Asymmetric Ring Opening of Terminal Epoxides via Kinetic Resolution Catalyzed by Chiral (Salen)Co Mixture¹

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Abstract—The highly enantioselective hydrolytic kinetic resolution (HKR) of racemic terminal epoxides by bimetallic chiral (salen)Co and (salen)Co(III)-OAc mixture provides a simple and effective method for the synthesis of enantiomerically enriched terminal epoxides (ee > 99%) and diols. At the equimolar amounts of bimetallic chiral (salen)Co and (salen)Co(II)-OAc, the catalytic activity increases more than two times in comparison with (salen)Co(III)-OAc used alone. The mixed catalytic system can be recycled and reused. No significant loss of catalytic activity was observed after three runs.

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Terminal epoxides are very important subclass of epoxides for organic synthesis [1]. The stereoselective synthesis of chiral terminal epoxide is of immense academic and industrial interest [2]. Hydrolytic kinetic resolution (**HKR**) provides very efficient, scalable and practical manner to prepare stereochemically enriched terminal epoxides [3–8]. Researchers have noted significant increase in activity using multiple (salen)Co oligomeric, dendritic, and polymeric catalysts for heterogenization of the expensive (salen)Co(III) catalysts to aid in their recovery and reuse [9]. A variety of methods have been introduced including ship-in-a-bottle synthesis, grafting to silica, membrane reactors, ionic liquids, and fluorous systems [9].

A lot of research on mechanism has been carried out, including the break through understanding of the reaction mechanism which came in collaborative work [5]. The authors showed that the kinetics of the reaction was consistent with the participation of two types of (salen)Co(III) complexes, one with a counterion X^- introduced at the start of the reaction (X = Cl⁻, OAc⁻ (acetate), OTs⁻ (tosylate), SbF₆⁻, etc.) and other Co(III)–OH, that is generated in situ via counterion addition to the epoxide.

Considering the catalyst deactivation, Jain et al. [10] showed that the highest rates occurred when the relative amounts of (salen)Co(III)–X and (salen)Co(III)–OH were equal. As a result, the use of (salen)Co(III) 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. Davis et al. [11] showed

that for the HKR of racemic epichlorohydrin, the counterion of the (salen)Co(III) catalyst is of great importance. The nature of the counterion determines whether the HKR reaction follows primarily a bimetallic or monometallic reaction path, which significantly affects the recyclability of the catalyst. Density functional theory calculations were also used to study the cooperative activations of the epoxide ring opening hydrolysis catalyzed by the Co-salen complexes [12]. It is found that the activation energies of the reactions with two Co-salen catalysts are significantly lower than those with single catalyst. The cooperation effect comes not only from the simultaneous activation of both reactants but also from the cooperative charge transfer during the reactions. The transition states analysis indicates that the preferential reaction pathway is a $S_N 2$ reaction.

It can be seen that asymmetric ring opening of terminal epoxides via kinetic resolution is quite mature. However, as far as we know, (salen)Co(III)-OAc catalyst is still the only catalyst in industrial application. The reason is that some catalysts have high activity, but are very difficult to prepare. This is one of the largest obstacles in industrial applications.

Working further with this idea, we thought that (salen)Co(III)-OAc(1) and an easily synthesized bimetallic complex 2 mixture might provide a better catalyst that would exhibit high activity and enantiose-lectivity. The mixture shows enhanced reactivity and may be employed at substantially lower loadings than its monomeric analogue 1 without suffering any solubility problems and diminished catalytic activity.

¹ The article is published in the original.



EXPERIMENTAL

Synthesis of (salen)Co(III)-OAc Catalyst (1)

The catalyst **1** was synthesized as reported previously [3]. A solution of (salen)Co(II) catalyst (6.95 g, 0.01 mol) was dissolved in dichloromethane (130 ml) in a 250 ml round bottom flask, then glacial acetic acid(1.2 g, 0.02 mol) was added by 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 of acetic acid was removed under vacuum. The resulting dark brown residue of catalyst **1** was used for reactions.

