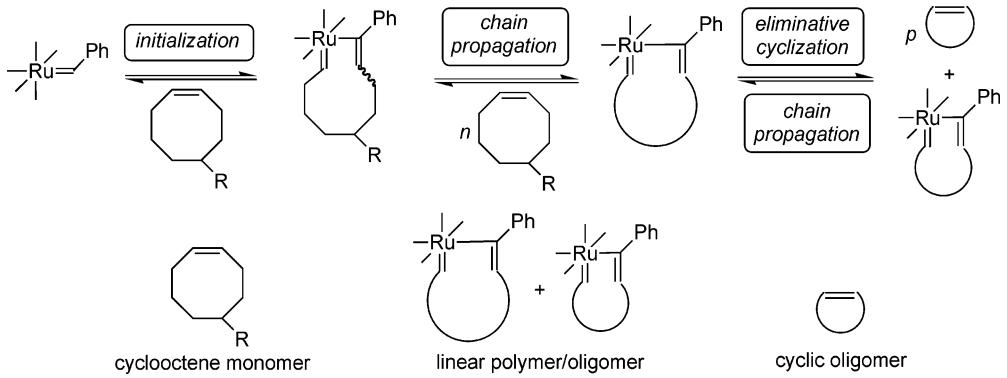
Scheme 3. Proposed Simplified Mechanism for the Formation of Oligomeric Macrocycles during Olefin Metathesis of Cyclooctene-Functionalized Monomers

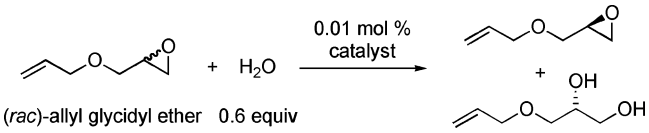


compounds with acyclic bis-acrylates or bis-vinyl ketones via sequential ring-opening, cross, and ring-closing metathesis reactions has been demonstrated.[37]

The ring-expanding metathesis of a medium-sized ring to macrocyclic oligomers under low concentrations as described here has several precedents.[23,24,38] Related work includes the use of an ill-defined Re_2O_7/Al_2O_3 catalyst for the dimerization of cycloheptene and cyclooctene[38] and the Schrock catalyst induced cyclooligomerization of cyclooctadiene and cyclobutene.[24a−d] To demonstrate how the macrocyclic oligomers are formed in the current systems, GPC analysis was employed to monitor the metathesis reaction of the salen monomer **7** (see Supporting Information).[39] Aliquots of the reaction mixture were taken at designated intervals, quenched with a solution of 1% (v/v) ethyl vinyl ether in THF (1 mL), and eluted with THF in a GPC instrument. Over a wide range of monomer concentrations, we have observed the existence of an equilibrium between cyclic oligomers and polymers during the metathesis reaction. At relatively low monomer concentrations (e.g., 0.1 M), the polymeric species was formed in the early stage of the metathesis and then gradually depolymerized completely over a period of 30 min, furnishing the ring-expanding metathesis product exclusively. At high monomer concentrations (e.g., 1.0 M), however, polymer formation predominates upon reaching the equilibrium in coexistence with approximately 5% of macrocyclic oligomers.

According to these findings as well as the established aspects of the cyclooligomerization in ROMP,[23−25] a simplified mechanism is illustrated in Scheme 3. The key lies in the competition between two reversible processes, the chain propagation and the eliminative cyclization (or backbiting). The chain propagation is an intermolecular reaction of first order in the monomer,[40] whereas the eliminative cyclization is an intramolecular reaction that is independent of the monomer. As a result, at a high monomer concentration the metathesis reaction favors the formation of polymers, while at a low concentration it tends to generate macrocyclic oligomers. Somewhat similar results have been previously reported in the Ru-catalyzed, entropically driven ROMP of unstrained large rings (ring size ≥13) that also favors the formation of macrocycles in high dilution.[25] In this case, the existence of low strain in the eight-membered ring as well as the bulk pendent salen substituent minimized the chance of backbiting to the monomer itself.

