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Importance of Counterion Reactivity on the Deactivation of Co–Salen Catalysts in the Hydrolytic Kinetic Resolution of Epichlorohydrin

Surbhi Jain,[†] Xiaolai Zheng,[‡] Christopher W. Jones,[‡] Marcus Weck,[‡] and Robert J. Davis*[,†]

Chemical Engineering Department, University of Virginia, Charlottesville, Virginia 22904, and
School of Chemistry & Biochemistry and School of Chemical & Biomolecular Engineering,
Georgia Institute of Technology, Atlanta, Georgia 30332

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Possible modes of deactivation of Jacobsen's Co–salen catalyst during the hydrolytic kinetic resolution (HKR) of epichlorohydrin were explored by UV–vis spectroscopy, X-ray absorption spectroscopy, and electrospray ionization mass spectrometry, combined with recycling studies. Although an active Co(III)–salen catalyst deactivated substantially after multiple cycles without regeneration, the catalyst maintained its +3 oxidation state throughout the runs. Thus, deactivation of Co–salen during HKR was not the result of Co reduction. The mass spectrum of a deactivated material showed that catalyst dimerization does not account for the loss of activity. Results from various catalyst pretreatment tests, as well as from catalysts containing various counterions (acetate, tosylate, chloride, iodide) indicated that the rate of addition of the Co–salen counterions to epoxide forming Co–OH during the reaction correlated with deactivation. The extent of counterion addition to epoxide was influenced by the exposure time and the nucleophilicity of the counterion. An oligo(cyclooctene)-supported Co–OAc salen catalyst, which was 25 times more active than the standard Co–salen catalyst, was recycled multiple times with negligible deactivation.

1. Introduction

The hydrolytic kinetic resolution (HKR) of terminal epoxides using Co−salen catalysts is one of the most important methods to produce chiral epoxides from racemic mixtures.[1−3] The use of water as the nucleophile makes this reaction straightforward to perform at a relatively low cost. Moreover, the diol that is obtained as the ring-opened product in high enantiomeric excess is often a key intermediate in the synthesis of fine chemicals.[4,5] The homogeneous Co(III) salen catalyst developed by Jacobsen's group provides high ee's for variety of terminal epoxides with only 0.2−2 mol % catalyst loading in solution.[6,7]

The proposed mechanism for the HKR of terminal epoxides involves the cooperativity of two Co−salen complexes, where one Co metal center activates the electrophile (epoxide) and the other Co metal center activates the nucleophile (water).[8,9] Hence, the observed rate depends on the square of the catalyst concentration. With this mechanism in mind, researchers have developed multimeric Co−salen catalysts that exhibit activities 1−2 orders of magnitude greater than that of the monomeric Co−salen catalyst.[10−19]

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* To whom correspondence should be addressed. E-mail: rjd4f@virginia.edu.

[†] University of Virginia.

[‡] Georgia Institute of Technology.

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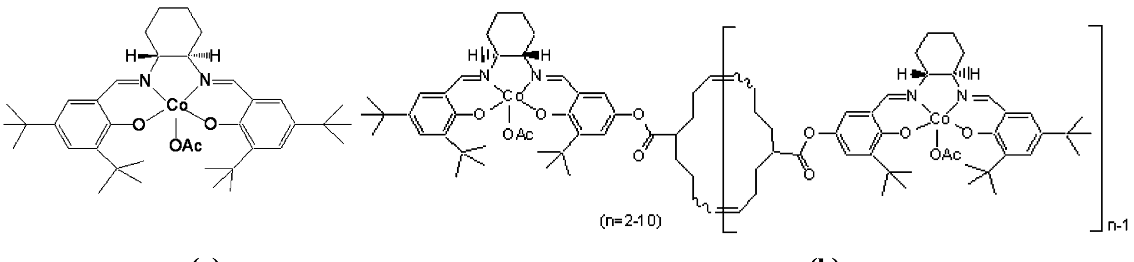
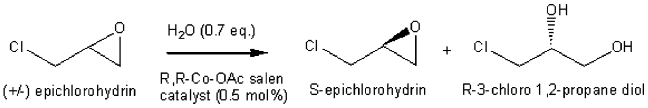


(a) **(b)**

Figure 1. (a) *R*,*R*-Jacobsen's Co−OAc salen catalyst. (b) *R*,*R*-Oligo(cyclooctene) supported Co−OAc salen catalyst.

Scheme 1. HKR of Epichlorohydrin in the Presence of *R*,*R*-Jacobsen's Co−OAc Salen Catalyst at ∼300 K



For example, Jacobsen's group has synthesized dimers and oligomers of Co−salen complexes, as well as created Co−salen complexes bound to polymeric or dendrimeric frameworks.[10−16] These systems reveal similar high enantioselectivity but substantially enhanced reactivity relative to the monomeric Co−salen analog. In related work, Song et al.[17,18] have synthesized polysalen−Co(III) complexes and obtained ee's up to 98% in the HKR of terminal epoxides. Zheng et al.[19] have synthesized poly(styrene)-supported Co−salen catalysts and found these to be active, selective, and recyclable. Kim's group[20−23] has prepared various dimeric and polymeric heterometallic chiral Co−salen catalysts linked with different Lewis acids such as BF_3, AlX_3, GaX_3, InX_3, and TlX_3, where X is a halogen. These catalysts demonstrated high catalytic activity and enantioselectivity in the asymmetric ring opening of epoxides with H_2O, HCl, and carboxylic acids. In addition to the polymeric catalysts, Shepperson et al.[24] obtained excellent enantioselectivities with fluorinated Co−salen catalyst in the HKR of 1,2-hexene oxide and recycled the catalyst by liquid−liquid extraction methods.

Recently, we have prepared an oligo(cyclooctene)-supported Co−salen catalyst (see Figure 1), with the idea that the presence of multiple Co−salen units as side chains on the oligomeric catalyst can enhance the reactivity and enantioselectivity.[25]

Most of these multimeric, homogeneous catalysts, as well as supported catalysts, are difficult to synthesize and need to be regenerated after the reaction. The general mode of catalyst deactivation has been reported in the literature to be the change of the active Co(III)−salen complex to an inactive Co(II)−salen complex.[26−28] However, no detailed spectroscopic studies have been carried out to confirm this suggestion. Moreover, the mechanism of the proposed Co reduction is not clear. In this work, we investigated the mode of catalyst deactivation during the HKR of epichlorohydrin by conducting recycling studies of homogeneous Co−salen catalysts without catalyst regeneration and following the chemical state of the catalyst by UV−vis and X-ray spectroscopy. The influence of counterion on the rate of epichlorohydrin HKR has also been evaluated. Finally, we compared the activity and recyclability of the oligo(cyclooctene)-supported Co−OAc salen catalyst (Figure 1) to that of the traditional Jacobsen Co−salen catalyst.

