



## Editor's choice paper

## Factors influencing recyclability of Co(III)-salen catalysts in the hydrolytic kinetic resolution of epichlorohydrin

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## ABSTRACT

The recyclability of Co(III)-salen catalysts, where salen is defined by (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine, for the hydrolytic kinetic resolution (HKR) of racemic epichlorohydrin is a strong function of the counterion of the Co(III)-salen catalyst. The nature of the counterion determines whether the HKR reaction follows primarily a bimetallic or monometallic reaction path, which significantly affects catalyst recyclability. For example, Co(III)-salen initially containing the nucleophilic Cl<sup>-</sup> counterion catalyzes the HKR of epichlorohydrin according to a bimetallic reaction path but loses activity upon recycle, as Cl<sup>-</sup> is replaced with OH<sup>-</sup> during the reaction. In contrast, a Co(III)-salen catalyst containing non-nucleophilic SbF<sub>6</sub><sup>-</sup> counterion catalyzes the reaction according to a monometallic reaction path and is quite stable during multiple recycles, albeit at a low rate with less selectivity. A mixed catalyst system with Co(III)-salen initially containing Cl<sup>-</sup> to which Co(III)-salen with SbF<sub>6</sub><sup>-</sup> is later added demonstrates high activity and high stability to recycling. Additional experiments with Co(III)-salen initially containing the acetate counterion reveal a progressive decline in activity with multiple recycles even after regeneration with acetic acid between runs, suggesting a destructive role of the regeneration process.

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## 1. Introduction

The hydrolytic kinetic resolution (HKR) of epoxides catalyzed by Co(III)-salen complexes, where salen is defined as (*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine, is now a pre-eminent method for the preparation of enantiopure terminal epoxides and/or 1,2-diols [1,2]. Introduced by Jacobsen in 1997, the reaction is both of synthetic significance and an intriguing reaction for catalysis science [1]. As early as the first report of the reaction, Jacobsen noted several unique features of the reaction including the second order dependence on the catalyst concentration, suggestive of a cooperative bimolecular reaction mechanism involving two Co-salen complexes in the rate-determining step of the catalytic reaction [1]. The authors reported that the catalyst was easily recoverable via evaporation of the volatile reactants and products, with the non-volatile residue remaining after removal of the reaction products containing the reduced catalyst (Co(II)-salen). The reduced (deactivated) catalyst could be regenerated by treatment in acetic acid under air, reproducing the Co(III)-salen

complex with an acetate counterion [1]. With catalyst regeneration, it was reported that the reaction could be recycled with no observable loss in activity or selectivity, based on what appears to be reproducible yield and enantiomeric excess (ee) after 12 h of reaction.<sup>1</sup>

The HKR reaction is closely related to the other metal-salen catalyzed epoxide ring-opening reactions such as the Cr(III)-salen catalyzed ring-opening of epoxides using azides as nucleophiles [2]. Also, the HKR reaction is a cooperative one involving two salen complexes activating both the epoxide and nucleophile. Jacobsen demonstrated that designing ligands that promoted cooperativity led to enhanced rates in most cases and also ee's if the appropriate transition state could be accommodated [2]. Konsler et al. showed that a "head-to-tail" transition state was likely the appropriate quasi-planar stacking structure for the catalytic reaction [3]. The Jacobsen group further established the generality of the cooperative mechanism in their subsequent studies of the epoxide ring-opening reaction using alcohols and phenols as the nucleophiles and Co(III)-salen complexes as catalysts [4,5].

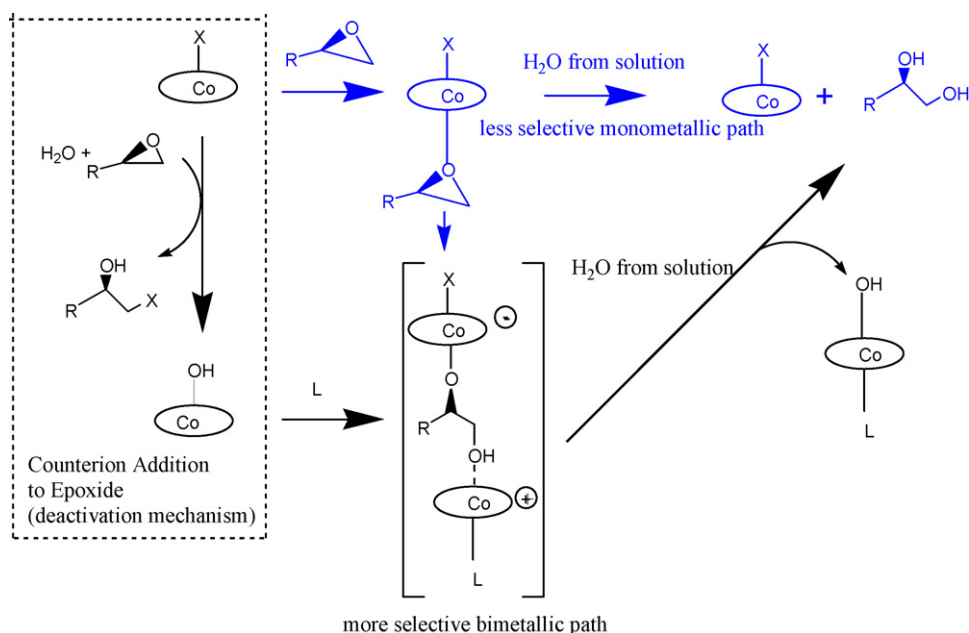
Recognizing that the cooperative epoxide ring-opening mechanism would allow supported catalysts to potentially achieve

<sup>1</sup> It should be noted that changes in reaction temperature may have been necessary to achieve equivalent conversions and ee's in a fixed reaction time [1].

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**Scheme 1.** Co-existence of monometallic and bimetallic paths in the HKR of terminal epoxides.

