Catalytic Activity and Recyclability of New Enantioselective Chiral Co—Salen Complexes in the Hydrolytic Kinetic Resolution of Epichlorohydrin

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Catalytic activity and recyclability of new enantioselective chiral Co–salen complexes in the hydrolytic kinetic resolution of epichlorohydrine

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Abstract—Chiral Co(III) salen catalysts bearing PF_6, BF_4 or Br counterions proved to be reactive and enantioselective in the hydrolytic resolution of terminal epoxides. The catalysts could be recovered and reused several times without further treatment after reaction, showing no loss of activity and enantioselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

Much effort has been devoted not only to the development of active catalysts but also to finding ways to enable repeated use. This is especially important for chiral catalysts, which are usually more expensive than achiral catalysts. The syntheses of optically pure chemicals have gained significant potential over recent years. The heterogeneous chiral catalysts offer practical advantages of the facile separation from reactants and products, as well as recovery and reuse. However, some disadvantages can be expected in heterogeneous catalysis in terms of reaction rates and enantioselectivity. It has been found that several systems based on chiral chromium– and cobalt–salen complexes are very efficient for the highly enantioselective reaction of nucleophiles with epoxides.[1–7] Especially, chiral Co(III)–OAc salen complex (**1**) is very enantioselective for the hydrolytic kinetic resolution (HKR) of racemic epoxides such as (±)-styrene oxide and (±)-epichlorohydrine(ECH) with water.[3–7] ECH is one of the attractive substrates for HKR because the racemates are available inexpensively and the chiral three carbon building blocks derived from that compound is extremely versatile synthetic intermediates. These recently developed chiral salen-based catalysts are appealing candidates for covalent attachment of homogeneous salen ligands to the solid supports, and for the development of new method for the recycling of chiral catalysts.[6–14] The features of HKR include the easy separation of diol product from unreacted epoxide due to large boiling point difference and recyclability of the catalysts. Whereas, the (salen)

Co(III)–OAc complex (**1**) shown in Scheme 1 must be regenerated by treatment with acetic acid in air after reaction and separation of products.[3] Furthermore, this type catalyst has the drawback of the racemization in HKR of ECH and it may stand as a critical issue.

Based on these facts, our attention was directed to the development of optically active catalysts desirable for repeated use without any treatment after HKR reaction, and the racemization of optically pure epoxide has been completely overcome by using the new catalysts bearing less coordinating counterions.

Here in this study, we have synthesized various counter anion-containing (salen) Co catalysts and these newly synthesized chiral salen Co(III) complexes have been applied as catalysts in the HKR of terminal epoxides.
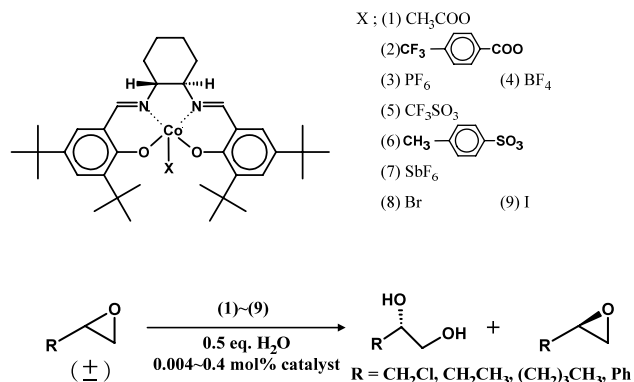
Scheme 1.