2. Experimental Section

2.1. Catalyst Preparation. 2.1.1. *R*,*R*-Jacobsen Co−OAc Salen Catalyst. The oxidation of traditional Jacobsen's Co(II)−salen catalyst to Co−OAc salen form has been performed by Schaus et al.[1] The same procedure was followed to prepare well-known Jacobsen's Co−OAc salen catalyst. The *R*,*R*-Jacobsen's Co(II)−salen catalyst (400 mg) (as received from Acros Organics) was dissolved in dichloromethane (13 mL) in a 25 mL round-bottom flask, after which acetic acid (10 equiv with respect to catalyst, 382.5 μL) was added via a microliter pipet. After the mixture was stirred with a Teflon stir bar for about 45 min, dichloromethane was removed with a rotorary evaporator, and the excess acetic acid was removed under vacuum. The resulting *R*,*R*-Jacobsen's Co−OAc salen catalyst was a dark brown residue. The elemental analysis (wt %) was obtained by Galbraith Laboratories (Knoxville, TN) for all of the catalysts. The results for Co−OAc were C, 63.45; H, 7.83; N, 3.58; Co,7.84%. The measured C/Co mole ratio was 39.69, which was in agreement with the ideal mole ratio of 38.

2.1.2. *R*,*R*-Jacobsen Co−OTs Salen Catalyst. The Jacobsen's Co−OTs salen catalyst was prepared by following the same procedure as reported by Lars et al.[9] The *R*,*R*-Jacobsen's Co(II)−salen catalyst (3 g) (as received from Acros Organics) was dissolved in dichloromethane (50 mL) in 100 mL round-bottom flask, after which *p*-toluene sulfonic acid monohydrate (1 g) (1.06 equiv with respect to catalyst) was added to the solution. After the mixture was stirred for about 45 min, dichloromethane was removed with

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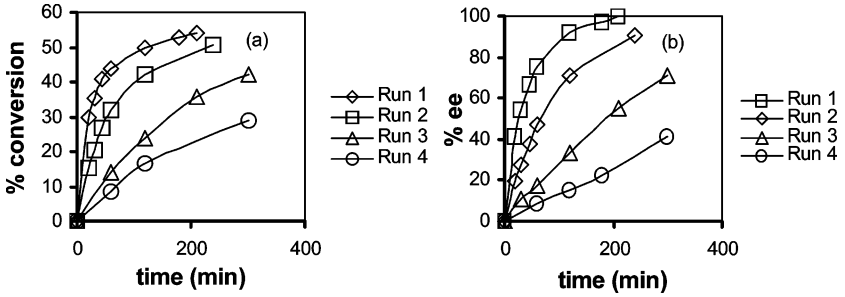

Figure 2. (a) Conversion of epichlorohydrin and (b) evolution of enantiomeric excess of epichlorohydrin for 4 successive HKR cycles of *R*,*R*-Jacobsen's Co−OAc salen catalyst (without acetic acid regeneration). Reaction conditions: 10 mmol epichlorohydrin, 0.7 equiv of water, 0.5 mol % catalyst, 120 μL chlorobenzene, ~300 K.

a rotorary evaporator, and the solid was further treated under reduced pressure. The resulting solid was then resuspended in pentane and filtered through a Whatman (grade 5) filter paper. The resulting *R*,*R*-Jacobsen's Co−OTs salen catalyst was a green residue. The elemental analysis results were C, 59.22; H, 7.20; N, 2.95; Co, 8.26; S, 5.14%. The measured S/Co mole ratio was 1.14.

2.1.3. *R*,*R*-Jacobsen Co−Cl Salen Catalyst. The Jacobsen's Co−Cl salen catalyst was prepared by following the same procedure as reported by Lars et al.[9] Approximately 2.5 g of *R*,*R*-Jacobsen's Co−OTs salen catalyst was dissolved in 100 mL of dichloromethane in a 500 mL separatory funnel. The organic layer was then rinsed with saturated aqueous NaCl solutions (3 × 100 mL), dried over Na_2SO_4 (crystalline, anhydrous), and concentrated in rotary evaporator. The residue was then resuspended in pentane and vacuum filtered to produce a very dark green material. The elemental analysis results were C, 67.25; H, 8.12; N, 4.37; Co, 9.67; Cl, 5.85%. The measured Cl/Co mole ratio was 1.0.

2.1.4. *R*,*R*-Jacobsen Co−I Salen Catalyst. The Jacobsen's Co−I salen catalyst was prepared by following the same procedure for Co−Cl salen catalyst as reported by Lars et al.,[9] with the substitution of NaI for NaCl. The elemental analysis results were C, 59.47; H, 7.17; N, 3.80; Co, 7.65; I, 17.33%. The measured I/Co mole ratio was 1.05.

2.2. Hydrolytic Kinetic Resolution (HKR) of Epichlorohydrin. Approximately 0.5 mol % of *R*,*R*-Jacobsen's Co−OAc salen catalyst (0.05 mmol, 33 mg) was dissolved in epichlorohydrin (10 mmol, 784 μL) in a 100 mL reaction flask immersed in a temperature controlled water bath (~300 K). Chlorobenzene (120 μL) was added to the reaction mixture via a microliter pipet as an internal standard. One aliquot (1−2 μL) of the reaction mixture was taken before starting the reaction, passed through a Pasteur pipet plugged with silica gel, and diluted with diethyl ether (~1−1.5 mL). Water (0.7 equiv, 126 μL) was then added to the mixture to start the HKR reaction. Approximately 1−2 μL samples were withdrawn periodically, passed through a Pasteur pipet plugged with silica gel, and diluted with diethyl ether. Reaction products were analyzed by gas chromatography using ChiralDex GTA capillary column and an FID detector. The percent conversion and percent ee of the recovered epoxide (*S*-epichlorohydrin) were monitored as a function of time. The same procedure was also followed for the oligo(cyclooctene)-supported Co−OAc salen catalyst.

2.3. Recycling of Co−Salen Catalyst after the HKR Reaction. The recycling studies were performed on R,R-Jacobsen's Co−OAc salen catalyst without intermediate regeneration with acetic acid. After the completion of the HKR reaction, all of the reaction products were removed by evacuation (epoxide was removed at room temperature (~300 K) and diol was removed at a temperature of 323−329 K). Fresh reagents were then added to the recovered catalyst, and a second run was performed. In a similar manner, the catalyst was recycled up to four times after the initial HKR of epichlorohydrin. The same recycling procedure was also followed for the oligo(cyclooctene)-supported Co−OAc salen catalyst.

