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Enantioselective hydrolytic kinetic resolution of 1,2-epoxy-3-phenoxy propane derivatives by new chiral (salen) cobalt complexes

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The enantioselective hydrolytic kinetic resolution (HKR) of racemic terminal epoxides catalyzed by new chiral (Salen) Co complex linked with Al or Ga provides a practical access of the enantiomerically enriched terminal epoxides ($>98\%$ ee) and 1,2-diols simultaneously. In the present method, bimetallic catalysts show dramatically increased reaction rates with high enantioselectivity relative to the monomeric salen catalyst.

KEY WORDS: hydrolytic kinetic resolution; chiral cobalt salen catalyst; terminal epoxides.

1. Introduction

Terminal epoxides are very important subclass of epoxides for organic synthesis [1]. As a consequence, the preparation of optically pure terminal epoxides has long stood as a most significant target for asymmetric, chiral building blocks [2]. Hydrolytic kinetic resolution (HKR) provides most efficient, scalable and practical manner to prepare stereochemically enriched terminal epoxides [3–7]. Pursuant to our own efforts directed toward the designing of the catalyst system for the HKR [8–11], we have synthesized new dimeric chiral cobalt salen catalyst containing anhydrous aluminium halide salts attached to oxygen of salen complex as a Lewis acid, and it could be applied successfully in the HKR of various terminal epoxides [8]. The mechanistic study for HKR of epoxides, as reported by Annis and Jacobsen [12], indicates that the epoxide ring opening reactions proceed through the mechanism involving cooperative interaction between salen catalyst units, so linking the salen catalysts as dimers or to dendrimeric frameworks leads to catalytic systems with similar high enantioselectivity and substantially enhanced reactivity relative to the monomeric salen catalyst. The nonlinear effects in kinetic resolution and second-order kinetic dependence on catalysts also suggest a mechanism wherein two discrete catalyst molecules cooperate to activate both epoxides and water.

Herein we report the synthesis of new chiral salen complexes having Al or Ga halide compounds and demonstrate that these catalysts exhibit substantially enhanced catalytic activity in the HKR of terminal epoxides as a dimeric form. The easily synthesized new bimetallic (salen) Co complex **2** catalyzes hydrolytic epoxide ring opening reactions with improved enantioselectivities and dramatically increased reaction rates relative to the monomeric catalyst **1**.

2. Experimental

2.1. *Synthesis of the catalyst* **1** *and* **2**

(R,R)-cobalt salen (structure A procured from Aldrich; 5.0 g, 8.28 mmol, 1.0 equiv.) was charged in the 100 mL flask equipped with a magnetic stir bar and was stirred in methylene chloride solvent (25 mL) at room temperature under the open atmosphere. The monomeric chiral Co (salen) catalyst **1** and bimetallic (salen) complex **2** were synthesized by mixing 1:1 and 1:2 mole ratios of chiral salen (R,R)-(-)-N,N′-bis (3,5-di-tert-butylsalicylidene)-1,2-cyclohexane diamino cobalt (II) **A** and hydrated Ga or Al halide salts at open atmosphere for 1 h reaction time.

Typically, the anhydrous gallium (III) chloride (1.458 g, 8.28 mmol, 1.0 equiv.) was added to a stirred solution of chiral salen Co (II) **A** in water and THF. The other Al and Ga salts such as $AlCl_3$, AlI_3, $Al(NO_3)_3$ and $Ga(NO_3)_3$ were used as a hydrated form for the preparation of catalysts. As soon as the gallium chloride was added, the color of solution changed from brick red to olive green. This mixture was stirred at room temperature for 1 h. The resulting solution was vaporized under the reduced pressure. Catalyst **1** and **2** were obtained (yield = 98–99%) as a dark brown solid powder. The insertion and array of linkage of Ga to Co salen unit can be evidenced by ^{69}Ga NMR taking $[Ga(D_2O)_6]^{3+}$ as a reference at 0 ppm. The chemical shift difference confirms the presence of the catalyst **1** and **2** as two distinct species. UV visible spectra of catalyst **1** and **2** show the strong absorbance on 375 nm. The characteristic absorption band of Co (II) salen **A** at 425 nm disappeared after treatment of