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The catalyst **2** was prepared by the same manner as catalyst **1** using α,α,α-trifluoro-*p*-toluic acid instead of HOAc. The (salen) Co(II) complex was oxidized in air in the presence of α,α,α-trifluoro-*p*-toluic acid and toluene, generating the corresponding salen complex **2**. For the synthesis of catalysts **3** or **4**, the chiral salen (*R,R*)-(−)-*N,N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diamino cobalt(II) was treated with ferrocenium hexafluorophosphate or ferrocenium tetrafluoroborate in acetonitrile under air, respectively. The mixtures were concentrated to dryness and washed with hexane to remove the side product, ferrocene. These catalysts will be denoted as Co(III)–(PF₆) and Co(III)–(BF₄). The other catalysts (**5**–**7**) bearing a fluoride compound were readily prepared from (*R,R*)-(−)-*N,N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclo hexanediamino cobalt(II) and corresponding silver salts such as AgCH₃C₆H₄SO₃, AgCF₃SO₃, AgSbF₆. In this case, the reaction flask was wrapped with aluminum foil and stirred for 8 h at room temperature. We have also synthesized bromo-(salen)Co(III) (**8**) and iodo-(salen) Co(III) (**9**) complexes by treatment of bromine and iodine with chiral Co(II) salen, respectively, and they were used as catalysts in the HKR of (±)-epichlorohydrine to evaluate catalytic activities.

The general procedure for the HKR of epoxides follows the method as shown in the reported papers.[3] The ee% values were determined by capillary GC using chiral columns (CHIRALDEXTM(D-TM), Gamma-cyclodextrin trifluoroacetyl, 40 m×0.25 mm i.d.; CHIRALDEX B-DM, beta cyclodextrin, 20 m×0.32 mm i.d. (Alltech)).

The new catalysts (**2**–**4**, **6**, **8**) afford highly valuable terminal epoxides in enantiomerically pure form for HKR of (±)-ECH as well as 1,2-epoxybutane, 1,2-epoxyhexane and styrene oxide. The identity of the counter ions in the catalysts was revealed to be a critical parameter for attainment of high enantioselectivity and fast reaction rates. The high asymmetry-inducing ability of the salen complexes in this work is attributed to the intense interaction of the substituent of salen ligands near the cobalt metal center with incoming substrates. The racemates of epichlorohydrine and epoxy styrene were enantioselectively hydrolyzed in a high yield and ee% over the chiral Co(III) salen catalysts containing the more electronegative fluoride ions at room temperature with or without addition of organic solvents, respectively.

Especially, Co(III)–(PF₆) and –(BF₄) salen complexes (**3**, **4**) showed the superior catalytic activities to those obtained by the conventional chiral (salen)Co(III)–(OAc) catalyst (**1**). As shown in Table 1, Co(III)–(PF₆) and –(BF₄) salen catalysts (**3**, **4**) displayed not only significantly high enantioselectivities but also improved activities. The maximum reactivity

Table 1. Enantioselective hydrolysis of terminal epoxides to diols on the various chiral Co(III) salen catalysts

R = CH₂Cl, CH₂CH₃, (CH₂)₃CH₃, Ph

Entry	R	Catalyst	Time (h)[b]	Yield of epoxide (%)	ee% of epoxide[b]	Yield of diol (%)	ee% of diol[b]	$k \times 10^3$ (M⁻¹ S⁻¹)[a]
1	CH₂Cl	1	6	43	98	45	96	8.1
2	CH₂CH₃	1	5	45	98	47	98	22.8
3	Ph	1	40	40	97	41	96	2.6
4	(CH₂)₃CH₃	1	5	46	98	48	98	20.4
5	CH₂Cl	2	10	42	98	46	97	6.2
6	CH₂Cl	3	5	43	99	44	98	10.3
7	CH₂CH₃	3	3	46	99	47	99	31.6
8	Ph	3	30	41	98	45	96	3.3
9	(CH₂)₃CH₃	3	5	46	99	47	98	29.9
10	CH₂Cl	4	6	44	99	46	98	8.8
11	CH₂CH₃	4	3	42	98	48	98	30.5
12	(CH₂)₃CH₃	4	5	45	98	47	98	26.1
13	CH₂Cl	5	52	40	92	43	98	1.3
14	CH₂Cl	6	4	45	83	38	98	8.3
15	CH₂Cl	6	18	40	97	42	95	–
16	CH₂CH₃	6	3	46	99	45	98	24.3
17	CH₂Cl	7	48	43	76	34	98	1.0
18	CH₂Cl	8	6	41	99	46	97	7.9
19	CH₂CH₃	8	5	44	99	48	99	24.0
20	(CH₂)₃CH₃	8	6	45	98	48	97	20.9
21	CH₂Cl	9	10	42	98	45	97	4.8

[a] 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 catalysts. Experimental procedure for the kinetic study was same as described in Ref. 13.