2.4. Spectroscopic Evaluation of the Catalysts. The UV−vis spectra of the Jacobsen Co(II)−salen catalyst (inactive) and Jacobsen Co(III)−salen catalyst (active) before and after the reaction were collected in transmission mode on a CARY-3E UV−vis spectrophotometer. All spectra were obtained by dissolution of the catalysts in epichlorohydrin. We also measured the X-ray absorption near edge structure, XANES, of the Jacobsen's Co−salen catalyst, as well as the supported oligo(cyclooctene) Co−salen catalyst. X-ray absorption spectroscopy was conducted on beamline X10-C at the National Synchrotron Light Source (NSLS), Brookhaven National Lab, Upton, NY. The Co K-edge (7709 eV) spectra of various catalysts were collected at room temperature in both fluorescence and transmission modes. For transmission measurements, all the ion chambers were filled with N_2. A Co foil of 5 μm was placed between the second and third ion chambers for energy calibration. At least four spectra were averaged for each sample studied in the transmission mode. For in situ XANES measurement, the HKR reaction was performed in a Teflon X-ray cell with a Kapton window. The homogeneity of the reaction mixture was maintained by adding isopropyl alcohol as the cosolvent. Each X-ray scan was collected after every 22 min of the reaction.

2.5. Electrospray Ionization-Mass Spectrometry (ESI-MS). Approximately, 5 mL of a 50 μM solution of Jacobsen's Co(II), Co−OAc, or deactivated Co−OAc salen catalyst was prepared in dichloromethane. The samples were then diluted 5 or 10 times with methanol. The solutions were pumped to the mass spectrometer system at a flow rate of 50 μL min^{-1}, and 600 scans were collected in 1 min.

3. Results and Discussion

3.1. Recycling Studies on Jacobsen's Co−OAc Salen Catalyst (Without Acetic Acid Regeneration). The HKR of racemic epichlorohydrin has been carried out in the presence of *R*,*R*-Jacobsen's Co(III)−salen catalyst according to Scheme 1.

With 0.5 mol % catalyst loading of Jacobsen's Co−OAc salen catalyst, a conversion of epichlorohydrin equal to 54% and an ee of >99% were obtained in about 200 min (see Figure 2, run 1). The catalyst was then recycled three times (without intermediate regeneration with acetic acid) by evaporation of all the products under vacuum at 329 K. With each subsequent run, the conversion and ee were lower (see Figure 2).

Kim et al.[26] observed that the enantiomeric excess of recovered epichlorohydrin was reduced to 17% in the second

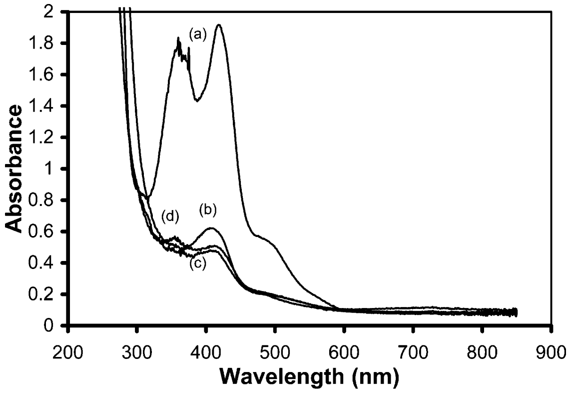

Figure 3. UV−vis spectra of various Co−salen complexes dissolved in epichlorohydrin (Co−salen concentration = 0.058 mg/mL): (a) Jacobsen's Co(II)−salen catalyst, (b) Jacobsen's Co(III)−OAc salen catalyst, (c) Jacobsen's Co−salen catalyst recovered after first run, (d) Jacobsen's Co−salen catalyst recovered after fourth run.

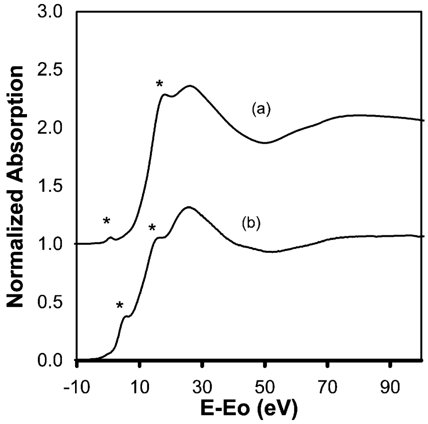

Figure 4. XANES of various Co−salen complexes: (a) Jacobsen's Co-(III)−OAc salen catalyst and (b) Jacobsen's Co(II)−salen catalyst. Spectra are offset for clarity. The energy is referenced to the K edge of Co metal. The asterisks indicate distinguishing features in the spectra.

hydrolysis reaction with Jacobsen's Co−OAc salen catalyst, if the catalyst was not regenerated with acetic acid in air. The same group[28] also observed deactivation with a polymeric Co−OAc salen catalyst. Although they attributed the loss of enantioselectivity to the reduction of Co(III) to Co-(II) after the HKR reaction, no spectroscopic evidence was provided. Therefore, we probed the catalyst by UV−vis and XANES spectroscopy before and after the HKR reaction.

3.2. UV−vis and XANES Spectroscopic Studies on Jacobsen's Co−Salen Catalyst. As shown in Figure 3, two strong absorption bands at ~360 and 415 nm were observed for the inactive Co(II)−salen complex, whereas a weak band at ~408 nm was present in the active Co(III) salen complex. It is important to emphasize that the active Co(III)−salen catalyst had no discernible features near 360 nm. As shown in Figure 3, the Co−salen complex after both the first and fourth runs in the HKR reaction had only a very small feature at ~360 nm, indicating only slight reduction of the metal center after multiple runs. Although the Co(III)−salen catalyst exhibited substantial deactivation, very little of the Co(III) reduced to Co(II).

Figure 4 shows the XANES of the oxidized and reduced forms of Co−salen. The normalized spectra clearly distinguish the Co−salen complexes in +2 and +3 oxidation states because there is a small preedge peak at about 2.1 eV, followed by a peak at ~19.2 eV above the edge in Co(III) salen catalyst, whereas a preedge peak at about 6.6 eV, followed by a peak at ~17.7 eV above the edge, is present in Co(II)−salen catalyst.

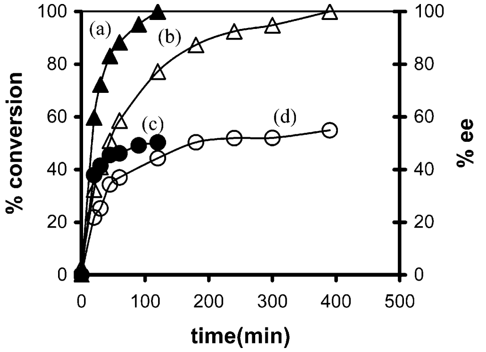

Figure 5. Single-phase HKR of epichlorohydrin in the presence of isopropyl alcohol: (a) % ee with stirring, (b) % ee without stirring, (c) % conversion with stirring, (d) % conversion without stirring. Reaction conditions: 10 mmol epichlorohydrin, 0.7 equiv water, 1 equiv isopropyl alcohol, 0.5 mol % *R,R*-Jacobsen's Co−OAc salen catalyst, 120 μL chlorobenzene (as internal standard), room temperature (no water bath).