Scheme 4. HKR of Racemic Allyl Glycidyl Ether



2. Hydrolytic Kinetic Resolution. (A) Activation of Co(II)(salen) Macrocycles. The oligo(cyclooctene)- and poly(cyclooctene)-supported Co(II)(salen) complexes were examined as catalyst precursors for the HKR of terminal epoxides. Throughout these catalytic studies, precatalyst **4** was used directly as a mixture of oligomeric macrocycles.[41] Two different oxidation conditions were applied to generate the corresponding catalytically active Co(III)(salen) species with different counterions.[42] Method A involved the aerobic oxidation of Co(II)(salen) precatalyst in the presence of an excessive amount of acetic acid. After the mixture was stirred in dichloromethane in the open air for 30 min, all volatiles were removed in vacuo to afford Co(III)(salen)(OAc) as a brown solid. Method B used 1.1 equiv of *p*-toluenesulfonic acid in THF as the acid reagent. The oxidation under similar conditions gave catalyst Co(III)(salen)(OTs) as a deep green solid.

(B) HKR of Racemic Allyl Glycidyl Ether as a Model Reaction. The HKR of allyl glycidyl ether was chosen as a model reaction to evaluate the catalytic properties of the new catalysts (Scheme 4, Figure 2). The resolution was carried out at ambient temperatures with 0.6 equiv of water and a 0.01 mol % catalyst loading based on cobalt. Chiral GC analysis showed

(36) (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (b) Han, S.-Y.; Chang, S. In *Handbook of Metathesis, Vol. 2 − Application in Organic Synthesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; pp 5−127. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3034. (d) Fürstner, A. Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449−451. (e) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145−2147.

(37) Lee, C. W.; Choi, T.-L.; Grubbs, R. H. *J. Am. Chem. Soc.* **2002**, *124*, 3224−3225.

(38) (a) Warwel, S.; Asinger, F.; Rauenbusch, C. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 702−703. (b) Warwel, S.; Kätker, H. *Synthesis* **1987**, 935−937.

(39) Though NMR spectroscopy has been established as the standard method to investigate the kinetics of ROMP (for example, see: Demel, S.; Schoefberger, W.; Slugovc, C.; Stelzer, F. *J. Mol. Catal. A: Chem.* **2003**, *200*, 11−19), it fails to distinguish between oligomer **8** and polymer **9** in this case, which is required for estimating the rate of the backbiting cyclization.

(40) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103−10109.

(41) If generated via the metallation of **8**, complex **4** is almost Ru-free because of column chromatographic workup of **8**. If generated via the metathesis of **3**, complex **4** contains ca. 0.096% (w/w) residual Ru according to elemental analysis. In the HKR reactions, the results of catalysts prepared via the above two methods are almost identical. In control experiments using the HKR of epichlorohydrin, addition of 1.0 mol % of third generation Grubbs catalyst with respect to the Jacobsen catalyst **1** (X = OAc) exhibited negligible changes in catalytic performance.

(42) For a detailed study on the effect of counterions on the HKR, see ref 11.

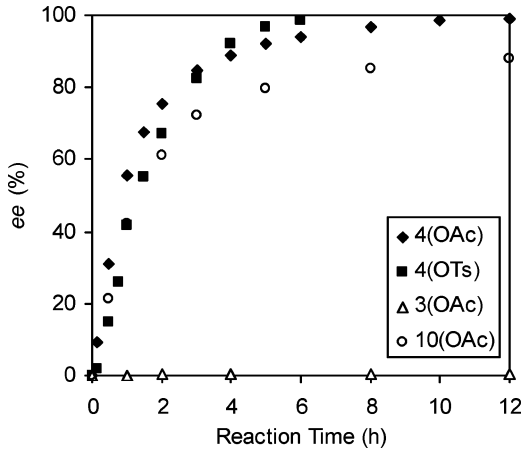
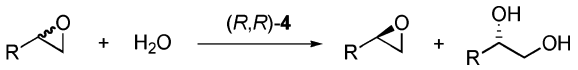


Figure 2. Kinetic plots of the HKR of racemic allyl glycidyl ether.

that the reaction proceeded to completion in 12 h in the presence of oligomeric **4**(OAc) as the catalyst (method A). The enantiomeric excess (ee) of the remaining allyl glycidyl ether was determined to be over 99% in 51% conversion. In comparison, the polymeric catalyst **10**(OAc) gave 88% ee for the remaining epoxide. Under the same reaction conditions, however, **3**(OAc) gave less than 1% ee, indicating that the monometallic catalyst could hardly effect the HKR of allyl glycidyl ether at such a low catalyst concentration. It is quite impressive that, by a simple metathesis transformation of monometallic Co(salen) complex **3** into multimetallic species, the catalytic performance can be improved dramatically for the HKR reactions involving a dual activation mechanism. The more desirable catalytic performance of the oligomeric catalyst **4**(OAc) than the polymeric analogue **10**(OAc) is presumably due to its macrocyclic framework that may provide a favorable geometry for the intramolecular bimetallic cooperative interactions. The use of less nucleophilic tosylate as the counterion for **4** (method B) gave even better catalytic results in the HKR of allyl glycidyl ether. Although a short induction period was observed if **4**(OTs) was employed, the total reaction time can be reduced to 6 h to reach 99% ee with a 51% conversion of the epoxide.