[b] The ee values were determined at the indicated reaction time.

was attained with catalyst **3**. Kinetic studies of the HKR of (±)-ECH revealed that the catalyst **3** was more reactive than the conventional catalyst **1** as shown in Table 1. The use of chiral salen catalyst **5** gave a disadvantage in reaction rates. But enantiomeric excess reached 92%, when the reaction time has prolonged up to 52 h using the catalyst **5**.

Recycling abilities of some catalysts have been investigated in HKR of (±)-ECH. Figure 1 shows that a series of epichlorohydrine HKR in which the chiral Co(III)–(PF$_6$) complex (**3**) could be reused for ten times after simple distillation of products. The salen Co(III)–(BF$_4$) type catalyst (**4**) can also be recycled more than five times. It is noteworthy that the salen Co(III)–(PF$_6$) catalyst (**3**) could be recycled without observable loss in activity and it was reused for further catalytic reactions. Use of Co(III)–(PF$_6$) and –(BF$_4$) type salen catalysts avoided the necessity of further treatment after separation of products. Whereas, as can be seen in Figure 1b, the salen Co(III)–(OAc) catalysts (**1**) must be regenerated with acetic acid in air after evaporation of products to enable their repeated use in HKR of ECH. The enantiomeric excess became reduced to 17% by using the conventional (Co-salen)–OAc catalyst in the second hydrolysis reaction, if not regenerated by HOAc in air. This is due to the reduction of Co(III) to Co(II). The Co(III)–(PF$_6$) complex (**3**) exhibited the same enantioselectivity up to 99% ee through the repeated use for six times in HKR, but

reaction time has prolonged to obtain the highest ee% as the number of recycling was increased.

The important feature in the HKR of ECH using Co(III)–(PF$_6$) or –(BF$_4$) salen catalyst is that no racemization is found not only during the distillation, but also after attaining to the highest ee% value of epoxide. The enantioselectivity of ECH on Co(III)–(PF$_6$) catalyst has not changed more or less until 48 h, showing up to 99% ee. In contrast, racemization of ECH was observed to take place with Co(III)–(OAc) catalyst (**1**) as well as bromo- and iodo-salen catalysts (**8**, **9**) during the reaction and product distillation as can be seen in Figure 2. The ee% of product epoxide slowly decreased via racemization over these –(OAc), –(Br) and –(I) containing chiral salen complexes.

Figure 3 shows the catalytic activities and recyclabilities of catalyst **1** and **3** in the asymmetric resolution of 1,2-epoxybutane. In the HKR of 1,2-epoxybutane, 1,2-epoxyhexane and styrene oxide, racemization was not