Figure 4 shows the XANES of the oxidized and reduced forms of Co−salen. The normalized spectra clearly distinguish the Co−salen complexes in +2 and +3 oxidation states since there is a small preedge peak at about 2.1 eV, followed by a peak at ~19.2 eV above the edge in Co(III)−salen catalyst, whereas a preedge peak at about 6.6 eV, followed by a peak at ~17.7 eV above the edge is present in the Co-(II)−salen catalyst.

With these distinguishing features of the Co−salen catalysts in two different oxidation states, we proceeded to measure the in-situ XANES spectra of Jacobsen's Co−salen catalyst under the HKR reaction conditions. The acquisition of spectra under the typical reaction conditions was not performed because phase separation of the reagents would occur under the static conditions of the measurement. Therefore, the HKR of epichlorohydrin was tested in the presence of cosolvent isopropyl alcohol with and without stirring the reaction mixture.[29] As shown in Figure 5, 50% conversion and >99% ee were obtained in ~6 h and 30 min under static conditions, compared to 2 h with vigorous stirring. Thus, quiescent reaction conditions at room temperature were used during the acquisition of X-ray spectra.

The in situ XANES obtained under nonstirred reaction conditions was collected every 22 min during the reaction. Representative spectra are shown in Figure 6. A preedge peak at about 2.1 eV above the Co metal edge was observed in the XANES spectrum in every case, and the overall XANES was characteristic of the Co metal center in a +3 oxidation state. These results are consistent with the UV−vis results presented earlier, which indicated negligible reduction of the Co(III) to Co(II) during the HKR of epichlorohydrin.

In summary, the results from both UV−vis and X-ray spectroscopic analysis suggest strongly that the vast majority

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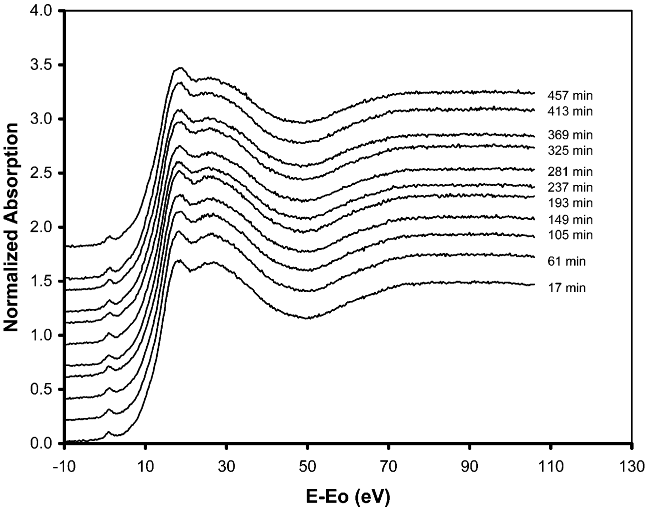


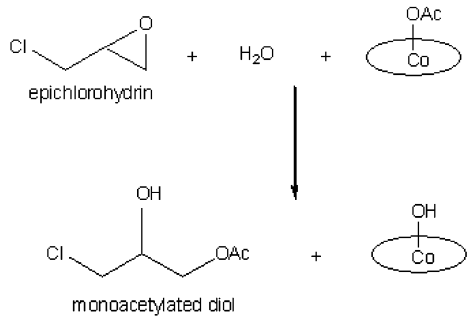
Figure 6. Normalized XANES spectra of *R,R*-Jacobsen's Co(III)−OAc salen catalyst obtained during the HKR of epichlorohydrin in the presence of isopropyl alcohol. Spectra are offset for clarity.

of the deactivation of the Co(III) salen catalyst during the HKR reaction was not a result of Co reduction.

3.3. Influence of Counterion in the HKR Reaction. Recent studies by the Jacobsen group indicate a significant role of the counterion on the observed activity of the Co−salen catalyst, which can be rationalized by the elementary steps involved in the reaction (Figure 7).[9] The well-recognized cooperative bimetallic mechanism of the HKR reaction of epoxides involves one Co−salen complex bound to OH and a second Co−salen complex containing a nonspecific counterion (denoted as X in Figure 7) such as acetate.

The kinetics of the HKR reaction are second order in Co−salen concentration because both Co complexes are needed to form the key reactive intermediate. Although the Co(OH)−salen complex is a necessary component of the bimetallic catalyst, the activity is improved when the counterion X is something other than hydroxyl. This observation is depicted schematically in Figure 8, which shows the rate of the ring-opening reaction as a function of the fraction of Co(OH)−salen in the reactor compared to Co−salen with SbF_6 counterion.[9] The important feature of Figure 8 is that a maximum rate of epoxide ring opening is achieved by a mixed Co−salen catalyst system in which 50% of the catalyst has an OH counterion. This parabolic behavior involving hydroxyl and counterions was observed for both SbF_6 and OTs.[9] Evidently, when the commonly studied Co(OAc)−salen catalyst is used for the HKR of epoxides in the presence of liquid water, part of the catalyst will convert to the hydroxyl form, Co(OH)−salen, during the course of the reaction. Indeed, Jacobsen's group has used reaction microcalorimetry to map the HKR rate as a function of conversion and partitioning of the counterion in various Co(X)−salen catalysts.[9] They found that the acetate counterion presents a nice balance of rates between acetate addition to the epoxide (generating the OH counterion on Co-salen) and the HKR reaction. Therefore, both forms of the Co−salen (OH and OAc) will be present throughout much of the HKR reaction. For strongly nucleophilic counterions such as Cl^-, the addition to epoxide is so rapid that the HKR reaction is carried out almost exclusively with Co(OH)−salen.

Scheme 2. Reaction of Acetate Counterion and Epoxide in the Presence of Water Forming Monoacetylated Diol as the Side Product in the HKR of Epichlorohydrin[9]



On the basis of those prior studies, we hypothesize that the observed deactivation of the Jacobsen's Co(OAc)−salen catalysts during epichlorohydrin HKR is a direct result of counterion addition to epoxide forming less-active Co−OH salen species during the reaction. This hypothesis is consistent with the notion that Co reduction cannot be the main reason for catalyst deactivation as described above. As shown by the Jacobsen group,[9] the addition of the acetate counterion to the epoxide leads to the formation of mono-acetylated diol as the side product. This reaction is represented in Scheme 2.

