

Oxidatively pure chiral (salen)Co(III)-X complexes *in situ* prepared by Lewis acid-promoted electron transfer from chiral (salen)Co(II) to oxygen: Their application in the hydrolytic kinetic resolution of terminal epoxides

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Abstract

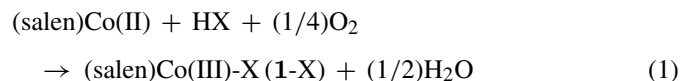
The Lewis acid (MX_3)-promoted oxidation of chiral (salen)Co(II) complex afforded neither the mononuclear nor dinuclear heterobimetallic chiral (salen)Co complexes, such as [(salen)Co(III)-X]· \cdot MX₃ or [(salen)Co(III)-X]₂· \cdot MX₃, as reported in the literatures, but rather the Jacobsen's complexes, chiral (salen)Co(III)-X. The chiral (salen)Co(III)-X complexes *in situ* generated by the reaction of MX₃ and (salen)Co(II) in molar ratio of 1:3 were shown to have identical catalytic properties in the hydrolytic kinetic resolution (HKR) reactions of racemic epoxides, in terms of activity, enantioselectivity and stability, to those of the purified (salen)Co(III)-X complex. This result strongly indicates that metallic residues of Lewis acids (e.g., metal oxide residues) remained in the reaction mixture did not display any negative influence on the catalytic efficiencies. Thus, the present *in situ* method for catalyst activation can be applicable for large scale process for HKR reactions of racemic epoxides.

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Keywords: Lewis acid-promoted electron transfer; Jacobsen's catalyst; Hydrolytic kinetic resolution (HKR)

1. Introduction

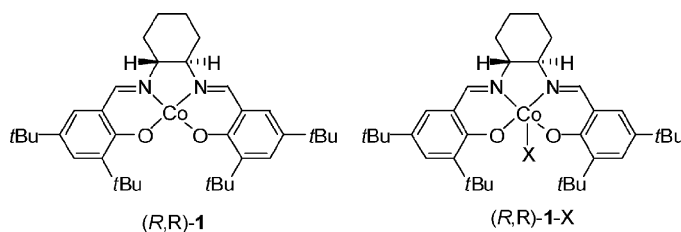
Hydrolytic kinetic resolution (HKR) of racemic epoxides using Jacobsen's chiral (salen)Co(III)-X complex **1-X** as a catalyst is one of the most powerful methods for the synthesis of both enantiomerically pure epoxides and diols [1]. So far, the chiral (salen)Co(III)-X complexes **1-X** are prepared by oxidation of catalytically inactive (salen)Co(II) complex **1** in the presence of Brønsted acids HX (Eq. (1)). Mechanistically, this oxidation process might proceed via one electron transfer from Co(II) to an oxygen molecule, resulting in the formation of an oxygen radical anion intermediate which can be stabilized by coordination with Brønsted acid, consequently lowering the activation energy (Scheme 1).



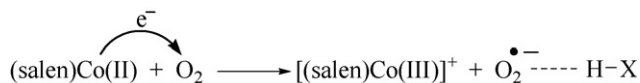
Abbreviation: OTf, trifluoromethanesulfonate

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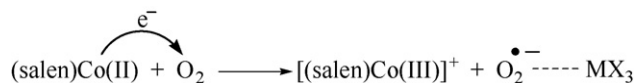
E-mail address: s1673@skku.edu (C.E. Song).



In principle, instead of Brønsted acids, Lewis acids can also promote the aerobic oxidation of catalytically inactive chiral (salen)Co(II) **1** to give the Jacobsen-type catalyst **1-X** (Eq. (2)) since the strong Lewis acids can also stabilize oxygen radical anion intermediate (Scheme 2). It has been well known that Lewis acids promote many other types of electron transfer reactions, in which the promoting effect profile of various Lewis acids is consistent with the relative Lewis acidity scale [2]. However, Kim and co-workers quite recently reported [3] that the aerobic oxidation of Co(II) complex **1** in the presence of Lewis acids (MX_3) afforded not the Jacobsen-type catalyst **1-X** but the heterobimetallic (salen)Co complexes such as [(salen)Co(III)-X]· \cdot MX₃ (**2**) or [(salen)Co(III)-X]₂· \cdot MX₃ (**3**), depending on