(C) HKR of Various Racemic Terminal Epoxides. The macrocyclic precatalyst **4** was employed in the HKR of a variety of structurally diverse terminal epoxides as outlined in Table 1. Since the activated catalysts showed good solubility in common epoxides, all resolution reactions were performed in solvent-free conditions[43] that are highly desirable for organic synthesis. Normal 1-alkene oxides are relatively easy substrates for the HKR reactions. For instance, the resolution of 1,2-epoxyhexane was complete in 2 h at ambient temperature with 0.01 mol % cobalt loading of **4**(OAc), affording the (*R*)-enantiomer of the epoxide in >99% ee and 43% isolated yield (49% GC yield) after vacuum transfer and dehydration treatment (Table 1, entry 1). Using the same catalyst loading, racemic epichlorohydrin was resolved in 2.5 h to give the enatiopure (*S*)-epoxide (>99% ee) in 43−44% isolated yields (Table 1, entry 2). In comparison, the standard monometallic Co(salen) catalyst **1** (X = OAc, OTs) required much higher catalyst loadings (0.2−0.5 mol %) and a prolonged reaction time (16 h) to reach >99% ee in this reaction.[10,11] At a catalyst loading level of 0.01 mol %, even the symmetrical cyclic oligomers **2** (X = OTs) need 11 h to reach >99% ee.[13a]

Table 1. HKR of Various Racemic Terminal Epoxides[a]



(*rac*)-epoxide 0.6 equiv

entry	R	method[b]	loading[c] (mol %)	time (h)	*ee*[d] (%)	yield[e] (%)
1	*n*-Bu	A	0.01	2	>99	43
2a	CH_2Cl	A	0.01	2.5	>99	44
2b	CH_2Cl	B	0.01	2.5	>99	43
3a	$CH_2OAllyl$	A	0.01	12	>99	48
3b	$CH_2OAllyl$	B	0.01	6	>99	46
4a[f]	CH_2OPh	A	0.01	20	>99	46
4b[f]	CH_2OPh	B	0.01	6	>99	44
5a[g]	Ph	A	0.1	24	>99	45
5b	Ph	B	0.1	18	>99	48
6	*t*-Bu	A	0.25	48	98	42

[a] Reactions were performed on 0.05−0.1 mol scales under solvent-free conditions at rt (except for entry 4). [b] Method A: **4**(OAc) as the catalyst; Method B: **4**(OTs) as the catalyst. [c] Catalyst loading based on cobalt. [d] Determined by chiral GC or HPLC methods. [e] Isolated yield based on racemic epoxides; theoretical maximum yield = 50%. [f] Resolutions were carried out at ambient temperature for 1 h and then heated to 40 °C. [g] 0.01 equiv of AcOH (based on the epoxide) was added.

In the HKR of glycidyl phenyl ether under neat conditions, the corresponding diol product, formed gradually during the reaction, can precipitate from the reaction mixture and hence hamper proper stirring. This problem was readily solved by performing the kinetic resolution at 40 °C after the reaction mixture was stirred at rt for 1 h. Enantiopure (*S*)-glycidyl phenyl ether was obtained in 44% isolated yield in 6 h with 0.01 mol % of **4**(OTs) as the catalyst (Table 1, entry 4). The resolution of a conjugated epoxide, styrene oxide, was complete in 18−24 h with 0.1 mol % catalyst loading (Table 1, entry 5). Even *tert*-butyloxirane, an epoxide of substantial steric hindrance, can be resolved in 48 h with a 0.25 mol % cobalt loading (Table 1, entry 6).