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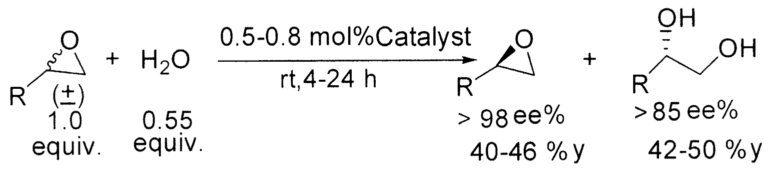
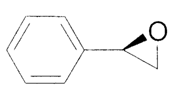
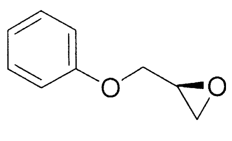
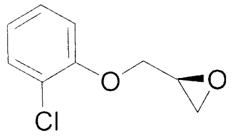
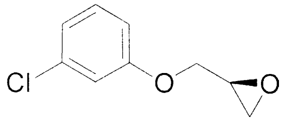
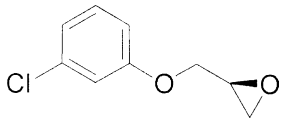
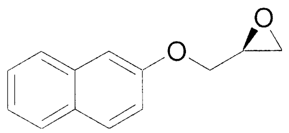
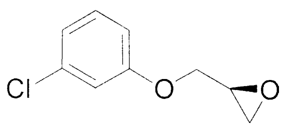
Ga compound. For Catalyst **1-I-a**, **1-II-a**, **2-I-a** and **2-II-b**, FAB-Mass analysis was also performed to investigate the structure of synthesized complexes. ^{1}H, ^{13}C and ^{67}Ga NMR were recorded using 400 MHz FT-NMR spectrophotometer (VARIAN UNITYNOVA4OO).

Table 1

The HKR of terminal epoxides catalyzed by the catalyst **1** or **2**



Entry	Isolated product[a]	Catalyst	Catalyst loading (mol %)[b]	Time (h)	% Yield (ee)[c]
1		1-I-a	0.8	4	34(76)
2		1-II-a			33(82)
3		2-I-a			35(93)
4		2-II-a			34(98)
5		2-II-b			36(98)
6		2-II-c			35(97)
7		1-I-a	0.8	4	44(72)
8		1-I-c			45(71)
9		1-II-a			43(79)
10		1-II-c			43(77)
11		2-I-a			44(91)
12		2-I-b			45(93)
13		2-II-a			46(98)
14		2-II-b			46(99)
15		2-II-c			46(97)
16		1-II-a	0.8	4	38(75)
17		2-II-a			37(97)
18		2-II-b			35(98)
19		1-I-a	0.8	4	37(69)
20		1-II-a			36(76)
21		2-I-a			38(88)
22		2-II-a			37(98)
23		1-I-a	0.8	4	38(71)
24		1-II-a			41(76)
25		2-I-a			42(90)
26		2-II-a			40(98)
27		1-I-a	0.8	4	34(65)
28		1-II-a			33(71)
29		2-I-a			36(87)
30		2-II-a			36(97)
31		1-II-a	0.8	4	43(66)
32		2-I-a			45(86)
33		2-II-a			46(98)

[a] Isolated yield is based on racemic epoxides (theoretical maximum = 50%).

[b] Loading of catalyst w.r.t. racemic epoxides.

[c] ee% was determined by chiral HPLC.

X-ray absorption spectroscopy (EXAFS) was examined by Rigaku Model R-XAS (Rigaku, Japan) applying Co K-edge energy (7708.9 eV), Ga K-edge energy (10,367.1 eV) radiation and data were simulated by using FEFF program to confirm the cobalt salen structure of monomer **1** and dimer **2**.