Since the side product contains C═O in the alkanoic part of the monoacetylated diol, we attempted to measure the C═O stretch in the solution recovered after HKR reaction by FT-IR. Although we did find an IR absorption peak at ∼1717 cm^{-1}, which tends to be a characteristic feature of C═O absorption from alkanoic acid, a small peak near the same region was also found from *R*-3-chloro-1,2-propane diol (the product of the HKR reaction of epichlorohydrin). We, therefore, tried to perform the GC-MS analysis of the HKR reaction products to see if we can detect any monoacetylated diol in the HKR reaction mixture. Jacobsen et al.[30] have delivered acetic acid quantitatively to cyclohexene oxide in the presence of Jacobsen's Co(II) salen complex and observed a low enantioselectivity of about 40% ee. We performed the HKR of 10 mmol of epichlorohydrin in the presence of 1 mol % Jacobsen's Co(II)−salen catalyst and 1 equiv acetic acid (wrt epichlorohydrin). The monoacetylated 3-chloro-1,2-propane diol was monitored by GC-MS. The same product was also detected in a trace amount in the HKR of epichlorohydrin with Jacobsen Co−OAc salen catalyst and water as the nucleophile. These results support the idea that reduction of active Co(III) to inactive Co(II) is not the cause of catalyst deactivation during HKR of epichlorohydrin, but instead the addition of acetate counterion to epichlorohydrin forming monoacetylated 3-chloro-1,2-propane diol and Co−OH species decreases the activity of the catalyst.

This hypothesis was confirmed by carrying out a kinetic study of the HKR of epichlorohydrin using Jacobsen Co-

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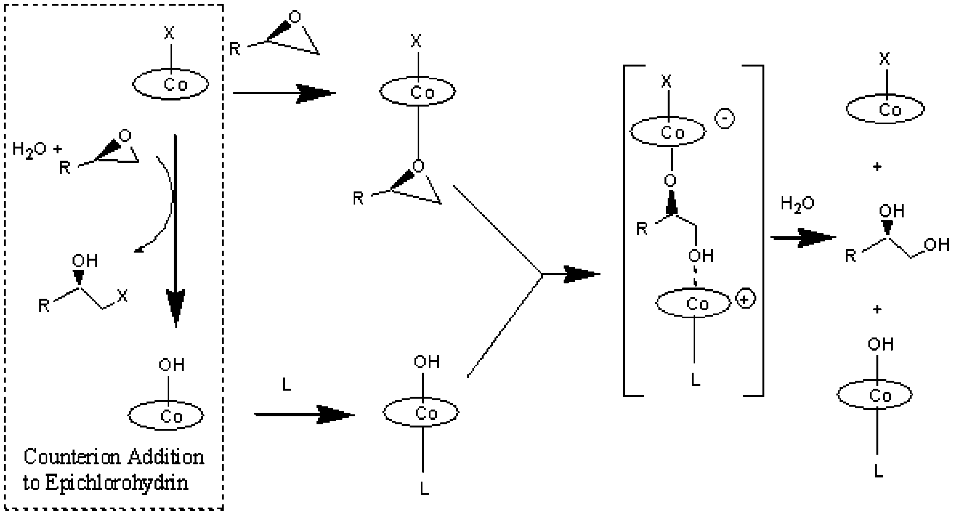

Figure 7. Proposed catalytic cycle involved in the HKR of terminal epoxides adapted from ref 9. The counterion addition reaction is needed to activate the catalyst for the HKR reaction. However, excessive counterion addition leads to deactivation.

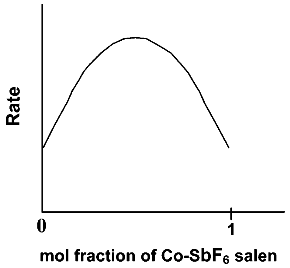

Figure 8. Dependence of rate on the relative amount of Co(OH)−salen and Co(SbF$_6$)−salen during ring-opening of 1-hexene epoxide.[9]

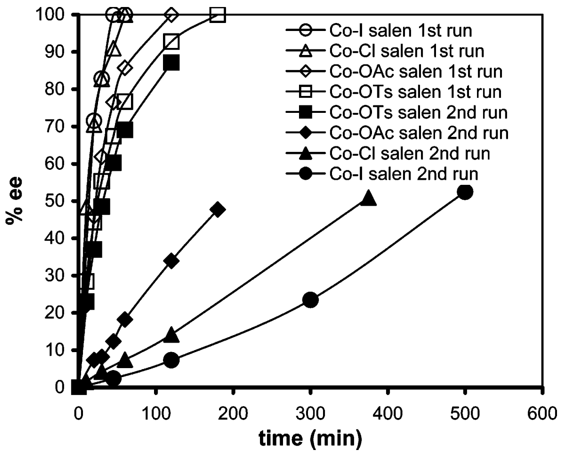

Figure 9. Effect of different counterions on deactivation of Jacobsen's Co−salen catalyst in the HKR of epichlorohydrin. Reaction conditions: 10 mmol epichlorohydrin, 120 μL chlorobenzene, 126 μL water, 0.5 mol % *R*,*R*-Jacobsen Co(III)−salen catalyst.

(III)−salen catalyst with four different counterions, namely, acetate (OAc), tosylate (OTs), chloride (Cl), and iodide (I). In the first runs, similar rates were observed with Co−OAc salen and Co−OTs salen catalysts. However, slightly higher rates were observed with Co−Cl salen and Co−I salen catalysts at 0.5 mol % catalyst loadings. The catalysts were then recycled after performing the HKR of epichlorohydrin for 12 h, followed by the evaporation of all the reaction products under vacuum and high temperature. The second runs were then performed with the recovered catalysts from the first runs. The results from the second runs are shown in Figure 9.

The rates with the recycled catalysts decreased in the following order: Co−OTs > Co−OAc > Co−Cl > Co−I, which is consistent with the idea of deactivation by counterion addition to epoxide. As reported by Lars et al.,[9] the rate of counterion addition to epoxide determines the kinetics of HKR. The iodide and chloride counterions undergo such rapid addition to epoxide that most of the HKR reaction occurred with the less active Co−OH catalyst formed in situ. On the other hand, the weakly nucleophilic tosylate counterion reacted more slowly with the epoxide, and therefore, the deactivation rate was decreased. The UV−vis spectra of the catalysts recovered after the second runs showed negligible reduction of the Co(III).

The influence of reaction time on the extent of deactivation is illustrated in Figure 10. The *R*,*R*-Jacobsen Co−OAc salen catalyst was treated in a HKR reaction of epichlorohydrin for 4 h and then reaction products were removed under vacuum. The catalyst was then recycled and treated for 7 h in the HKR of epichlorohydrin. Again, the reaction products were removed under vacuum, and the catalyst was recycled the second time producing 17% ee in 60 min. A fresh *R*,*R*-Jacobsen Co−OAc salen catalyst was then treated for 12 h in the HKR of epichlorohydrin and recycled producing an ee of 18% in 60 min. Therefore, it was observed that a similar time pretreatment (11 vs 12 h) produced almost similar ee's in the HKR of epichlorohydrin.