The aforementioned data clearly demonstrate that the new cyclic oligomeric catalytic system generally possesses outstanding activities and enantioselectivities in the HKR of epoxides. As outlined in the introduction, we and others have investigated the HKR of unsymmetrically functionalized Co-salen catalysts before. In comparison to these known unsymmetrical Co(salen) analogues supported on dendrimers,[12] poly(styrene)s,[15,17] or poly(norbornene)s,[18] the cyclic oligomeric catalyst **4** is significantly more active. Prior to this work, the best unsymmetrically functionalized Co-salen catalyst for the HKR was a system reported by Weberskirch and co-workers.[19] This system utilized amphiphilic block-polymeric micellar aggregates as supports. In comparison to these micellar aggregate-based catalysts, the new cyclic oligomers were demonstrated at lower catalyst loadings (routinely 0.01 mol % catalyst loadings were used here, while the lowest catalyst loadings reported for the micellar aggregates were 0.02 mol % with the majority of reactions employing 0.06−0.1 mol % catalyst). It is suggested the enhanced activities of complex **4** as evidenced by the lower catalyst loadings and/or shortened reaction times can be attributed to the catalyst's unique flexible macrocyclic structure. While the search for superior supported salen catalysts for

(43) (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025−1074. (b) Metzger, J. O. In *Organic Synthesis Highlights V*; Schmalz, H.-G., Wirth, T., Eds.; Wiley-VCH: Weinheim, 2003; pp 82−92.

chemistries that utilize a bimetallic transition state (i.e., HKR,[10] enantioselective conjugate additions,[20] etc.) is still ongoing, the current work pushes the catalytic performance of unsymmetrical Co(salen) complexes to a level matching and sometimes exceeding the best symmetrical, oligomeric counterparts.

Concluding Remarks

In summary, we have demonstrated that the ring-expanding olefin metathesis of the cyclooct-4-en-1-yl substituted Co(salen) derivative **3** at relatively low monomer concentrations afforded oligomers with a unique macrocyclic structure. The resulting complex **4** represents the first unsymmetrical macrocyclic salen oligomer designed for HKR reactions. Upon aerobic oxidation under acidic conditions, **4** exhibited excellent catalytic properties in the HKR of a variety of racemic terminal epoxides under neat conditions with very low catalyst loadings. The HKR using polymeric analogues (**10**) as catalysts resulted in lower activities, demonstrating the superiority of the macrocyclic system. The high reactivity and enantioselectivity of the macrocycle-based catalytic system can be explained in terms of its appealing structural features. The extreme flexibility of the oligomer backbone as well as the pendent immobilization motif of the Co(salen) moieties makes the catalytic sites highly accessible to a diverse spectrum of substrates. Moreover, the macrocyclic framework of the catalyst increases the local concentration of the Co(salen) species. This may significantly promote the chance of the intramolecular bimetallic cooperative interactions that have played a key role in many salen complex-catalyzed reactions.

Experimental Section

Cyclooct-4-enecarboxylic Acid 3-*tert*-Butyl-5-formyl-4-hydroxyphenyl Ester (5). 3-*tert*-Butyl-2,5-dihydroxybenzaldehyde (0.97 g, 5.0 mmol), dicyclohexyl carbodiimide (DCC, 1.03 g, 5.0 mmol), and 4-dimethylaminopyridine (DMAP, 30.5 mg, 0.25 mmol) were charged into a 100 mL two-neck flask equipped with a condenser, an addition funnel, and an argon outlet. The system was purged with argon, and anhydrous dichloromethane (10 mL) was added. A solution of cyclooct-4-enecarboxylic acid (0.75 g, 5.0 mmol) in anhydrous dichloromethane (10 mL) was added dropwise over a period of 5 min, during which time a fine white solid was formed gradually. The reaction mixture was stirred at rt for 30 min and heated at reflux for 16 h. The white solid was separated by filtration and washed with dichloromethane (2 × 10 mL). The filtrates were combined and concentrated to give an oily liquid. The desired product was isolated by flash column chromatography on silica gel (10/90 to 30/70 ethyl acetate/hexane) as a pale yellow oil (1.57 g, 95%) that solidified to a waxy solid upon storage in a refrigerator. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9 H, CMe_3), 1.40−1.60 (m, 2 H, cyclooctenyl), 1.66−1.82 (m, 3 H, cyclooctenyl), 2.00−2.08 (m, 1 H, cyclooctenyl), 2.15−2.25 (m, 3 H, cyclooctenyl), 2.41−2.51 (m, 1 H, cyclooctenyl), 2.69−2.77 (m, 1 H, cyclooctenyl), 5.65−2.80 (m, 2 H, CH═CH), 7.14 (d, J = 2.8 Hz, 1 H, Ph), 7.17 (d, J = 2.9 Hz, 1 H, Ph), 9.81 (s, 1 H, OH), 11.70 (s, 1 H, CHO). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 24.2, 26.1, 28.0, 29.2, 29.7, 31.7, 35.2, 43.4, 120.2, 123.3, 128.2, 129.6, 131.0, 140.2, 142.8, 159.0, 176.6, 196.6. IR (HBr): ν 2743 (CHO), 1751 (C═O), 1659 (C═C) cm^{-1}. UV−vis (THF): λ 258, 343 nm. MS (EI): m/z (*I*rel) 330 (15, M^+), 194 (100, $M^+ - C_8H_{13}CO + H$), 137 (20, $C_8H_{13}CO^+ - H$). HRMS Calcd for $C_{20}H_{26}O_4$: 330.1831. Found: m/z 330.1829. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.35, H, 8.10.