2.2. *General procedure for HKR*

An oven dried 25 mL flask equipped with a stir bar was charged with (R,R) catalyst **1** or **2** (0.2 mmol, 0.5–0.8 mol%) and (±)-terminal epoxides (40 mmol, 1.0 equiv.), and the substrates were stirred at room temperature. H_2O (22 mmol 0.55 equiv.) was added slowly drop by drop. The reaction was mildly exothermic. The reaction mixture was stirred up to the occurrence of optically pure terminal epoxides. The reaction mixture was checked periodically by Chiral GC (Hewlett-Packard 6890 Series II instruments equipped with FID detector) using a chiral column (CHIRALDEX G-TA, 20m × 0.25 mm i.d. (Astec)) and by chiral HPLC (Regis (S,S)Whelk-O1 column at 254 nm).

It was found that neither chiral salen Co (II) **A** nor Lewis acid MX_3 alone induce any HKR reaction. However, bimetallic catalyst could be generated readily, *in-situ* by suspension of the Co (salen) A in epoxide or epoxide/solvent and addition of monomer. The optimum ratio of Co (salen) and Lewis acid was found to be 1:2, respectively, in the present study.

2.3. *Experimental procedure for the kinetic measurements [13,14]*

In a representative kinetic run, 20 mL vials were charged with a stir bar and 0.2 mmol catalysts. The catalyst was dissolved in THF (5.00 mL), then (*rac*)-ECH (3.70 mL, 40 mmol) and bromobenzene (250 μL; as an internal standard) were added to the olive green catalyst solution. After the mixture had been stirred for 1 h at 25 °C, water (0.39 mL, 22 mmol) was added. Initial rate of the reaction conversion was monitored by GC analysis of 20 μL aliquots withdrawn periodically from the reaction mixture. Even though the reactions were kinetically well behaved over several halflives, initial rates were used to avoid complications.

3. Results and discussion

Hydrolytic kinetic resolution reactions can be typically carried out in the absence of solvents and the resolved products are separated by simple extraction and distillation. The HKR reactions catalyzed by **1** and **2** were examined with terminal epoxides having phenyl groups as substrates.

The new catalysts **2-I** and **2-II** afford highly valuable terminal epoxides in enantiomerically pure form for HKR of (±) phenoxy epoxide derivatives. Styrene oxide and phenoxy epoxide derivatives are particularly attractive substrates for HKR because the racemates are available inexpensively and on a large scale, and the chiral three-carbon building blocks derived from these compounds are extremely versatile synthetic intermediates. Under a standard condition employing 0.8 mol% (R,R)-catalyst **1** or **2** and 0.55 equiv. of H_2O, optically pure phenoxy epoxide derivatives were obtained in >98% ee and 33–46% isolated yield (table 1). It has been investigated that the catalytic activities changed significantly with the salen structure. The highest reaction rate and optical purity were obtained on the dimeric salen **2-II** containing gallium halides under the same reaction conditions. However, the use of different type anions in gallium salts has resulted in no remarkable effect on the catalytic activities as indicated in table 1.

The dimeric Ga–salen complex **2-II-a** afforded not only remarkably enhanced reactivity, but also significantly higher enantioselectivities for the HKR of the terminal epoxides having phenyl groups, relative to monomeric Ga–salen catalyst **1-II-a** as shown in figure 1. For the dimeric catalyst **2-II**, all racemic substrates were hydrolyzed to give the optically pure epoxide within 8 h. However, the monomeric salen catalyst **1-II** showed lower reaction rates than the dimer catalyst, but almost similar high enantioselectivity with a prolonged reaction time.