Synthesis of Bimetallic (salen)Co Complexes

The catalysts **2** were synthesized as reported previously [1]. Typically, to a solution of anhydrous $ZnCl_2$ (13.6 g, 0.1 mol) in dichloromethane (50 ml) (salen)Co(II) (1) (6.95 g, 0.01 mol) in dichloromethane (100 ml) (the flask was wrapped with aluminum foil) was added. The colour of the solution turned dark within a few seconds. 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 solid.

Hydrolytic Kinetic Resolution of Epichlorohydrin

Various loadings of (salen)Co catalysts mixture (0.1-2 mol %) were dissolved in 1 mol racemic epichlorohydrin (**ECH**) and 500 ml tetrahydrofuran in a 1000 ml reaction flask immersed in a temperature controlled water bath (293 K). Chlorobenzene as internal standard was added to the reaction mixture. Distilled, deionized water (0.55 equivalents) was then added to the mixture to start the HKR reaction. Approximately 0.5 ml sample was withdrawn periodi-

cally, passed through a Pasteur pipette plugged with silica gel. Reaction products were analyzed by gas chromatography using GAMMA DEXTM 225 capillary column and FID detector. The conversion and enanthiomeric excess (*ee*) of the recovered epoxide were monitored as a function of time.

Catalyst Recycling

The recycling studies were performed on various homogeneous (salen)Co catalysts mixture without intermediate regeneration of the catalyst. After performing the HKR reaction for a period of 3-5 h, solvent and all reaction products were removed by reduced pressure distillation in 0.5-1 h. 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.

RESULTS AND DISCUSSION

Catalysts Characterization

Infrared spectroscopy was used to characterize the mixture. All samples were dried sufficiently under the vacuum and heating, the infrared spectra are shown in Fig. 1.

The characteristic band of Schiff base corresponds to the ligands in the absorption range of $1610-1635 \text{ cm}^{-1}$ due to the imine group. (Salen)Co(III)-OAc and (salen)Co–ZnCl₂ show absorption bands at 1608 and 1633 cm^{-1} , (salen)Co(III)-OAc and (salen)Co–FeCl₃ exhibit absorption bands at 1609 and 1631 cm^{-1} , however (salen)Co–SnCl₄ and (salen)Co–AlCl₃ demonstrate absorption bands at 1610 and 1625 cm^{-1} . Experimentally, (salen) Co(III)-OAc and (salen)Co–ZnCl₂ or (salen)Co–FeCl₃ proved superior for the kinetic resolution of terminal epoxides, thus activity is structure-dependent.



Fig. 1. Infrared spectra of bimetallic (salen)Co and (salen)Co(III)-OAc mixture: (a) (salen)Co(III)– $ZnCl_2$, (b) (salen)Co(III)– $FeCl_3$, (c) (salen)Co(III)– $SnCl_4$, (d) (salen)Co(III)– $AlCl_3$.

According to the literature, H_2 -salen exhibits a broad band absorption at 3300–3400 cm⁻¹ due to the phenolic OH group [12]. In this study, this band is not observed in the spectra of the corresponding (salen)Co(III)-OAc and bimetallic (salen)Co catalysts, which suggests that there is no phenolic OH group in the complexes. This corresponds to the loss of hydrogen bonding and the formation of a new chelate ring between the imine nitrogens and the cobalt atom.