***(R,R)*-*N*-(3,5-Di-*tert*-butylsalicylidene)-*N*′-[3-*tert*-butyl-5-(cyclooct-4′-enecarboxy)salicylidene]-1,2-cyclohexanediamine (7).** A 250 mL flask was charged with (1*R*,2*R*)-1,2-diaminocyclohexane mono(hydrogen chloride) (1.51 g, 10.0 mmol), activated 4 Å molecular sieve (2.0 g), and anhydrous methanol (50 mL). 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (2.34 g, 10.0 mmol) was added in one portion and the reaction mixture was stirred at rt for 4 h. Monitoring the reaction by TLC showed the complete consumption of the aldehyde during this time. A solution of cyclooct-4-enecarboxylic acid 3-*tert*-butyl-5-formyl-4-hydroxyphenyl ester (3.30 g, 10.0 mmol) in anhydrous dichloromethane (50 mL) was then added to the reaction system, followed by the slow addition of triethylamine (2.7 mL, 20.0 mmol). After the reaction mixture was stirred at rt for an additional 4 h, all solvents and the excessive triethylamine were removed under a vacuum. The residue was dissolved in dichloromethane (50 mL), washed with water (2 × 50 mL), and dried with magnesium sulfate. Flash chromatography of the crude material on silica gel (10/90 ether/hexanes) afforded compound **7** as a bright yellow solid (5.38 g, 84%). Mp: 101−104 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 9 H, CMe_3), 1.38 (s, 9 H, CMe_3), 1.36−1.58 (m, 4 H, cyclooctenyl, cyclohexyl), 1.41 (s, 9 H, CMe_3), 1.62−2.49 (m, 14 H, cyclooctenyl), 2.63−2.71 (m, 1 H, $CHCO_2$), 3.32 (m, 2 H, 2 NC*H*CH_2), 5.64−2.78 (m, 2 H, CH═CH), 6.73 (d, J = 2.7 Hz, 1 H, Ph), 6.91 (d, 7.14, J = 2.7 Hz, 1 H, Ph), 6.98 (d, J = 2.8 Hz, 1 H, Ph), 7.32 (d, J = 2.8 Hz, 1 H, Ph), 8.21 (s, 1 H, CH═N), 8.32 (s, 1 H, CH═N), 13.62 (s, br, 1 H, OH), 13.84 (s, br, 1 H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 24.3, 24.5, 26.1, 26.2, 28.0, 29.3, 29.6, 29.7, 31.6, 31.7, 31.8, 33.3, 34.2, 35.0, 35.1, 43.4, 72.4, 72.6, 117.9, 118.4, 121.5, 122.9, 126.2, 127.1, 129.7, 130.9, 136.6, 138.6, 140.2, 141.9, 158.1, 158.2, 165.0 (C═N), 166.1 (C═N), 176.7 (C═O). IR (KBr): ν 1751 (C═O), 1632, 1593 cm^{-1}. UV−vis (THF): λ 256, 331 nm. MS (FAB+): m/z (I_{rel}) 642 (100, M^+), 587 (10, $M^+ - Bu + H$), 506 (30, $M^+ - C_8H_{13}CO + H$). HRMS Calcd for $C_{41}H_{58}N_2O_4$: 643.4475. Found: m/z 643.4485. Anal. Calcd for $C_{41}H_{58}N_2O_4$: C, 76.60; H, 9.09; N, 4.36. Found: C, 76.70; H, 9.25; N, 4.36.