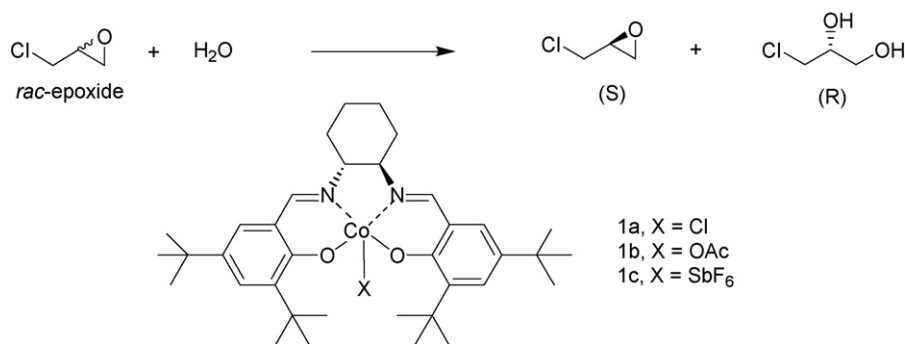
higher reaction rates at a given catalyst loading as a result of enhanced salen-salen interactions, Annis and Jacobsen reported poly(styrene) resin and silica supported Co(III)-salen catalysts for the HKR of epoxides [6]. The polymer resin supported catalyst had rates and selectivities similar to the homogeneous catalyst. Silica catalysts with a low density of grafted salen complexes displayed little to no activity, whereas those with higher densities of salen complexes linked to the surface with long flexible linkers displayed activities similar to the homogeneous and polymer supported catalysts. The catalysts were recovered and recycled, with the authors again noting that regeneration of the catalyst using a 9:1 toluene:acetic acid mixture under air was required. This reactivation was suggested to reoxidize the catalyst, implying the deactivated catalysts were reduced to Co(II) complexes [6].

Building off the success of the solid supported catalysts [6] and dimeric catalysts [3], Jacobsen and coworkers next developed dendrimeric [7] and cyclic oligomeric [4] Co(III)-salen complexes for epoxide ring-opening reactions. They showed that the dendrimeric catalysts displayed higher activities than comparable dimeric analogues, suggesting higher order catalyst interactions are possible with structures with more than two salen units [7]. They reported that the reactions using the oligomeric catalysts displayed a first order dependence on catalyst concentration, unlike the unsupported monomeric catalyst, supporting the cooperative bimetallic mechanism proposed in their previous work [4]. Furthermore, they demonstrated that a variety of alcohols and phenols could be used as nucleophiles [4]. In another study on the cyclic oligomeric catalysts, the authors suggested the possibility of two distinct reaction paths, a more active and selective bimetallic pathway and less active and less selective monometallic route when using the monomeric catalyst [5]. However, no kinetic data in support of the monomeric pathway were presented. Owing to the enhanced cooperativity imparted by the cyclic oligomeric catalysts, these catalysts had enantioselectivities that were independent of catalyst loading, an observation consistent with solely the bimetallic pathway operating with the oligomeric systems [5].

A breakthrough in the understanding of the reaction mechanism came from a collaborative work published in 2004 from Jacobsen and Blackmond [8]. Detailed kinetic studies using a variety of different Co(III)-salen complexes allowed development of a

reaction scheme that was kinetically consistent with the observed results. The authors showed that the kinetics of the reaction were consistent with the participation of two types of Co(III)-salen complexes, one with a counterion  $X^-$  introduced at the start of the reaction [ $X = Cl^-$ ,  $OAc^-$  (acetate),  $OTs^-$  (tosylate),  $SbF_6^-$ , etc.] and one, Co(III)-OH, that is generated in situ via counterion addition to the epoxide (Scheme 1). Although the hypothetical Co(III)-OH complex has not been isolated and characterized experimentally, both kinetic and other evidence for its existence appears strong [8]. Associated with the role of the counterion in the cooperative reaction, Nielsen et al. [8] showed that the highest rates occurred when the relative amounts of the Co(III)-X and Co(III)-OH salen were equal. As a result, use of Co(III)-salen complexes with relatively nucleophilic counterions such as  $Cl^-$  or  $OAc^-$  led to the rapid build-up of Co(III)-OH and deactivation of the catalyst [8].

Building on the work described above, we and coworkers have sought to develop improved supported cooperative Co(III)-salen catalysts for epoxide ring-opening reactions, with an eye towards gaining insight into the preparation of more effective supported catalysts for cooperative catalytic reactions [9–14]. The advantages of supported catalysts for these reactions include: (i) ease of catalyst separation from the products, (ii) the potential for easier catalyst recycle, and (iii) improved catalytic activity and selectivity associated with improved cooperative interactions among the salen complexes. However, catalyst recycle requires not only recovery of the catalyst, but also good catalyst stability as well as either limited catalyst deactivation or an understanding of the deactivation process so that regeneration methods can be developed. As noted above, Jacobsen and coworkers noted in their early work that the prototypical catalysts such as Co(III)-OAc are sometimes reduced to Co(II) after reaction, and they reported that these catalysts are regenerated by an oxidative treatment using acetic acid under air. The reports of catalyst reduction were often associated with a change of the catalyst color from brown to brick red after reaction and workup. Others have also reported that Co(III)-salen catalysts are deactivated by reduction to Co(II) species after the reaction. For example, Kim and coworkers, who developed a series of dimeric and polymeric heterometallic Co-salen catalysts linked with different Lewis acids [15,16], have reported that supported and unsupported Co-salen catalysts are deactivated by reduction,



**Scheme 2.** HKR of epichlorohydrin using Co(III)-salen-X.

in some cases providing UV–vis spectroscopic evidence to support this claim [17–19]. Seeking to understand the factors that affect catalyst deactivation, we evaluated the deactivation and recycling of soluble and supported Co(III)-salen HKR catalysts [20]. Our findings were consistent with the work of Nielsen et al. [8] who first suggested that the nature of the counterion ( $X^-$  in Scheme 1) on the Co(III)-salen catalyst is one of the most important factors in the mechanistic understanding of the HKR reaction. They showed that the nucleophilicity of the counterion  $X^-$  as well as the stability of  $X^-$  (which depends on the pKa of its conjugate acid) influenced the rates of HKR and recyclability of Co(III)-salen in this system. The formation of the bimetallic transition state as depicted in Scheme 1 (lower pathway) illustrates how the observed kinetics of HKR are statistically optimized with a 1:1 ratio of Co(III)-salen with  $\text{OH}^-$  as a counterion during the reaction [8].