There are many dates in the literature on the catalysts (salen)Co(III)-OAc, (salen)Co–ZnCl₂, (salen)Co– FeCl₃, (salen)Co–SnCl₄, and (salen)Co–AlCl₃ used alone [13]. Terminal epoxides reacted readily with water alone in the presence of (salen)Co catalysts. The solvent-free reaction of racemic ECH (1.0 mol) with 0.55 equivalent of water in the presence of 0.2 mol % of (salen)Co(III)-OAc complex (1) proceeded within 12 h at room temperature to afford a mixture of unreacted epoxide and propylene glycol [3]. At 20°C, with the water equivalent of 0.55, and the catalyst concentration of 0.25 mol %, the activity of (salen)Co–ZnCl₂, (salen)Co–FeCl₃, (salen)Co–SnCl₄, and (salen)Co– AlCl₃ was better than that of (salen)Co(III)-OAc, and the *ee* of the (*S*)-epichlorohydrin could reach 99.0% in 10 h [13]. Here we have mixed these two kinds of catalyst in the mole ratio of 1 : 1.

Recycling (salen)Co(III)-OAc and Bimetallic Chiral (salen)Co Catalysts in the HKR of Epichlorohydrin

(Salen)Co(III)-OAc and bimetallic chiral (salen)Co catalysts mixtures were evaluated in the HKR of epichlorohydrin (Figs. 2-5). A slight difference in activity was observed between these mixtures. For the homogeneous (salen) Co(III)-OAc and (salen)Co-ZnCl₂ (Fig. 2) or (salen)Co-FeCl₃ (Fig. 3) catalysts mixture at 0.25 mol % loading after 150 min, enantiomeric excesses surpassed 99%. However, when (salen)Co-SnCl₄ and (salen)Co-AlCl₃ were used, it was difficult to get the ee 99% at 3 h (Figs. 4 and 5). These results were similar to that when bimetallic chiral (salen)Co was used alone [13]. The activity of the homogeneous catalyst improved. The activity loss upon recycling was primarily due to the forming small quantity of (salen)Co(III)-OH. For (salen)Co(III)-OAc catalyst, the activity could be initially recovered by



Fig. 2. Recycling (saIen)Co(III)-OAc + (salen)Co–ZnCl₂ (equimolar amounts). Reaction conditions: amounts of **1** and **2a** 0.0025 mol (0.25 mol %), (±)-epichlorohydrin—1 mol, water—0.55 mol, chlorobenzene as internal standard (12 ml), temperature 298 K.



Fig. 3. Recycling (salen)Co(III)-OAc + (salen)Co–FeCl₃ (equimolar amounts). Reaction conditions: amounts of **1** and **2b**— 0.0025 mol (0.25 mol %), (\pm)-epichlorohydrin—1 mol, water—0.55 mol, chlorobenzene as internal standard (12 ml), temperature 298 K.



Fig. 4. Recycling (salen)Co(III)-OAc + (salen)Co–SnCl₄ (equimolar amounts). Reaction conditions: amounts of **1** and **2c**—0.0025 mol (0.25 mol %), (\pm)-epichlorohydrin—1 mol, water—0.55 mol, chlorobenzene as internal standard (12 ml), temperature 298 K.

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ASYMMETRIC RING OPENING OF TERMINAL EPOXIDES

HKR of epoxides catalyzed by chiral (salen)Co(III)-OAc and bimetallic chiral (salen)Co catalysts