Synthesis of Co(II)(salen) Complex 3. The salen ligand **7** (3.21 g, 5.0 mmol) and cobalt(II) acetate tetrahydrate (1.50 g, 6.0 mmol) were charged to a 100 mL Schlenk flask. After the system was thoroughly purged with argon, degassed methanol (50 mL) was added to the system and a red suspension formed almost immediately. The reaction mixture was stirred at rt for 4 h. With careful exclusion of the air, the solid was collected by filtration, washed with methanol (2 × 25 mL), and dried under a high vacuum overnight to give **3** as a brick red solid (3.30 g, 94%). Mp: 305−308 °C (decomp., change of color). IR: ν 1744 (C═O), 1599, 1526 cm^{-1}. UV−vis (THF): λ 265, 370, 420 nm. MS (ESI): m/z (I_{rel}) 699 (100, M^+). HRMS Calcd for $C_{41}H_{56}N_2O_4Co$: 699.3567. Found: m/z 699.3564. Anal. Calcd for $C_{41}H_{58}N_2O_4Co$: C, 70.37; H, 8.07; N, 4.00. Found: C, 70.46; H, 8.18; N 4.18.

Synthesis of Oligomeric Salen Ligand 8. The salen ligand **7** (161 mg, 0.25 mmol) was dissolved in degassed dichloromethane (2 mL) under argon. The third generation Grubbs catalyst (8.8 mg, 0.01 mmol, 2.0 mol %) in dichloromethane (0.5 mL) was added to the reaction. After the mixture was stirred at rt for 30 min, ethyl vinyl ether (100 μL) was added to quench the reaction. The solvent was removed under a vacuum, and the residue was purified by flash column chromatography on silica gel (30/70 ether/hexanes) to give **8** as a yellow powder (154 mg, 96%). ^{1}H NMR ($CDCl_3$): δ 1.27 (s, 9 H, CMe_3), 1.42 (s, 9 H, CMe_3), 1.30−2.30 (m, 18 H), 1.44 (s, 9 H, CMe_3), 2.58 (m, 1 H, $CHCO_2$), 3.33 (m, 2 H, 2 NC*H*CH_2), 5.35−2.55 (m, br, 2 H, CH═CH), 6.77 ("s", 1 H, Ph), 6.92 (d, 7.14, J = 2.7 Hz, 1 H, Ph), 7.01 (d, J = 2.0 Hz, 1 H, Ph), 7.34 (d, J = 1.9 Hz, 1 H, Ph), 8.26 (s, 1 H, CH═N), 8.33 (s, 1 H, CH═N), 13.64 (s, br, 1 H, OH), 13.91 (s, br, 1 H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 24.3, 26.8−27.6 (m), 29.3, 29.6, 30.2−30.8 (m), 31.6, 32.1, 32.5, 33.3, 33.6, 34.2, 35.0, 35.1, 43.3−45.3 (m, 1 C, *C*HCO_2, multiple chemical environments), 72.3, 72.7, 117.9, 118.4, 121.5, 122.9, 126.2, 127.1, 128.7−132.5 (m, 2 C, CH═CH, multiple chemical environments), 136.6, 138.7, 140.2, 141.7, 158.1, 158.3, 164.9, 166.1, 175.2. IR: ν 1753 (C═O), 1628, 1593 cm^{-1}. UV−vis (THF): λ 258, 330 nm. MS (MALDI-TOF) Calcd for $(C_{41}H_{58}N_2O_4)_n$: m/z (I_{rel}) 1286 (100%, M^+, n = 2), 1928 (65%, M^+,

$n = 3$), 2571 (15%, M^+, $n = 4$), 3213 (4%, M^+, $n = 5$). Anal. Calcd for $(C_{41}H_{58}N_2O_4)_n$: C, 76.60; H, 9.09; N, 4.36. Found: C, 76.69; H, 9.29; N 4.25.