Despite numerous reports suggesting reduction of Co(III) to Co(II) to be the cause of catalyst deactivation, based on our previous work, we have shown that the deactivation of the Co-salen catalysts upon multiple cycles was not attributed to reduction of Co or to dimerization of the Co complexes in the HKR, under our reaction conditions<sup>2</sup> [20]. Instead, the rate of counterion addition to epichlorohydrin, which ultimately formed the less active Co(III)-salen-OH complex, correlated to the loss in activity, as suggested by Nielsen et al. [8]. In particular, we observed that on recycling Co(III)-salen-X catalysts, the loss in catalyst activity during HKR of epichlorohydrin occurred in the following order, with X: iodide > chloride > acetate > tosylate [20]. However, the measured activity of the fresh catalysts in the first run showed nearly the same trend with the counterion, which contrasts the results reported earlier by Nielsen et al. [8] with 1,2-epoxyhexane as the substrate. This result suggests that, in addition to the Co-salen counterion, the nature of the substrate may also affect the rate of change of Co(III)-salen-X to Co(III)-salen-OH during the HKR reaction.

More recently, recycling studies of some supported Co(III)-salen-OAc catalysts have suggested that catalyst deactivation can also occur due to salen ligand hydrolysis during the HKR reaction or regeneration [13]. Thus, three mechanisms appear in the literature that are associated with Co(III)-salen-X deactivation in HKR reactions: (i) counterion exchange, (ii) reduction of Co(III) to Co(II) and (iii) salen ligand hydrolysis. Here, we explore the kinetics of the epichlorohydrin HKR during the recycling of various Co(III)-salen catalysts to gain insight into the stability of Co-salen HKR catalysts. A series of Co(III)-salen catalysts containing different counterions, ranging from non-nucleophilic  $\text{SbF}_6^-$  to a highly nucleophilic  $\text{Cl}^-$ , are examined in the HKR of epichlorohydrin. Although at one time

Ready and Jacobsen [5] have suggested that a less enantioselective monometallic mechanism involving a single Co(III)-salen complex in the transition state may play a role in HKR at low catalyst concentrations, no specific kinetic results were presented.<sup>3</sup> We report conclusive evidence of this less selective monometallic mechanism and how it couples to the well-recognized bimetallic path of the HKR of epichlorohydrin during the recycling of Co-salen catalysts containing specific counterions at specified catalyst concentrations. In addition, the influence of acetic acid regeneration on the recyclability of Co-salen catalyst containing acetate counterion is explored in the HKR of epichlorohydrin.

## 2. Results and discussion

### 2.1. Monometallic route to HKR with non-nucleophilic counterion ( $\text{SbF}_6^-$ )

The HKR of epichlorohydrin was evaluated in the presence of Co(III)-salen- $\text{SbF}_6$  since the non-nucleophilic  $\text{SbF}_6^-$  counterion should not react with the epoxide to form the Co(III)-salen-OH species. Therefore, the bimetallic reaction path should not be available when Co(III)-salen- $\text{SbF}_6$  is used as a catalyst.

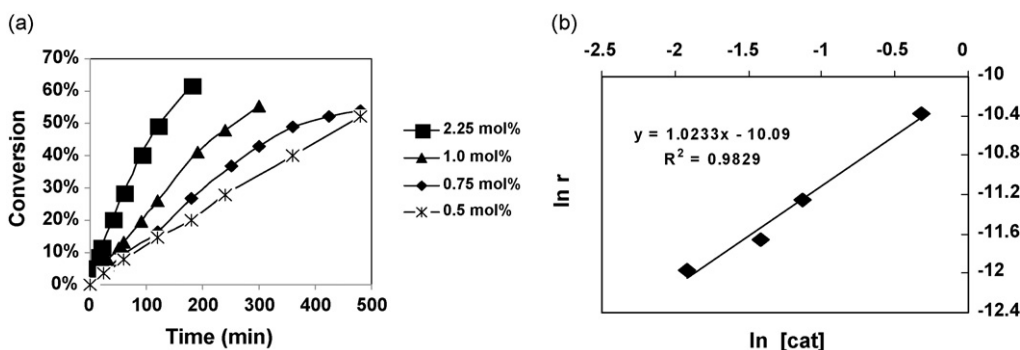
Various concentrations of Co-X salen complexes (0.1–2 mol%) containing different counterions, namely,  $\text{Cl}^-$  (**1a**)  $\text{OAc}^-$  (**1b**), and  $\text{SbF}_6^-$  (**1c**) were utilized in the HKR of epichlorohydrin using water (0.7 eq.) as a nucleophile, as shown in Scheme 2.