As described in table 1, the catalyst **2-I** or **2-II** exhibited a higher level of reactivity than **1-I** or **1-II**, respectively. The effects of metal halide source on the catalytic activities in HKR of phenoxy epoxides can be also compared in figures 1 and 2. Figure 2 shows the activities of catalyst **1-I-a** and **2-I-a** in the HKR reaction of 1,2-epoxy-3-phenoxy propane and 1,2-epoxy-3-*m*-chlorophenoxy propane. The dimeric Al–salen **2-I-a** gave remarkably enhanced reactivity as compared to the monomeric Al–salen catalyst **1-I-a**. However, the gallium-containing dimeric salen catalyst **2-II** is more active

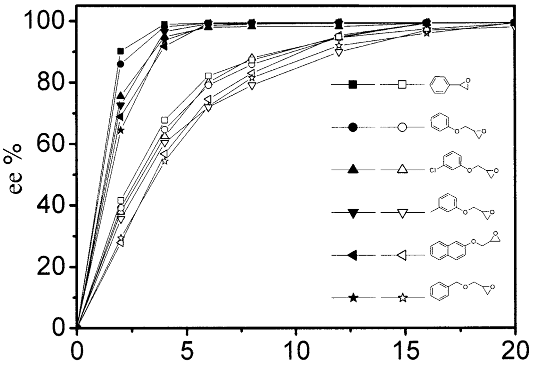


Figure 1. The catalytic activities of the catalyst **1-II-a** and **2-II-a** for asymmetric HKR of terminal epoxides using 0.5 mol% catalyst at ambient temperature.

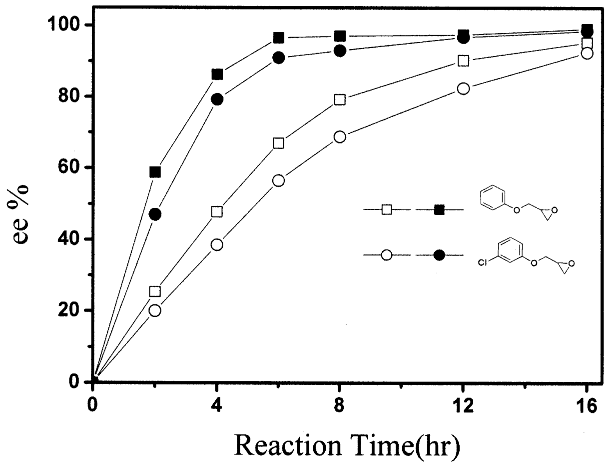


Figure 2. The catalytic activities of the catalyst **1-I-a** and **2-I-a** for asymmetric HKR of racemic 1,2-epoxy-3-phenoxy propane and 1,2-epoxy-3-*m*-chlorophenoxy propane using 0.5 mol% catalyst at ambient temperature.

than aluminum containing one **2-I** under the same reaction conditions. These results suggest that the metal halides used as a Lewis acid to link the salen complexes gave an effect on asymmetric induction.

The HKR of 1,2-epoxy-3-phenoxy propane was investigated using the chiral catalyst **2-II-a** at different substrate/catalyst mole ratios and the results are summarized in figure 3. The ee% of epoxide increased with the high loading of catalyst at the same reaction time. When the substrate-to-catalyst ratio is so high, the efforts to recycle the chiral catalysts become superfluous. The reaction with catalyst **2-II-a** at the 0.2 mol% level led to 98% ee for epoxide after 16 h.

The feature of metal-salen catalyzed ring opening reactions for epoxides is the second-order dependence on catalyst concentration. This shows that the HKR reaction follows the cooperative bimetallic catalysis [5] where epoxide and nucleophile activate simultaneously by two different (salon) catalyst molecules. Cooperative reactivity between multiple metal centers is commonly postulated for enzymatic systems [15].

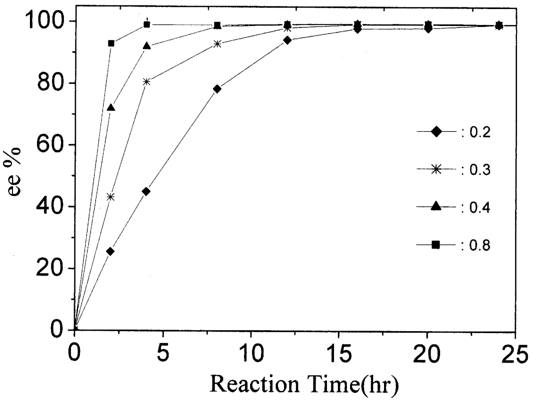


Figure 3. The effect of loading amount of catalyst **2-II-a** on the enantioselectivity of the HKR of racemic 1,2-epoxy-3-phenoxy propane (0.1–0.8 mol% of catalyst is used for 1 equiv. reactant racemates).