Although our results suggest that deactivation of the Co−salen catalyst during the HKR reaction depends on the ease of counterion addition to the epoxide, the possibility of catalyst deactivation due to catalyst dimer formation was investigated by ESI-MS. Figure 11 a and b show the mass spectra of Jacobsen's Co(II) and Co−OAc salen catalysts in dichloromethane. A major peak at *m*/*z* of 603.5 was found for both the complexes, whereas small peaks were obtained

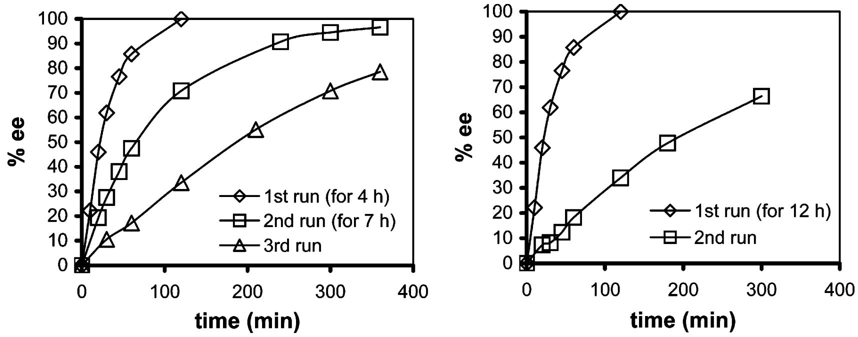

Figure 10. Effect of reaction time on catalyst deactivation. Reaction conditions: 10 mmol racemic epichlorohydrin, 120 μL chlorobenzene, 126 μL water, 0.5 mol % *R*,*R*-Jacobsen Co–OAc salen catalyst, room temperature.

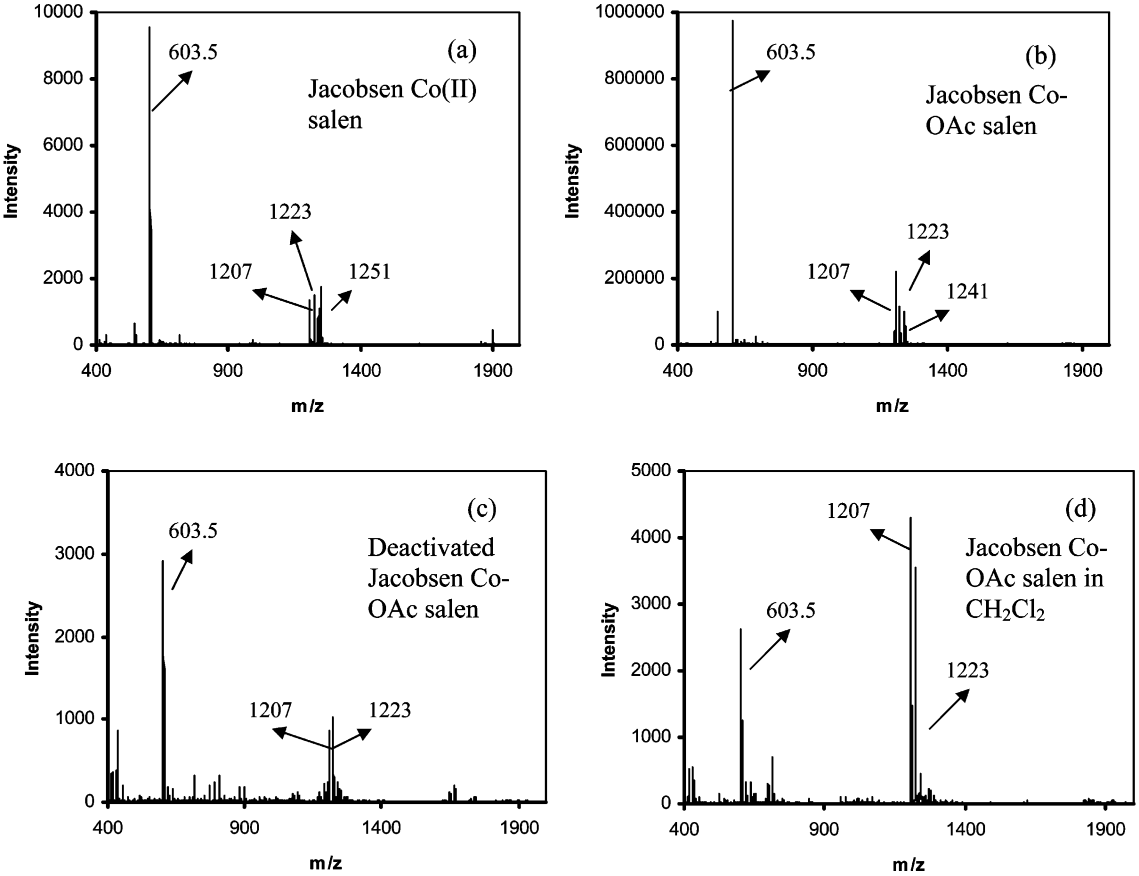

Figure 11. ESI mass spectra of various Co–salen complexes: (a) Jacobsen's Co(II)–salen catalyst, (b) fresh Co–OAc salen, (c) Co–OAc salen recovered after 12 h HKR reaction with epichlorohydrin, and (d) Co–OAc salen after 24 h in dichloromethane.

in the *m*/*z* range of 1207–1251. The major feature at 603.5 corresponds to parent peak of Jacobsen Co(II) salen catalyst (formula weight = 603.76). Apparently, fragmentation in the ESI-MS gives the same parent peak for the Co–OAc salen catalyst. The minor peaks in the range of 1207–1251 are attributed to dimer formation in the solution or the ESI-MS. The mass spectrum of the deactivated Co–salen catalyst (recovered after the 12 h HKR reaction with epichlorohydrin) is shown in Figure 11c. The major feature at 603.5 suggests that only a small amount of dimer species was formed during the HKR reaction. Interestingly, the mass spectrum of a fresh Co–OAc salen catalyst diluted in dichloromethane for 24 h showed substantial formation of dimer (Figure 11d). Since ESI-MS revealed dimer formation by long-term exposure of Co–OAc to dichloromethane, we recovered this material and tested it in the HKR reaction. Figure 12 compares the conversion and % ee during HKR with the dimerized material to those with a fresh Co–OAc catalyst. Within experimental error, the curves were superimposible, indicating identical reactivity of the dimer material and the fresh catalyst. Therefore, deactivation of Co–salen catalysts appears to occur mainly by counterion addition to the epichlorohydrin.