In some cases, the solvent 2-propanol was used to make the reaction mixture a single-phase [20], hence eliminating any induction period due to the presence of the initial biphasic reaction mixture of epichlorohydrin and water in the absence of solvent. A control experiment confirmed that 2-propanol does not participate in the reaction but functions only as an inert solvent in the reaction mixture.<sup>4</sup> The initial rates were evaluated at various catalyst loadings to evaluate the role of catalyst concentration on the observed activity. Table 1 summarizes the observed reaction orders for catalysts containing various counterions. The kinetic data and experimental details of the determination of reaction order in catalyst concentrations as a function of different counterions are given in the supporting information. It should be noted that the catalysts containing nucleophilic counterions (i.e. **1a** and **1b**) are continuously undergoing chemical change during the reaction to form

<sup>3</sup> In early work, Jacobsen and coworker suggest that a less selective, slower monometallic pathway exists [5]. Later work by Jacobsen and Blackmond suggested (Fig. 1) that Co(III)-salen- $\text{SbF}_6$  in the absence of Co-salen-OH is inactive [8]. Indeed, they suggest that Co(III)-salen- $\text{SbF}_6$  is inactive if purified carefully, in contrast to the work of Kim et al. [17].

<sup>4</sup> 2-propanol acts as an inert solvent except when Co(III)-salen- $\text{SbF}_6$  complexes were used, in which case additional reactions occur. Thus, 2-propanol was not used as a solvent when  $\text{SbF}_6^-$  complexes were used. These reactions were run in the absence of solvent.

<sup>2</sup> Recycling of the soluble molecular catalyst via recovery from reaction media by distillation can lead to catalyst reduction if careful control of the distillation temperature is not practiced. Limiting the heating to a maximum of 50–55 °C leads to recovery of the unreduced Co(III) complex in our hands under typical conditions.



**Fig. 1.** (a) HKR of epichlorohydrin with different loadings of Co(III)-salen-SbF<sub>6</sub> (**1c**) catalyst. Reaction conditions: Co(III)-salen-SbF<sub>6</sub> (**1c**) (0.50, 0.75, 1.00, and 2.25 mol%, respectively), 3 mmol racemic epichlorohydrin, distilled deionized water (0.7 eq., 126  $\mu$ L), 120  $\mu$ L chlorobenzene (as internal standard), room temperature. (b) Plot of ln *r* vs. ln [cat] showing the reaction order in concentration of Co(III)-salen-SbF<sub>6</sub> (**1c**) catalyst.

**Table 1**

Observed order of reaction with respect to catalyst concentration in the HKR of epichlorohydrin.

Catalyst	Counterion X	Order of reaction, <i>n</i> [catalyst] <sup>a</sup>
<b>1a</b>	Cl <sup>-</sup>	1.95 (1.97) <sup>a</sup>
<b>1b</b>	OAc <sup>-</sup>	1.26 <sup>a</sup>
<b>1c</b>	SbF <sub>6</sub> <sup>-</sup>	1.02

<sup>a</sup> Order when 2-propanol is used as a solvent.

Co(III)-salen-OH species. Thus, the orders of reaction with respect to catalyst concentration as reported in Table 1 are not true orders, but instead are *observed* orders of reaction that suggest a bimetallic or monometallic reaction path.

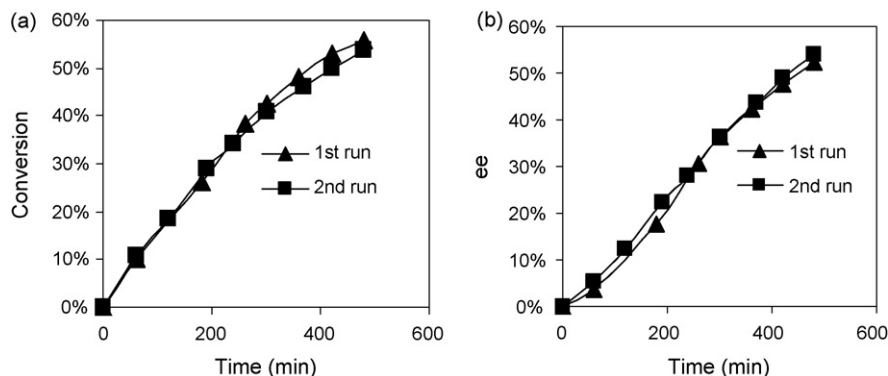
Under our standard reaction conditions, the observed order of reaction with respect to catalyst concentration for Co(III)-salen containing the highly nucleophilic chloride counterion was very nearly 2, which is consistent with the bimetallic HKR reaction mechanism as reported by Nielsen et al. [8]. For a catalyst containing the moderately nucleophilic acetate counterion, the reaction order was 1.26, suggesting neither the monometallic nor the bimetallic mechanism was the exclusive reaction path. Unfortunately, the fact that the catalyst is changing throughout the reaction prevents a more quantitative conclusion based on the data in hand. However, for the catalyst with SbF<sub>6</sub><sup>-</sup>, the reaction order was unity, which suggests the reaction path is exclusively monometallic.

The observed reactivity with Co(III)-salen-SbF<sub>6</sub> is interesting because there is conflicting information in the literature with regard to its reactivity. Kim et al. reported in 2003 that the Co(III)-salen-SbF<sub>6</sub> complex was active but relatively unselective [17]. Subsequently, Nielsen et al. suggested in a footnote that Co(III)-salen-SbF<sub>6</sub> was inactive when purified carefully [8]. To this end, we