The linking of two (salen) Co unit through the Ga induces the dual activation mechanism, albeit through a far less enantiodiscriminating transition state than that attained with the catalyst **1**.

The HKR of 1,2-epoxy-3-phenoxy propane was studied as a model reaction for kinetic studies (table 2). It shows the two-term rate equation involving both intra- and intermolecular components (equation (1)) [13,14].

$$\text{Rate} = k_{\text{intra}}[\text{catalyst}] + k_{\text{inter}}[\text{catalyst}]^2 \qquad (1)$$

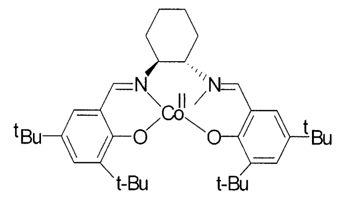
Plots of rate/[catalyst] versus [catalyst] should be linear with slopes equal to k_{inter} and y-intercepts corresponding to k_{intra}. Analysis of such plots with rate data obtained with bimetallic catalyst **2-II-a** revealed linear correlations with positive slopes and nonzero y-intercepts, consistent with participation of both inter- and intramolecular pathways in the HKR. Similar analysis of rate data obtained with monomeric catalyst **1-II-a** revealed y-intercepts of zero, reflecting the absence of any first-order pathway. Thus, the bimetallic catalyst **2** provides appropriate relative proximity and orientation, which eventually reinforces the reactivity and selectivity (scheme 1). Kinetic studies on the HKR indicated a second order dependence on the monomeric (salen) Co catalyst **1-I-a**. Although the HKR reaction is easily carried out with Co (II) complexes **1** and **2** as pre-catalysts, it appears that the reactive species is in fact Co (III). The active intermediate during HKR may be Co^{III}–OH complex [5]. The bimetallic chiral (salen) Co catalysts show several orders of magnitude times more reactive than the monomeric catalyst for the HKR. It provides high enantiopure terminal epoxides in one-step process.

UV visible spectra of catalyst 1 and 2 show the strong absorbance on 375 nm. The characteristic absorption band of Co (II) salen (1) at 425 nm disappeared after treatment of Al or Ga halide compounds. The catalyst is quite stable during and after the HKR, showing that the

Table 2
Kinetic data for the HKR of racemic 1,2-epoxy-3-phenoxy propane catalyzed by catalysts **1-II-a** and **2-II-a**

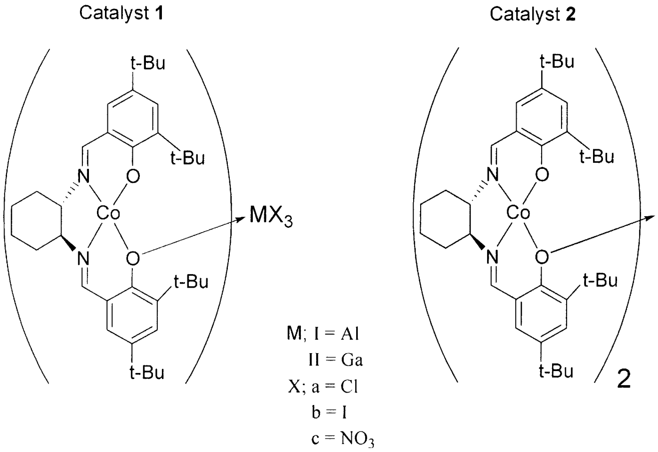
Catalyst	No. of (salen) Co unit	k_{intra} ($\text{min}^{-1} \times 10^{-2}$)[a]	k_{inter} ($\text{M}^{-1} \times \text{min}^{-1}$)[a])
1-I-a	1	–	2.1
2-I-a	2	21.7	10.5
1-II-a	1	–	4.2
2-II-a	2	29.3	12.6

[a] Calculated using equation (1).