Synthesis of Oligomeric Co(II)(salen) Complex 4. Method 1 (via the Ring-Expanding Olefin Metathesis of 3). The Co(II)(salen) complex **3** (700 mg, 1.0 mmol) was dissolved in degassed dichloromethane (9 mL) under argon resulting in a deep red solution. The third generation Grubbs catalyst (33 mg, 0.04 mmol, 4.0 mol %) in dichloromethane (1 mL) was added to the reaction. After the mixture was stirred at rt for 60 min, ethyl vinyl ether (200 μL) was added to quench the reaction. The reaction mixture was concentrated to ca. 5 mL, and degassed methanol (10 mL) was added to precipitate a red solid. The solid was collected on a frit, washed with methanol (3 × 10 mL) under argon, and dried under a vacuum to afford **4** as a deep red powder (650 mg, 93%). IR: ν 1747 (C═O), 1600, 1526 cm^{-1}. UV−vis (THF): λ 264, 370, 420 nm. MS (MALDI-TOF) Calcd for $(C_{41}H_{56}N_2O_4Co)_n$: m/z (I_{rel}) 1400 (100%, M^+, $n = 2$), 2099 (62%, M^+, $n = 3$), 2799 (24%, M^+, $n = 4$), 3498 (3%, M^+, $n = 5$). Anal. Calcd for $(C_{41}H_{58}N_2O_4Co)_n$: C, 70.37; H, 8.07; N, 4.00. Found: C, 69.90; H, 8.07; N, 4.00.

Method 2 (via the Metalation of 8 with Cobalt(II) Acetate Tetrahydrate). The oligomeric salen ligand **8** (130 mg, 0.20 mmol) and cobalt(II) acetate tetrahydrate (60 mg, 0.24 mmol) were charged to a 50 mL Schlenk flask. After the system was thoroughly purged with argon, degassed methanol (5 mL) and dichloromethane (5 mL) were added to the system and a red solid formed gradually. The reaction mixture was stirred at rt for 24 h. With careful exclusion of the air, dichloromethane was roughly removed under a vacuum. The solid was collected by filtration on a frit, washed with methanol (2 × 10 mL), and dried under a high vacuum overnight to give **4** as a brick red solid (135 mg, 96%). Complex **4** prepared via Method 2 showed the same MALDI-TOF MS pattern as that via Method 1.

Synthesis of Polymeric Salen Ligand 9. The salen ligand **7** (161 mg, 0.25 mmol) was dissolved in degassed dichloromethane (0.15 mL) under argon. A solution of the third generation Grubbs catalyst in dichloromethane (0.05 M, 100 μL, 0.005 mmol, 2.0 mol %) was injected into the reaction system via a microsyringe. After the reaction mixture was stirred at rt for 30 min, ethyl vinyl ether (100 μL) was added to quench the reaction. Methanol (5 mL) was added to the reaction mixture to precipitate a yellow solid. The solid was dissolved in dichloromethane (200 μL) and reprecipitated from methanol (5 mL). The solid was collected on a frit, washed with methanol, and dried under a vacuum to give the polymeric salen ligand **9** (contaminated with ca. 5% oligomers) as a yellow powder (141 mg, 88%). ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 9 H, CMe_3), 1.38 (s, 9 H, CMe_3), 1.30−2.20 (m, 18 H), 1.40 (s, 9 H, CMe_3), 2.58 (m, 1 H, $CHCO_2$), 3.30 (m, 2 H, 2 NC*H*CH_2), 5.33−2.56 (m, br, 2 H, CH═CH), 6.75 (d, $J = 2.2$ Hz, 1 H, Ph), 6.89 (d, $J = 2.0$ Hz, 1 H, Ph), 6.99 (d, $J = 2.2$ Hz, 1 H, Ph), 7.31 (d, $J = 0.5$ Hz, 1 H, Ph), 8.23 (s, 1 H, CH═N), 8.30 (s, 1 H, CH═N), 13.62 (s, br, 1 H, OH), 13.87 (s, br, 1 H, OH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 24.5, 27.0−27.7 (m), 29.3, 29.7, 30.75, 31.6, 32.3, 32.7, 33.3, 33.6, 34.2, 35.0, 35.1, 43.5−45.5 (m, 1 C, *C*HCO_2, multiple chemical environments), 72.3, 72.7, 117.9, 118.4, 121.5, 122.9, 126.2, 127.1, 128.8−132.5 (m, 2 C, CH═CH, multiple chemical environments), 136.6, 138.7, 140.2, 141.7, 158.1, 158.3, 164.9, 166.1, 175.2. IR: ν 1753 (C═O), 1631, 1595 cm^{-1}. UV−vis (THF): λ 262 331 nm. GPC (THF): $M_n = 33\,500$, PDI = 2.84. Anal. Calcd for $(C_{41}H_{58}N_2O_4)_n$: C, 76.60; H, 9.09; N, 4.36. Found: C, 76.10; H, 9.05; N 4.32.