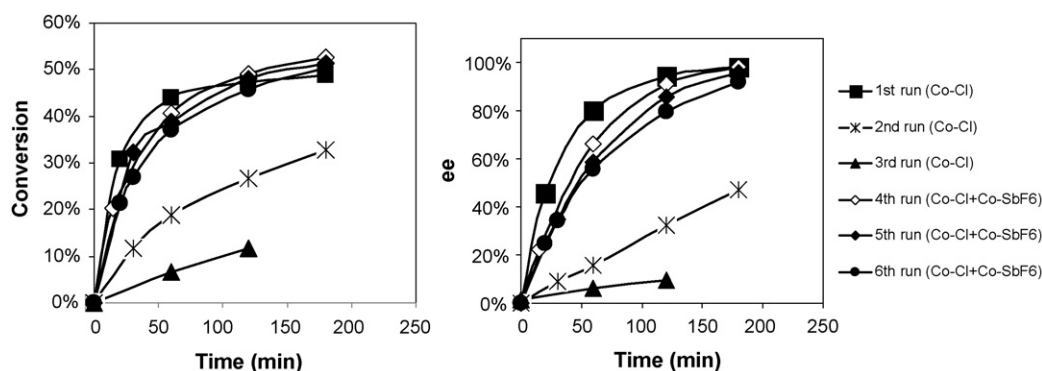
repeated our reactions with two different samples of Co(III)-salen-SbF<sub>6</sub> prepared in different ways. The original sample used was the product of oxidation of Co(II)-salen with AgSbF<sub>6</sub>, which was the same synthetic method used by Kim et al. [17] A second sample was made via the more laborious path used by Nielsen et al. converting Co(III)-salen-OTs to Co(III)-salen-Cl followed by counter ion exchange to Co(III)-salen-SbF<sub>6</sub>. [8] The Co(III)-salen-SbF<sub>6</sub> was characterized using different techniques including <sup>1</sup>H NMR, elemental analysis and single crystal X-ray diffraction. The molecular structure of Co(III)-salen-SbF<sub>6</sub> is given in the [supplementary material](#). Both the Co(III)-salen-SbF<sub>6</sub> catalysts behaved the same in the HKR of epichlorohydrin, leading us to conclude that the Co(III)-salen-SbF<sub>6</sub> complex is indeed active for the HKR reaction. Furthermore, the kinetic results suggest the reaction is first order with regard to the concentration of the cobalt complex (Fig. 1). For the reaction with 0.50 mol% catalyst loading, only 30 min was needed to reach 36% conversion and 59% ee of recovered S-epichlorohydrin with **1a**, whereas 4 h were needed to reach the same level of conversion and only 31% ee with **1c**. Thus, the monometallic path for HKR with Co(III)-salen-SbF<sub>6</sub> (**1c**) was not only less active, but also less selective compared to the bimetallic path presumably followed by the Co(III)-salen-Cl (**1a**), which is consistent with the suggestion by Ready and Jacobsen [5] that a hypothetical monometallic path has poor enantioselectivity. It should be noted that these are the first kinetic data that directly illustrate the presence of a monometallic pathway in the Co-salen catalyzed HKR reaction (upper pathway in Scheme 1).

## 2.2. Recycling Co-salen catalysts in the HKR of epichlorohydrin

The co-existence of two reaction paths (as described above) can now be used to reconcile the trends observed in activity



**Fig. 2.** Recycling of Co(III)-salen-SbF<sub>6</sub> in the HKR of epichlorohydrin (a) % conversion vs time and (b) % ee vs time. Reaction conditions: **1c** (0.5 mol%, 0.05 mmol, ~42 mg), (±) epichlorohydrin (10 mmol, 784  $\mu$ L), water (0.7 eq., 126  $\mu$ L), chlorobenzene was used as an internal standard (120  $\mu$ L), room temperature, 1st run was performed for 12 h.



**Fig. 3.** Recycling studies of Co(III)-salen-Cl in the HKR of epichlorohydrin followed by the addition of an equimolar amount of Co(III)-salen-SbF<sub>6</sub> catalyst. Reaction conditions: **1a** or **1c** (0.25 mol%, 0.025 mmol), (±) epichlorohydrin (10 mmol, 784 μL), water (0.7 eq., 126 μL), chlorobenzene as an internal standard (120 μL), room temperature. In the 4th run, 0.25 mol% (~21 mg) of Co(III)-salen-SbF<sub>6</sub> catalyst was added to the reaction mixture. The runs were performed for 8 h.

and recyclability with catalysts containing various counterions. As mentioned earlier, the loss of activity of these catalysts is the result of Co(III)-salen-OH formation during the HKR reaction [8,20]. The observed order of deactivation, Co(III)-salen-Cl > Co(III)-salen-OAc > Co(III)-salen-OTs, is related to the order of reactivity of the counterions with the epoxide to form the Co(III)-salen-OH species [20]. A catalyst such as Co(III)-salen-SbF<sub>6</sub> with a non-reactive counterion should therefore not suffer activity loss. To test this hypothesis, 0.5 mol% of catalyst **1c** (~42 mg) was recycled in the HKR of epichlorohydrin (10 mmol) using water (0.7 eq.) as the nucleophile. The reaction was performed for a period of 12 h followed by the evaporation of products under vacuum and addition of fresh reagents to the recovered catalyst to perform the 2nd run. The conversion and enantiomeric excesses of the residual epichlorohydrin for both runs are summarized in Fig. 2. As seen in the figure, approximately 41% conversion and 36% ee were obtained after 5 h reaction time with both fresh Co(III)-salen-SbF<sub>6</sub> catalyst (1st run) and the catalyst recycled after 12 h (2nd run). The negligible activity loss of this catalyst upon recycle is completely consistent with the proposed idea that the counterion addition to epoxide and subsequent formation of Co(III)-salen-OH causes catalyst deactivation [8].

In contrast to the Co(III)-salen-SbF<sub>6</sub> complex, the Co(III)-salen-Cl catalyst is quite active and selective, but undergoes substantial activity loss upon recycle by conversion to the OH<sup>-</sup> form throughout the reaction. Simple addition of Co(III)-salen-SbF<sub>6</sub> to the system containing Co(III)-salen-OH should promote the reaction via the bimetallic reaction path involving the OH<sup>-</sup> complex [8]. Therefore, the Co(III)-salen-Cl catalyst (**1a**) was recycled in the HKR of epichlorohydrin followed by the addition of Co(III)-salen-SbF<sub>6</sub> (**1c**) to the deactivated Co(III)-salen-Cl (which should be mostly Co(III)-OH at that point [8]) recovered after the HKR reaction. The recyclability of **1a** during HKR of epichlorohydrin is illustrated in the reaction profiles shown in Fig. 3, where 0.25 mol% of catalyst **1a** (~16 mg) was utilized in the HKR of (±) epichlorohydrin (10 mmol) using water (0.7 eq.) as a nucleophile. In the first run, 47% conversion and 94% ee were obtained after 2 h. After allowing the reaction to continue for a total of 8 h, products were removed under vacuum and fresh reagents were added to allow the 2nd run to be performed under similar reaction conditions.