3.4. Pretreatment Tests. Since exposure of the Co–salen catalyst to the HKR reaction mixture deactivated the catalyst, we pretreated the Co–salen in individual reagents and products to explore their effect on deactivation. Specifically, the active *R*,*R*-Jacobsen Co–OAc salen catalyst was pretreated with different compounds for a period of 12 h at room

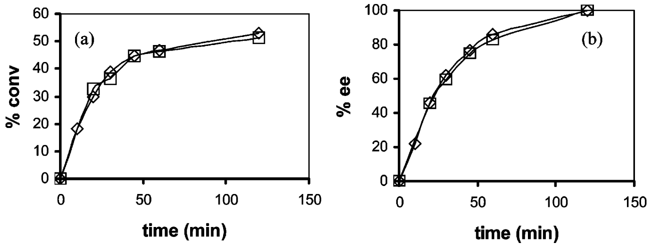

Figure 12. Comparison of Co−OAc catalysts before and after exposure to dichloromethane: (◇) HKR of epichlorohydrin with fresh Jacobsen Co−OAc salen catalyst, (□) HKR of epichlorohydrin with Jacobsen Co−OAc salen catalyst recovered after 24 h exposure to dichloromethane; (a) % conv vs time and (b) % ee vs time. Reaction conditions: 10 mmol epichlorohydrin, 0.7 equiv water, 0.5 mol % catalyst, 120 μL chlorobenzene, ∼300 K reaction temperature.

Table 1. Results of Co−OAc Pretreatment Tests[a]

entry	pretreatment[b]	% conv[c]	% ee[c]
1	no pretreatment	30	42
2	(±)-ECH + water + CB	5	5
3	*S*-ECH	12	16
4	*R*-ECH	10	13
5	*R*-diol + THF	32	47
6	*R*-diol + water + THF	25	34
7	*S*-diol + THF	26	38
8	*S*-ECH[d]	5	6
9	*R*-ECH[d]	4	7

[a] Reaction conditions: 10 mmol of (±)-epichlorohydrin (ECH), 5 mmol of *R*/*S*-ECH, 120 μL of chlorobenzene (CB), 126 μL of water, 1 mL of tetrahydrofuran (THF), 33 mg of *R*,*R*-Jacobsen Co−OAc salen catalyst. [b] Catalyst was pretreated with different reagents for 12 h; then all products were evaporated under vacuum in about 1 h 15 min to 3 h at room temp or 323−329 K for diols. Fresh HKR reagents were added to the recovered catalyst, and the reaction was performed at room temperature (RT). [c] % conversions and % ee's are listed at a reaction time of 20 min. [d] After the pretreatment, the products were evaporated under vacuum for 12 h at 323 K

temperature, followed by a subsequent recovery of the catalyst by removal of the products under vacuum. Then, the HKR reaction was performed at room temperature. The results of the reaction tests are summarized in Table 1.

The regular HKR reaction (no pretreatment) with 10 mmol of racemic epichlorohydrin (entry 1) produced 30% conversion and 42% ee in 20 min of reaction time. After 12 h of reaction, the catalyst was severely deactivated, producing 5% conversion and 5% ee in 20 min of reaction time (entry 2). Upon exposure of a fresh catalyst to S-ECH for a period of 12 h and then evacuation of the products under vacuum at room temperature, the subsequent HKR reaction produced 12% conversion and 16% ee in 20 min (entry 3). A similar level of deactivation was also observed after the pretreatment of 12 h with R-ECH, producing 10% conversion and 13% ee in 20 min (entry 4). We conclude that the epichlorohydrin reacted with the counterion during pretreatment and subsequently converted to monoacetylated diol upon hydrolysis of Co-salen during the HKR reaction or in the presence of trace water to give poorly active Co−OH salen. The catalyst was also pretreated with the major and minor HKR reaction products *R*/*S*-3-chloro-1,2-propane diol. Tetrahydrofuran was added to solubilize the mixture of catalyst and diol. A 12 h pretreatment with diols did not significantly reduce the conversion and ee (entries 5 and 7). We suspect that the product diol does not bind unproductively to the catalyst, which is consistent with the lack of product inhibition reported by Lars et al.[9] Last, we pretreated the catalyst with a mixture of *R*-3-chloro-1,2-propane diol, THF, and water for 12 h. The results from subsequent HKR reaction showed about 25% conversion and 34% ee after 20 min of reaction time (entry 6). Therefore, water itself does not facilitate catalyst hydroxylation.

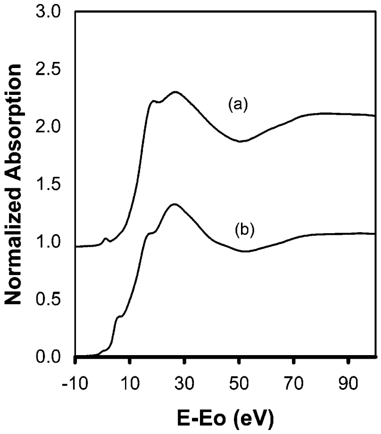

Figure 13. XANES of various Co−salen complexes: (a) oligo(cyclooctene) supported Co(III)−OAc salen catalyst, (b) oligo(cyclooctene)-supported Co(II) salen catalyst. Spectra are offset for clarity. The energy is referenced to the K edge of Co metal.

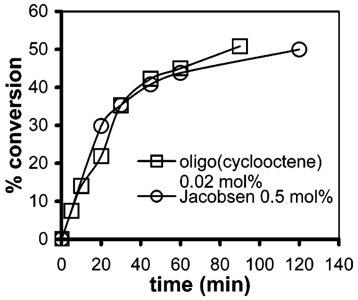

Figure 14. Comparison of *R*,*R*-Jacobsen's Co−OAc salen catalyst with *R*,*R*-oligo(cyclo-octene)-supported Co−OAc salen catalyst in the HKR of epichlorohydrin. Reaction conditions: 10 mmol epichlorohydrin, 0.7 equiv water, 120 μL chlorobenzene (as internal standard), room temperature.

It is also interesting to note that the vacuum treatment conditions at the time of product removal may affect the state of the catalyst. We observed partial reduction of the catalyst by UV−vis spectroscopy when the sample was exposed to moderate temperature (323 K) for long times (12 h), thereby producing low conversions and ee's (entries 8 and 9).

3.5. Oligo(cyclooctene)-Supported Co−OAc Salen Catalyst. Recently, we have reported a cyclic oligo(cyclooctene)-supported Co-salen catalyst synthesized by ring expanding olefin metathesis as the key step.[25] As a follow-up, we measured the XANES of this oligomeric catalyst to probe the effect of immobilization of Co−salen onto the polymeric support. As shown in Figure 13, the normalized XANES of immobilized Co−salen catalysts resembled the standard Jacobsen Co−salen catalysts in their respective oxidation states, indicating efficient immobilization of the Co−salen ligand onto the polymeric support.