Figure 1. The catalytic activities and recyclabilities of Co(III) salen complex **1** and **3** in the asymmetric HKR of (±)-ECH. 0.4 mol% catalyst, reaction at rt.
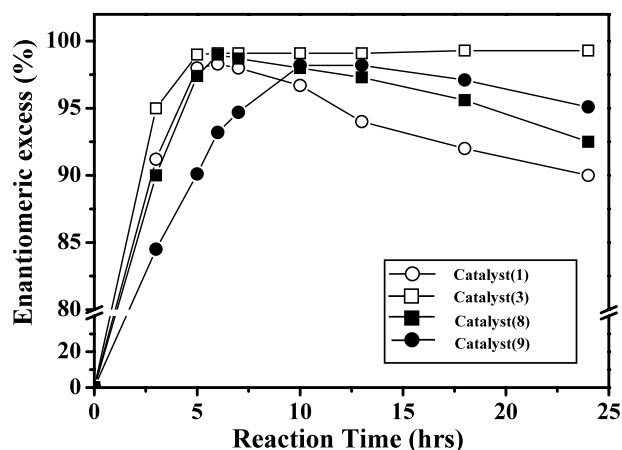
Figure 2. Racemization of (*S*)-ECH on the catalysts **1**, **8** and **9** with prolonged reaction time. 0.4 mol% catalyst, reaction at rt.
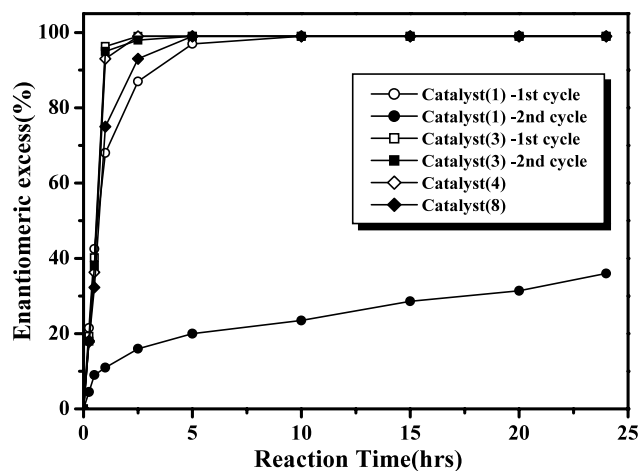
Figure 3. The catalytic activities and recyclabilities of Co(III) salen complexes **1** and **3** in the asymmetric HKR of (±)-1,2-epoxybutane. 0.4 mol% catalyst, reaction at rt.

observed on the catalyst (**1**–**9**), showing the constant enantioselectivity (up to 99% ee) with the prolonged reaction time. In contrast to the slow HKR rate of styrene oxide, 1,2-epoxybutane was found to undergo hydrolytic resolution rapidly. The catalysts **3** and **4** could be reused with no loss of activity or enantioselectivity after separation of products for the HKR of above reactants.

The HKR of ECH was investigated using the Co(III)-(PF$_6$) catalyst at different substrate/catalyst mole ratios and the results are summarized in Figure 4. The conversion and the ee% of epoxide increased as the substrate/catalyst ratio decreased 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 **3** at the 0.2 mol% level led to 99% ee for epoxide after 8 h. It is, however, noteworthy that the catalysts **3** and **4** showed almost the same enantioselectivity (up to 99% ee) in the case of very high substrate/catalyst mole ratio (2.5×10^6), even though the prolonged reaction time up to 40 h was needed.
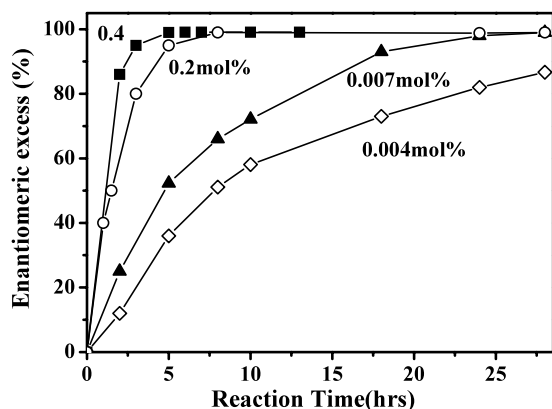
Figure 4. The effect of loading amount on the enantioselectivity in the HKR of (±)-ECH using catalyst **3**.

In conclusion, the new chiral (salen) Co(III) complexes could be synthesized and these salen catalysts showed to be effective in asymmetric hydrolytic resolution of epoxides with promising enantioselectivities. The catalysts could be recovered and reused several times without further treatment after reaction, showing no loss of activity and enantioselectivity. On the basis of asymmetric HKR of various epoxides, the chiral (salen) complexes obtained by the present procedure can be applied as an effective recyclable catalyst for the asymmetric HKR reactions.

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