In the 2nd run, the partially deactivated catalyst produced about 26% conversion and 33% ee after 2 h. After allowing the 2nd run to continue for 8 h, the catalyst was recycled again to allow the 3rd run of the HKR of epichlorohydrin to be performed under identical reaction conditions as those of the 1st and the 2nd runs. In the 3rd run, the catalyst was deactivated even more, producing only about 11% conversion and 10% ee after 2 h. After performing the 3rd run (for 8 h), the catalyst was recovered by removing

the products and residual reagents under vacuum. At this point, the inactive catalyst should be primarily Co(III) in the ineffective OH<sup>-</sup> form [8]. This inactive catalyst<sup>5</sup> should be useful in a reaction that follows the bimetallic reaction path (Scheme 1) as long as additional Co(III)-salen catalyst is added in a non-OH<sup>-</sup> form. The profile for the 4th run in Fig. 3 illustrates the high activity and selectivity of a reaction in which an equimolar amount of Co(III)-salen-SbF<sub>6</sub> **1c** (0.25 mol%, ~21 mg) was added to the deactivated catalyst obtained after the 3rd run using **1a**. Approximately 49% conversion and 91% ee were obtained after 2 h with the mixed catalyst system (4th run), results that were quite similar to the values obtained with 0.5 mol% of fresh Co(III)-salen-SbF<sub>6</sub> alone in 2 h. Evidently, the electronic structure around the Co metal center with an OH<sup>-</sup> counterion prevents significant participation in the monometallic path. These results are completely consistent with those of Nielsen et al. [8] who reported that the rate of the HKR increased substantially in a mixed catalyst system operating via the bimetallic mechanism. However, the Cl<sup>-</sup> form of Co-salen under their conditions with 1,2-epoxyhexane as substrate was proposed to undergo complete conversion to the OH<sup>-</sup> form very early in the reaction. The apparently slower replacement of Cl<sup>-</sup> with OH<sup>-</sup> during our studies illustrates the important role of the epoxide in determining the form of the catalyst. According to the above results, once Co(III)-salen-X (X = nucleophilic counterion such as Cl<sup>-</sup>, OAc<sup>-</sup>, OTs<sup>-</sup>) has converted to the OH<sup>-</sup> form, addition of Co(III)-salen-SbF<sub>6</sub> should create a system that does not deactivate significantly. Fig. 3 illustrates the repeated runs with a 50:50 mixture of deactivated Co(III)-salen-Cl with Co(III)-salen-SbF<sub>6</sub> (runs 5 and 6). The system was quite stable since the non-nucleophilic SbF<sub>6</sub><sup>-</sup> counterion does not react with epichlorohydrin. These results suggest a possible catalyst design strategy for enhanced durability under recycling conditions. Recent works by several groups have shown how immobilizing Co(III)-salen in flexible oligomers or on solid supports can dramatically enhance the reaction rate by facilitating the bimetallic reaction path [4,5,9,10,12,13,21,22]. However, these systems still lose activity by counterion replacement as described above. The results of the current study as well as those of Nielsen et al. [8] suggest that a mixed catalyst containing both nucleophilic and non-nucleophilic counterions (such as SbF<sub>6</sub><sup>-</sup>) could provide a new highly active HKR system, where the catalyst can be repeatedly recycled without suffering from loss in the activity and selectivity.

<sup>5</sup> The Co(III)-salen-OH catalyst should be essentially inactive when it is present alone without any other Co(III)-salen-X where X is for example, Cl<sup>-</sup>, OAc<sup>-</sup>, etc., according to Ref. [8].

### 2.3. Effect of acetic acid regeneration on Co-salen

A common method to overcome loss in activity of Co(III)-salen-X catalyst systems that contain a single type of counterion is to regenerate the catalysts after each run. Indeed, Co(III)-salen-OAc is commonly regenerated after reaction by subsequent treatment with acetic acid in air. This may accomplish two goals, replacement of OH<sup>-</sup> counterions with OAc counterions in Co(III)-salen-X complexes as well as reoxidation of Co(II)-salen complexes to Co(III)-salen-X complexes, should any reduction of the cobalt occur during the reaction or workup. Recently, Gill et al. [13] reported the insoluble silica supported polymeric Co(III)-salen-OAc complexes deactivated on repeated recycling with intermediate acetic acid regeneration. In addition to metal leaching, polymer loss and counterion exchange, salen ligand decomposition was observed to be an underlying cause of deactivation in their system. They speculated that cleavage of the imine bonds in the salen ligand might have occurred in the presence of water and acetic acid used for regeneration. It should be noted that this observation contrasts previous reports that suggest that catalysts can be recycled with intermediate acetic acid regeneration without loss of activity<sup>6</sup> [23]. Such observations led us to evaluate deactivation pathways that may be associated with the regeneration process.