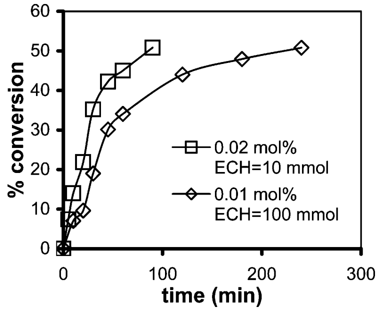

Figure 15. HKR of epichlorohydrin (ECH) with oligo(cyclooctene)-supported Co−OAc salen catalyst at different catalyst loadings. Reaction conditions: 0.7 equiv water (relative to epichlorohydrin), chlorobenzene (as internal standard), room temperature.

3.6. Comparison of Kinetics of Oligo(cyclooctene)-Supported Co−OAc Salen Catalyst versus Homogeneous Jacobsen's Co−OAc Salen Catalyst. We were able to use the oligomeric catalyst at very low loadings (0.01 mol %) in the HKR of a variety of terminal epoxides[25] and observed high conversion and ee in a short reaction time. Here, the *R*,*R*-oligo(cyclooctene)-supported Co−OAc salen catalyst was examined for its efficiency in the HKR of epichlorohydrin. Consistent with our prior results,[25] the rate and selectivity of the HKR of epichlorohydrin with the oligo(cyclooctene) Co−OAc salen catalyst were superior to those observed with the original Co−OAc salen catalyst. As shown in Figure 14, the conversion of epichlorohydrin in the presence of 0.02 mol % (based on Co) oligo(cyclooctene)-supported Co−OAc salen catalyst was similar to that of 0.5 mol % of Jacobsen's Co−OAc salen catalyst, which corresponds to an activity enhancement of 25 at our conditions. Interestingly, the oligomeric catalyst was more selective than Jacobsen's catalyst, producing >99% ee at 50% conversion in 90 min versus 92% ee at 50% conversion in 120 min for the Jacobsen's Co−OAc salen catalyst. As suggested previously,[25] this high activity and selectivity can be attributed to the close proximity of two Co-centers in the oligo(cyclooctene) Co−OAc salen catalyst, that is, an increase in local molarity of the cobalt centers, in contrast to the high dilution of the small-molecule Jacobsen catalyst.

The effect of concentration of the oligomeric catalyst on the rate of the reaction was also studied. The reaction profiles for two different catalyst loadings are shown in Figure 15. As the catalyst concentration was doubled, the conversion of epichlorohydrin at short reaction times also doubled (see Table 2). Thus, the rate was directly proportional to catalyst loading, unlike the reported behavior of the monomeric, homogeneous catalyst.[9]

The recycling of oligo(cyclooctene) Co−OAc salen catalyst without intermediate regeneration with acetic acid was then performed. With only 0.02 mol % catalyst loading of the oligomeric catalyst, approximately 51% conversion and >99% ee were achieved in about 90 min. The catalyst was recycled up to three times by evaporation of the reaction products from the previous run under vacuum. The reaction profiles (conversion and ee as a function of time) for the first 4 h of each run are shown in Figure 16.

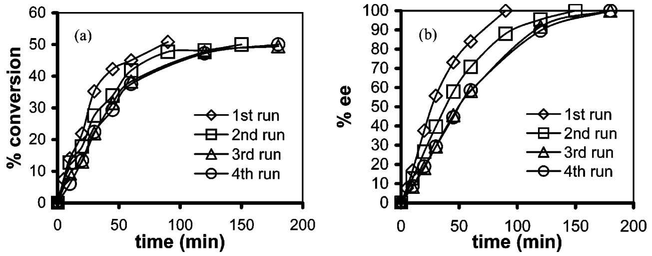

Figure 16. (a) Reaction profiles and (b) evolution of enantiomeric excess of epichlorohydrin HKR for four successive cycles of *R*,*R*-oligo(cyclooctene) supported Co−OAc salen catalyst (without acetic acid regeneration). Reaction conditions: 10 mmol epichlorohydrin, 0.7 equiv water, 0.02 mol % catalyst, 120 μL chlorobenzene (as internal standard), room temperature.

Table 2. Effect of Catalyst Loading on the HKR of Epichlorohydrin with Oligo(cyclooctene)-Supported Co−OAc Salen Catalyst

	% conversion	
reaction time (min)	0.01 mol % catalyst	0.02 mol % catalyst
5	-	7
10	7	14
20	10	22

As seen in the figure, no significant deactivation was observed with each run. The oligomeric catalyst shows substantial improvements to the Jacobsen catalyst in terms of rate, selectivity, and stability. Recycling the oligomeric catalyst after 12 h of the HKR reaction confirmed substantial deactivation, which supports the idea that counterion addition to the epoxide also occurred with this material.

4. Conclusions

The HKR of epichlorohydrin was performed in the presence of Jacobsen's Co−OAc salen catalyst, while the chemical state of the catalyst was examined by UV−vis and X-ray absorption spectroscopy. Recycling studies without intermediate regeneration of Jacobsen's Co−salen catalyst revealed catalyst deactivation with each run; however, almost negligible reduction of Co(III) to Co(II) species was observed spectroscopically during the HKR reaction. The effect of different counterions was explored in the HKR of epichlorohydrin. The Co−I salen catalyst revealed the highest level of catalyst deactivation upon recycle without regeneration, presumably because of the fast addition of iodide to epoxide, and the rapid formation of Co−OH salen species. In contrast, Jacobsen's Co−OTs salen catalyst revealed negligible deactivation after recycle. Apparently, an appropriate balance of Co−OTs and Co−OH salen species was maintained throughout much of the HKR reaction. Results from various catalyst pretreatments showed that long time exposure to *R*/*S*-epichlorohydrin will lead to significant deactivation of the catalyst. Since water alone did not deactivate the catalyst, counterion addition to the epichlorohydrin is apparently the major route leading to catalyst hydroxylation. Results from ESI-MS of a deactivated catalyst did not show significant formation of a dimer species, which is consistent with the idea that deactivation is a result of counterion addition to the epichlorohydrin. Moreover, dimer species formed after exposing a fresh catalyst to dichloromethane did not result in deactivation. The rate of HKR with a oligo(cyclooctene)-

supported Co−OAc salen was found to be about 25 times greater than the traditional Jacobsen's catalyst and could be easily recycled without significant drop in the rate and ee, even without acetic acid regeneration. The rate of the HKR reaction was found to be directly proportional to the concentration of the oligomeric catalyst, unlike the standard Jacobsen's catalyst. These new multimeric catalysts hold a significant promise in the HKR reaction because they can be used at very low loadings and can perform the HKR reaction in very short time periods without significant loss of activity. However, prolonged exposure of these catalysts to the HKR reaction led to deactivation.

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