Synthesis of Polymeric Co(II)(salen) Complex 10. The polymeric salen ligand **9** (77 mg, 0.12 mmol) and cobalt(II) acetate tetrahydrate (36 mg, 0.144 mmol) were charged to a 50 mL Schlenk flask. After the system was thoroughly purged with argon, degassed methanol (2 mL) and dichloromethane (2 mL) were added to the system and a red solid formed gradually. The reaction mixture was stirred at rt for 24 h. With careful exclusion of the air, dichloromethane was roughly removed under a vacuum. The solid was collected by filtration on a frit, washed with methanol (3 × 5 mL), and dried under a high vacuum overnight to give **10** as a brick red solid (72 mg, 94%). Elemental analysis of **10** gave a cobalt content of 7.60%, indicating 90.3% of the salen centers were functionalized with the metal. IR: ν 1770 (C═O), 1635, 1614 cm^{-1}. UV−vis (THF): λ 259, 344, 415 nm.

General Procedures for the Hydrolytic Kinetic Resolution: (*S*)-Allyl Glycidyl Ether (Table 1, Entry 3). Method A. Preoxidation of (*R*,*R*)-**4** with acetic acid (AcOH). The Co(II)(salen) precatalyst (*R*,*R*)-**4** (3.5 mg, 0.005 mmol on the basis of cobalt, 0.01 mol %) was dissolved in dichloromethane (1 mL) in a 25 mL flask. Glacial acetic acid (10 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. The solvent and the excess acetic acid were roughly removed by rotary evaporation. The residue was pumped under a vacuum (1 mbar) for 5 min to give (*R*,*R*)-**4**(OAc) as a dark brown solid. The activated catalyst was dissolved in racemic allyl glycidyl ether (5.71 g, 50 mmol) (in the cases of kinetic studies, chlorobenzene was added as an internal reference for the GC analysis). The flask was immersed into a water bath at ambient temperature, and deionized water (0.54 mL, 30 mmol, 0.60 equiv) was added to the system to start the reaction. The resolution process was monitored by chiral GC method. After the reaction was stirred at rt for 12 h, the remaining epoxide was vacuum-transferred (40 °C, 0.15 mbar) to a receiving flask precooled at −78 °C. The recovered epoxide was passed through a plug of silica gel packed in a Pasteur pipet to give (*S*)-allyl glycidyl ether as a clear colorless liquid (2.73 g, 48%) in >99% ee according to chiral GC analysis (γ-TA, 80 °C, isothermal, t_R(*S*, major) = 8.8 min, t_R(*R*, minor) = 7.7 min). **Method B:** Preoxidation of (*R*,*R*)-**4** with *p*-toluenesulfonic acid (TsOH). The Co(II)(salen) precatalyst (*R*,*R*)-**4** (3.5 mg, 0.005 mmol on the basis of cobalt, 0.01 mol %) was charged to a 25 mL flask. A solution of *p*-toluenesulfonic acid monohydrate in THF (0.01 M, 0.55 mL, 0.0055 mmol, 1.1 equiv) was added, and the reaction mixture was stirred in the open air for 30 min, during which time the color changed from deep red to deep green. The solvent was roughly removed by rotary evaporation. The residue was pumped under a vacuum (1 mbar) for 5 min to give (*R*,*R*)-**4**(OTs) as a deep green solid. The activated catalyst was dissolved in racemic allyl glycidyl ether (5.71 g, 50 mmol) (in the cases of kinetic studies, chlorobenzene was added as an internal reference for the GC analysis). The flask was immersed into a water bath at ambient temperature, and deionized water (0.54 mL, 30 mmol, 0.60 equiv) was added to the system to start the reaction. The resolution process was monitored by a chiral GC method. After the reaction was stirred at rt for 6 h, the remaining epoxide was vacuum-transferred (40 °C, 0.15 mbar) to a receiving flask precooled at −78 °C. The recovered epoxide was passed through a plug of silica gel packed in a Pasteur pipet to give (*R*)-allyl glycidyl ether as a clear colorless liquid (2.62 g, 46%) in >99% ee according to chiral GC analysis.

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Supporting Information Available: Additional experimental procedures as well as in situ ^{1}H NMR spectra and GPC traces of the ring expanding metathesis reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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