In this work, as in the work of Gill et al. [13], we also observed a small peak near 10.29 ppm in the <sup>1</sup>H NMR spectrum of the deactivated molecular Co(III)-salen catalyst recovered after the HKR reaction, which is a characteristic of an aldehyde proton. The presence of this peak suggests partial decomposition of the salen ligand in the HKR of epichlorohydrin, which may also account for some part of the catalyst deactivation. To further study the modes of activity loss in the Co(III)-salen-X system, we performed multiple recycles of the catalyst **1b** in the HKR of epichlorohydrin with intermediate acetic acid regeneration. In addition, catalyst **1c** was also recycled repeatedly under identical reaction conditions without intermediate regeneration. Since the Co(III)-salen-SbF<sub>6</sub> complex did not lose activity in the HKR reaction (Fig. 2), recycling of Co(III)-salen-SbF<sub>6</sub> served as a control experiment to investigate whether catalyst decomposition occurred during the HKR reaction or during the regeneration step.

1 mol% of Co(III)-salen-OAc catalyst **1b** was utilized in the HKR of epichlorohydrin. In the first run, almost 52% conversion and >99% ee were obtained in about 30 min. After performing the reaction for about 75 min, the products were removed under vacuum and the catalyst was regenerated with acetic acid/dichloromethane mixture (stirring in air for 30 min) prior to re-use. In a similar manner, the catalyst was recycled five times after the HKR of epichlorohydrin with intermediate acetic acid regeneration after every run. Although the enantioselectivity was retained after the five recycles, the catalytic activity decreased, i.e. it took longer reaction times to achieve >99% ee. The initial turnover frequency (TOF) in the first run was 6.45 min<sup>-1</sup>, which decreased to 2.67 min<sup>-1</sup> in the 6th run. The values of initial TOF's for the six runs are summarized in Table 2.

The first few runs illustrate the reproducibility of the process and the efficacy of the regeneration treatment. However, the later runs (runs 4–6) clearly show a loss in activity. To explore the reason for the decrease in TOF even after acetic acid regeneration, Co(III)-salen-SbF<sub>6</sub> catalyst **1c** was repeatedly recycled without intermediate regeneration under similar reaction conditions as those used for Co(III)-salen-OAc catalyst **1b**. Thus, 1 mol% of catalyst **1c** was utilized in the HKR of epichlorohydrin. After running the reaction for a period of 8 h, all residual reagents and products

**Table 2**

Influence of catalyst recycling on the initial TOF of the homogeneous Co(III)-salen-OAc catalyst (**1b**) in the HKR of epichlorohydrin with 2-propanol solvent and with intermediate acetic acid regeneration.

Run	Initial TOF (min <sup>-1</sup> )
1	6.4
2	6.6
3	5.8
4	4.4
5	3.2
6	2.7

**Table 3**

Influence of catalyst recycling on the initial TOF of Co(III)-salen-SbF<sub>6</sub> catalyst (**1c**) in the HKR of epichlorohydrin without intermediate regeneration.

Run	Initial TOF (min <sup>-1</sup> )
1	0.25
2	0.23
3	0.23
4	0.24

were removed under vacuum and catalyst was recycled in the 2nd run. In a similar manner, a total of four runs were performed. In all four runs, there was negligible loss in catalyst activity, which is consistent with the stable monometallic path mentioned above when using Co(III)-salen-SbF<sub>6</sub> as a catalyst. The conversion versus time data for the four runs are shown in supporting information. This stability is associated with the non-nucleophilicity of the SbF<sub>6</sub><sup>-</sup> counterion as well as the absence of the application of any regeneration process.

Although the calculated TOFs using the Co(III)-salen-SbF<sub>6</sub> catalyst (**1c**) (summarized in Table 3) were lower than those of the Co(III)-salen-OAc catalyst (**1b**), the SbF<sub>6</sub><sup>-</sup> catalyst was quite stable to repeated recycling without regeneration. Thus, the decrease in TOF of Co(III)-salen-OAc (**1b**) after acetic acid regeneration is likely the result of catalyst decomposition in the presence of acetic acid (and trace water), consistent with the results reported by Gill et al. [13] These observations contrast previous reports that suggest the Co(III)-salen-OAc catalyst can be recycled without activity loss if regenerated, with most reports not including kinetic plots of reaction recycles [9,23]. It appears under our conditions that regeneration leads to stable activity for only a few cycles. These results indicate a very important principle regarding the stability of Co(III)-salen-X catalysts for long term use. Since intermediate regeneration of used catalysts can lead to irreversible activity loss after multiple recycles, the best strategy for prolonging catalyst lifetime is to prepare the mixed Co(III)-salen-X system containing both nucleophilic and non-nucleophilic X counterions. These very active mixed counterion systems do not require intermediate regeneration (see Fig. 3).

### 3. Conclusions

Activity loss upon recycling Co(III)-salen-X catalysts containing nucleophilic X counterions such as Cl<sup>-</sup> and OAc<sup>-</sup> was primarily the result of forming excess Co(III)-salen-OH. For a Co(III)-salen-OAc catalyst, the activity could be initially recovered by regeneration with acetic acid treatment, but the catalyst was eventually deactivated irreversibly by the treatment conditions. Addition of an equimolar amount of Co(III)-salen-SbF<sub>6</sub>, where SbF<sub>6</sub> represents a suitable non-nucleophilic counterion, to in situ generated Co(III)-salen-OH, produced a mixed catalyst system that was recycled without significant loss in activity or selectivity. The mixed Co-salen system was the preferred form of the catalyst since it avoided

<sup>6</sup> The catalyst could be recycled with constant reaction selectivity and yield. Kinetic data were not presented, so reaction rates cannot be directly inferred.

the need for intermediate regeneration and thus catalyst decomposition.

## 4. Experimental section

### 4.1. General

Reagents were used as received unless otherwise noted.  $^1\text{H}$  spectra were acquired with a Varian Mercury 400 MHz spectrometer, and chemical shifts were reported in ppm with reference to the corresponding residual nuclei of the deuterated solvents. Enantiomeric excesses were determined by capillary gas-phase chromatography (GC) analysis on a Shimadzu GC 14A instrument equipped with a FID detector and a ChiralDex  $\gamma$ -TA column (40 m  $\times$  25 mm  $\times$  0.25  $\mu\text{m}$ ). Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN).