$$R^{0} + H_{2}O \xrightarrow{Catalyst}_{rt, 3h} R^{0} + R^{O}$$

Entry	R	Catalyst	1 : 2 ratio	Solvent	Epoxide		Diol		$k \times 10^{3} d$,
					Yield ^a ,%	ee ^b , %	Yield ^a , %	ee ^c , %	$1 \mathrm{mol}^{-1}\mathrm{s}^{-1}$
1	CH ₂ Cl	1 + 2a	1:2	THF	44	97	43	96	16.5
2	CH ₂ Cl	1 + 2b	1:2	THF	45	98	44	95	16.1
3	CH ₂ Cl	1 + 2c	1:2	THF	45	95	42	93	14.6
4	CH ₂ Cl	1+2d	1:2	THF	44	96	42	94	13.2
6	CH ₂ Cl	1 + 2a	1:3	THF	43	97	43	94	11.7
7	CH ₂ Cl	1 + 2b	1:3	THF	42	98	45	94	11.5
8	CH ₂ Cl	1 + 2c	1:3	THF	44	94	43	95	11.2
9	CH ₂ Cl	1+2d	1:3	THF	40	89	41	95	10.9
10	CH ₂ Cl	1 + 2a	1:1	None	41	90	41	93	3.56
11	CH ₃	1 + 2a	1:1	THF	43	98	44	95	19.8
12	CH ₃	1 + 2b	1:1	THF	44	99	42	96	19.0
13	CH ₃	1 + 2c	1:1	THF	45	96	41	92	16.2
14	CH ₃	1 + 2d	1:1	THF	41	97	42	91	16.3
15	CH ₃	1 + 2a	1:1	CH_2Cl_2	42	89	43	95	7.0
16	CH ₃	1 + 2a	1:1	None	42	90	44	93	6.8
17	PhOCH ₂	1 + 2a	1:1	THF	44	99	43	96	6.3
18	PhOCH ₂	1+2b	1:1	THF	43	98	44	95	5.7
19	PhOCH ₂	1 + 2c	1:1	THF	44	97	43	93	5.6
20	PhOCH ₂	1 + 2d	1:1	THF	42	97	43	92	5.4
21	PhOCH ₂	1 + 2a	1:1	CH_2Cl_2	40	90	46	91	0.8
22	PhOCH ₂	1 + 2a	1:1	None	41	90	47	89	0.6
23	CH ₂ Cl	1	-	THF	44	93	45	92	8.9
24	CH ₃	1	-	THF	43	91	44	89	3.3
25	PhOCH ₂	1	-	THF	44	92	43	91	2.5

^a The isolated yield of the epoxide and diol is based on the racemic epoxide added.

^b *ee* values were determined by the next ways: propylene oxide – GC analysis using chiral capillary column (γ -cyclodextrin trifluoroacetyl) 40 m × 0.25 mm (i.d.); epichlorohydrine – GC analysis using chiral capillary column (Gamma-225) 30 m × 0.25 mm (i.d.); phenyl glycidyl ether – HPLC analysis using a chiral OD-H column (hexanes : *i*-PrOH = 90 : 10, 1 ml/min, 254 nm).

^c Determined by capillary GC analysis of the isolated product on a HP Chiral-20% permethylated β -cyclodextrin column.

^d Reaction rate constants were obtained from the plots of $\ln[epoxide]/[epoxide]_0$ versus time and calculated by dividing the slopes by the absolute concentration of catalyst.

regeneration with acetic acid treatment, but the catalyst was eventually deactivated irreversibly in this treatment conditions. Addition of an equimolar amount of bimetallic chiral (salen)Co, where Lewis acid may represent a suitable non-nucleophilic counterion, to in situ generated (salen)Co(III)-OH produced a mixed catalyst system that was recycled without significant loss in activity or selectivity. The mixed (salen)Co system was the preferred form of the catalyst since it avoided the need for intermediate regeneration and thus catalyst decomposition.

(Salen)Co (III)-OAc and Bimetallic (salen)Co Catalysts in the HKR of Epoxides

(Salen)Co(III)-OAc and bimetallic (salen)Co in the ratio of 1:2 or 1:3 displayed relatively poor activity in the HKR. As demonstrated the data in entries 1-



Fig. 5. Recycling (salen)Co(III)-OAc + (salen)Co–AlCl₃ (equimolar amounts). Reaction conditions: amounts of **1** and **2d**— 0.0025 mol (0.25 mol %), (\pm)-epichlorohydrin—1 mol, water—0.55 mol, chlorobenzene as internal standard (12 ml), temperature 298 K.

10 (see the table), 1,2-diols and epoxy compounds were synthesized in relatively poor yield and optical purity. It is noteworthy that *ee* values in entries 1-10 are 2-3% smaller than at the ratio of 1:1.