A

(R, R)-(-)-N, N′-bis (3,5-di-tert-butylsalicylidene)-1,2-cyclohexane diamino cobalt (II)

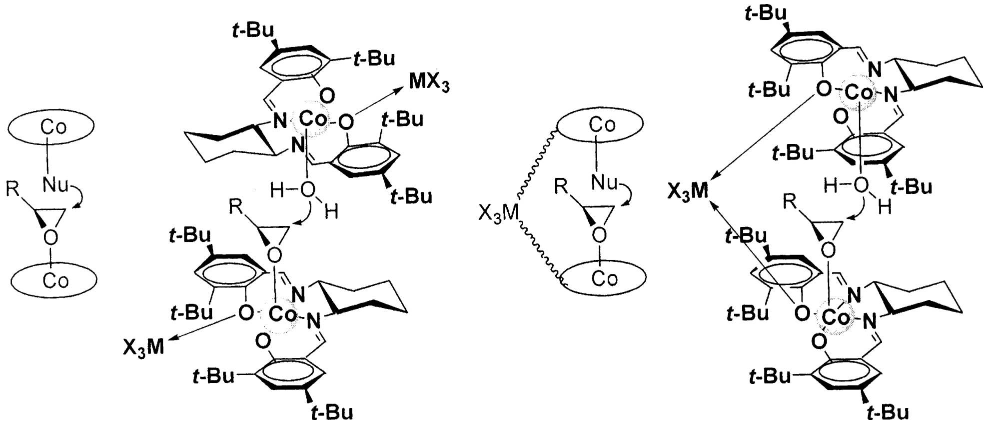


Scheme 1. Schematic Structures of the new chiral (salen) Co Catalysts.

linkage of Ga to oxygens in salen molecule is strong enough to maintain the dimeric structure. The presence of cobalt salen **1** by the dissociation of catalyst **2** was not found on the UV spectra during the reaction.

The insertion and array of linkage of Ga to Co salen unit can be evidenced by ^{69}Ga NMR taking $[Ga(D_2O)_6]^{3+}$ as a reference at 0 ppm. The chemical shift confirms the presence of the catalyst **1-II-a** and **2-II-a** as two different distinct species. The monomeric chiral (salen) Co **1-II-a** shows chemical shift δ on 78.2 ppm, while bimetallic chiral (salen) Co complex **2-II-a** δ on 52.4 ppm.

The FAB-Mass also supports the configuration of monomeric and bimetallic forms. For Catalysts **2-I-a** and **2-II-a**, FAB-Mass also indicated the dimeric structure (The observed molecular weight was more than 1240). Whereas, the monomeric Co-salen **A** has the molecular weight about 602. In addition X-ray absorption spectroscopy (XAFS) was examined to confirm the cobalt salen structure of monomer **1** and dimer **2**. The coordination parameter was calculated by fitting a model spectrum of EXAFS to the measured spectrum. The length between Ga and oxygen was same in both the monomer **1-II-a** and dimer **2-II-a**. The coordination number of Ga–O was near 1 for the monomer salen **1-II-a** but it was increased two times for dimeric form **2-II-a**. Therefore these results show the evidence for the dimeric structure of salen catalyst **2**. It is well known that oxygen



Scheme 2. Proposed mechanism for a cooperative bimetallic catalysis in the HKR of terminal epoxides catalyzed by **1** and **2**.

atoms of the metal complexes of Schiff bases are able to coordinate to the transition as well as group 13 metals to form a new complex [16,17].

On this basis, the proposed structure in the HKR reaction is given in scheme 2.

4. Conclusion

The HKR provides straightforward and one pot synthesis of chiral building blocks. The present catalyst can be synthesized easily and recycled up to three cycles without noticeable loss in enantioselectivity. We hope this catalyst can also be used as a general catalyst for the asymmetric ring opening of terminal epoxide with H_2O and other nucleophiles.

Acknowledgments

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