For single crystal X-ray diffraction, a suitable crystal of **1c** was coated with Paratone N oil, suspended in a small fiber loop, and placed in a cooled nitrogen gas stream at 173 K on a Bruker D8 APEX II CCD sealed tube diffractometer with graphite monochromated  $\text{MoK}\alpha$  (0.71073 Å) radiation. Data were measured using a series of combinations of phi and omega scans with 10 s frame exposures and 0.5° frame widths. Data collection, indexing and initial cell refinements were carried out using APEX II software [24]. Frame integration and final cell refinements were done using SAINT software [25]. The final cell parameters were determined from least-squares refinement on 3626 reflections. The structure was solved using Direct methods and difference Fourier techniques (SHELXTL, V6.12) [26]. Hydrogen atoms were placed in their expected chemical positions using the HFIX command and were refined as riding atoms. All non-hydrogen atoms were refined anisotropically except the cyclohexyl group which was disordered. The cyclohexyl group was split over two positions and refined isotropically.

### 4.2. Catalyst preparation

#### 4.2.1. Synthesis of Co(III)-salen-Cl catalyst (**1a**)

The catalyst (**1a**) was synthesized as previously reported [8]. 2.5 g of Co-salen-OTs was dissolved in 100 mL dichloromethane in a 500 mL separatory funnel. The organic layer was then rinsed with saturated aqueous NaCl solutions (3  $\times$  100 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated in rotary evaporator. The residue was then re-suspended in pentane and vacuum filtered to produce a very dark green material. Elemental analysis for  $\text{C}_{37}\text{H}_{55}\text{O}_2\text{ClCoN}_2$ , calcd: C 67.93, H 8.47, N 4.28, Co 9.01, Cl 5.42 found C 67.25, H 8.12, N 4.37, Co 9.67, Cl 5.85.

#### 4.2.2. Synthesis of Co(III)-salen-OAc catalyst (**1b**)

A solution of Co(II) salen catalyst (400 mg) was dissolved in dichloromethane (13 mL) in a 25 mL round bottom flask after which glacial acetic acid (as received from Aldrich, 10 eq. with respect to catalyst, 382.5  $\mu\text{L}$ ) was added via a micro liter pipette. After stirring the mixture with a teflon stir bar for about 45 min, dichloromethane was removed with a rotovap and the excess acetic acid was removed under vacuum. The resulting catalyst **1b** was a dark brown residue used for reactions.

#### 4.2.3. Synthesis of Co(III)-salen-SbF<sub>6</sub> (**1c**)

The catalyst (**1c**) was synthesized as previously reported [17]. To a solution of  $\text{AgSbF}_6$  (0.48 g, 1.39 mmol) in dichloromethane (5 mL) was added Co(II) salen (**1**) (0.84 g, 1.39 mmol) in dichloromethane (10 mL) (the flask was wrapped with aluminum foil). The color of the solution turned green within a few seconds followed by precipitates of silver. The solution was stirred for 2 h, filtered through a frit that was loaded with celite (the filtration process was carried

out twice). The solvent was removed using rotovap and the solid was dried under vacuum for 4 h to get dark green solid. The green solid was crystallized using dichloromethane and heptane at low temperature. Yield: 1.0 g (86%). The crystallized material was characterized using single crystal X-ray crystallography and  $^1\text{H}$  NMR (400 MHz,  $(\text{CD}_3)_2\text{SO}$ , 25 °C)  $\delta$  7.80 (s, 2H), 7.45 (d,  $J$  = 2.4 Hz, 2H), 7.42 (d,  $J$  = 2.8 Hz, 2H), 3.59–3.57 (m, 2H), 3.06–3.03 (m, 2H), 2.00–1.98 (m, 2H), 1.90–1.87 (m, 2H), 1.72 (s, 18H), 1.59–1.54 (m, 2H), 1.28 (s, 18H). The crystallized material was used for kinetic studies.

#### 4.2.4. Hydrolytic kinetic resolution (HKR) of epichlorohydrin

Various loadings of Co-salen catalysts (**1a–1c**) (0.1–2 mol%) were dissolved in racemic epichlorohydrin (as received from Acros, 10 mmol, 784  $\mu\text{L}$ ) in a 100 mL reaction flask immersed in a temperature controlled water bath ( $\sim$ 300 K). An internal standard chlorobenzene (as received from Sigma–Aldrich, 120  $\mu\text{L}$ ) and co-solvent 2-propanol (as received from Acros, 1 eq., 760  $\mu\text{L}$ ) were added to the reaction mixture via a micro liter pipette. One aliquot (1–2  $\mu\text{L}$ ) of the reaction mixture was taken before starting the reaction, passed through a Pasteur pipette plugged with silica gel and diluted with diethyl ether ( $\sim$ 1–1.5 mL). Distilled, deionized water (0.7 eq., 126  $\mu\text{L}$ ) was then added to the mixture to start the HKR reaction. Approximately 1–2  $\mu\text{L}$  samples were withdrawn periodically, passed through a Pasteur pipette 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.

### 4.3. Catalyst recycling

The recycling studies were performed on various homogeneous Co-salen catalysts (**1a–1c**) with or without intermediate regeneration of the catalyst. After performing the HKR reaction for a period of 8–12 h, all of the reaction products were removed by evacuation (epoxide was removed at room temperature,  $\sim$ 300 K, and diol was removed at a temperature of 323–329 K). Fresh reagents were then added to the recovered catalyst and a 2nd run was performed. In a similar manner, the catalyst was recycled again to perform subsequent runs. In some cases, catalyst **1b** was recycled with intermediate regeneration, where the recovered catalyst was treated with an acetic acid/dichloromethane mixture prior to re-use.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2009.10.025.

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