The identity of the counterions in the catalysts was revealed to be a critical parameter for attainment of high enantioselectivity and reaction rates. (Salen)Co(III)-OAc and (salen)Co–ZnCl₂ or (salen)Co–FeCl₃ proved superiority relative to (salen)Co–SnCl₄ or (salen)Co–AlCl₃ in the kinetic resolution of terminal epoxides. They were found to display activity in the HKR of terminal epoxides about two times in comparison with (salen) Co(III)-OAc used alone.

The results of entries 11-16 with propylene oxide highlight the practical aspects of reactions using (salen)Co(III)-OAc and (salen)Co-ZnCl₂ or (salen)Co(FeCl₃) catalyst to provide recovered epoxide *ee* 98–99% and diol *ee* 95–96%.

As demonstrated the data in entries 17-22, styrene oxide and styrenediol were obtained with high yield and enantiomeric excess of epoxide and diol after 3 h using 0.25 mol % Co was 90–99% and 89–96%, respectively.

The use of tetrahydrofurane in the HKR of epoxides offers the advantage in comparison with CH_2Cl_2 or without solvent (cp. entries 11 and 15, 16; 20, 21 and 22).

So, the HKR provides straightforward and one pot synthesis of chiral building blocks. The catalyst can be synthesized easily and recycled up to three cycles without noticeable loss in enantioselectivity. Using equimolar amounts of bimetallic chiral (salen)Co and (salen)Co(III)-OAc increases the catalytic activity more than two times relative to (salen)Co(III)-OAc used alone. Catalytic system can be recycled and reused for three runs without any significant loss of catalytic activity. It is expected that this catalyst can also be used as a general catalyst for the asymmetric ring opening of terminal epoxide with H_2O and other nucleophiles.

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REFERENCES

- 1. Jiang, C.J. and Chen, Z.R., *Kinet. Catal.*, 2008, vol. 49, p. 447.
- Ready, J.M. and Jacobsen, E.N., J. Am. Chem. Soc., 2001, vol. 123, p. 2687.
- 3. Tokunaga, M., Larrow, J.F., Kakiuchi, F., and Jacobsen, E.N., *Science*, 1997, vol. 277, p. 936.
- Furrow, M.E., Schaus, S.E., and Jacobsen, E.N., J. Org. Chem., 1998, vol. 63, p. 6776.
- Nielson, L.P.C., Stevenson, C.P., Backmond, D.G., and Jacobsen, E.N., *J. Am. Chem. Soc.*, 2004, vol. 126, p. 1360.
- Kawthekar, R.B., Bi, W.T., and Kim, G.J., *Appl. Organomet. Chem.*, 2008, vol. 22, p. 583.
- Song, Y.M., Yao, X.Q., Chen, H.L., Bai, C.M., Hu, X.Q., and Zheng, Z., *Tetrahedron Lett.*, 2002, vol. 43, p. 6625.
- Aertsa, S., Buekenhoudta, A., Weytena, H., Vankelecomb, I.F.J., and Jacobs, P.A., *Tetrahedron: Asymmetry*, 2005, vol. 16, p. 657.
- Jiang, C.J. and Chen, Z.R., *Prog. Chem.*, 2008, vol. 20, p. 1294.
- 10. Jain, S., Zheng, X.L., and Jones, C.W., *Inorg. Chem.*, 2007, vol. 46, p. 8887.
- 11. Jain, S., Venkatasubbaiah, K., Jones, C.W., and Davis, R.J., *J. Mol. Catal. A: Chem.*, 2010, vol. 316, p. 8.
- 12. Sun, K.J., Li, W.X., Feng, Z.C., and Li, C., Chem. Phys. Lett., 2009, vol. 470, p. 259.
- 13. Jiang, C.J., *Dissertation*, Zhejiang, China: Zhejiang Univ. 2009.