

# Mechanistic Factors Influencing Recyclability of Co-Salen Catalysts in the Hydrolytic Kinetic Resolution of Epichlorohydrin

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## Introduction

The hydrolytic kinetic resolution (HKR) of racemic terminal epoxides using Co-salen catalysts provides a convenient route to the synthesis of enantioenriched chiral compounds by selectively converting one enantiomer of the racemic mixture with a maximum yield of 50% and enantiomeric excess (ee) of >99%. The proposed mechanism of HKR 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) [1]. With this bimetallic mechanism of HKR, researchers have developed multimeric Co-salen catalysts that exhibit activities 1-2 orders of magnitude greater than that of the monomeric Co-salen catalyst [2]. The general mode of catalyst deactivation in the HKR has been reported to be the change of the active Co(III) salen complex to an inactive Co(II) salen complex [3].

In this work, possible modes of deactivation of homogeneous Jacobsen's Co-salen catalyst during the HKR of epichlorohydrin were explored by UV-Vis, IR and X-ray absorption spectroscopies, and electrospray ionization mass spectrometry (ESI-MS) combined with catalyst recycling studies. In addition, the role of the Co-salen counterion on the HKR reaction mechanism, catalytic activity, enantioselectivity and stability was explored. Different counterions with varying nucleophilicities were used to elucidate when a bimetallic or monometallic transition state is formed during the HKR of a terminal epoxide and how the nature of the reaction path (mono vs bimetallic) affects the observed catalyst lifetime.

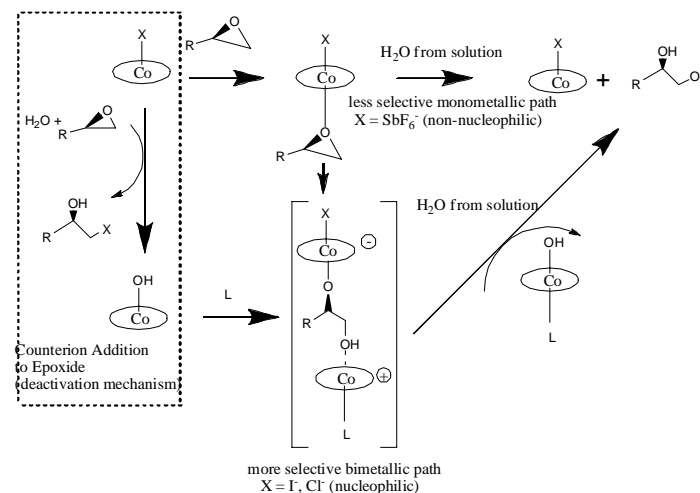
## Materials and Methods

Approximately 0.5 mol% of various R,R-Jacobsen's Co(III)-salen catalysts containing different counterions such as I<sup>-</sup>, Cl<sup>-</sup>, OAc<sup>-</sup>, OTs<sup>-</sup> and SbF<sub>6</sub><sup>-</sup> were recycled in the HKR of epichlorohydrin (10 mmol, as received from Acros) using water (0.7 eq.) as a nucleophile. The percent conversion and ee were monitored with time using GC-FID. The oxidation state of the catalyst before, during and after the HKR reaction was measured with UV-Vis and XANES spectroscopies. Catalyst dimerization was probed by ESI-MS. The influence of the Co-salen counterion on the HKR reaction mechanism and catalyst recyclability was evaluated by performing kinetic studies and catalyst characterization with <sup>1</sup>H NMR and IR spectroscopy.

## Results and Discussion

Although an active homogeneous, molecular Co(III) salen catalyst lost substantial activity after multiple cycles without regeneration, neither reduction to +2 form nor catalyst

dimerization was observed. Results from catalyst pretreatment tests as well as studies with catalysts containing various counterions indicated that the rate of addition of the counterions to the epoxide correlated with the loss in catalyst activity. As elucidated by Nielsen et al. [1], the nature of the counterion determined whether the HKR reaction followed a bimetallic or monometallic reaction path (see Figure 1). For example, Co(III)-salen with the nucleophilic Cl<sup>-</sup> counterion catalyzed the HKR of epichlorohydrin with a bimetallic transition state and deactivated rapidly as Cl<sup>-</sup> was replaced with OH<sup>-</sup> during the reaction. A Co(III)-salen catalyst with non-nucleophilic SbF<sub>6</sub><sup>-</sup> counterion catalyzed the reaction at a low rate via a monometallic transition state, but it exhibited a much longer lifetime. Multiple regenerations of an acetate-containing catalyst eventually caused irreversible loss in activity. A mixed catalyst system with both nucleophilic and non-nucleophilic counterions showed the greatest potential for activity and stability, as indicated by Nielsen et al. [1].



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

## Significance

The fundamental modes of catalyst deactivation outlined in this work impact the discovery and design of new oligomeric and multimeric solid-supported Co-salen systems for the production of fine chemicals and pharmaceutical intermediates.

## References

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