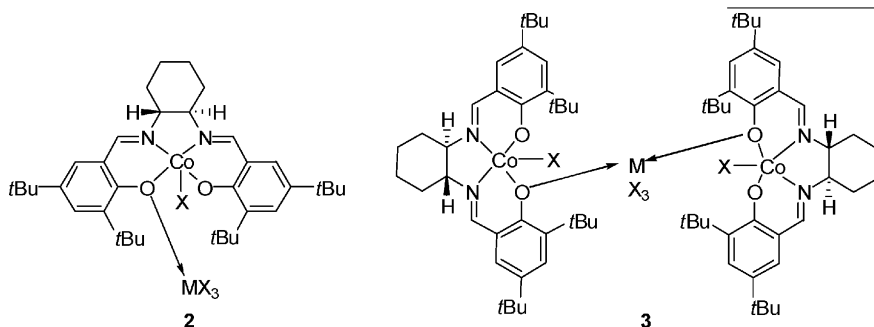
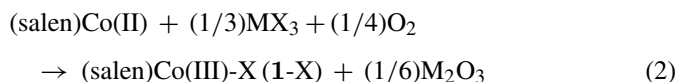


Scheme 1.



Scheme 2.

the molar ratio of **1** and MX_3 (1:1 for **2** and 2:1 for **3**).



Herein, we report that the Lewis acid (MX_3 ; $\text{M} = \text{Al}, \text{Sc}, \text{Ga}, \text{In}$; $\text{X} = \text{Cl}, \text{OTf}$)-promoted oxidation of chiral (*salen*)Co(II) (**1**) afforded neither mononuclear nor dinuclear heterobimetallic (*salen*)Co complexes, such as $[(\text{salen})\text{Co}(\text{III})\text{-X}] \cdot \text{MX}_3$ (**2**) or $[(\text{salen})\text{Co}(\text{III})\text{-X}]_2 \cdot \text{MX}_3$ (**3**), but rather selectively the Jacobsen's complexes, (*salen*)Co(III)-X (**1-X**). The *in situ* generated (*salen*)Co(III)-X catalysts **1-X** were shown to have identical catalytic properties as those of the extra-purified (*salen*)Co(III)-X complex which strongly indicate that metallic residues (e.g., metal oxides) of Lewis acids remained in the reaction mixture did not display any negative influence on the catalytic efficiencies in the HKR reactions of racemic epoxides.

2. Experimental

2.1. General and chemicals

Metal chlorides and triflates used in this study were purchased from Aldrich and used without further purification. All other chemicals were also obtained from commercial sources and used without further purification. ^1H NMR (300 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on Varian 300 spectrometers using either Me_4Si as an internal standard for ^1H NMR or CFCl_3 as an external standard for ^{19}F NMR. Gas chromatography analyses were performed on YOUNGLIN 600D equipped with FID detectors. UV spectra were recorded on a UV-vis spectrophotometer (HEWLETT PACKARD 8453).

2.2. Representative procedure for *in situ* generation of oxidatively pure (*salen*)Co(III)-X complexes **1-X**

(*R,R*)-(*salen*)Co(II) (**1**) (64 mg, 0.1 mmol) and MX_3 (0.033 mmol) ($\text{Sc}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, AlCl_3 , GaCl_3 and ScCl_3) were stirred under oxygen atmosphere in 1 mL CH_2Cl_2 at room temperature. After completion of oxidation, the reaction mixture was used directly for UV-vis analysis. For ^1H and ^{19}F NMR analysis, the reaction mixture was concentrated under vacuo to afford the dark brown solid for **1-OTf** and the green solid for **1-Cl**. ^1H and ^{19}F NMR data of **1-OTf** and **1-Cl** are given below.

^1H NMR of **1-OTf** (*in situ* generated) ($\text{DMSO}-d_6$, 300 MHz): δ 1.30 (s, 18H), 1.59–1.63 (m, 2H), 1.74 (s, 18H), 1.90–2.03 (m, 4H), 3.02–3.10 (m, 2H), 3.60–3.64 (m, 2H), 7.45 (s, 2H), 7.47 (s, 2H), 7.78 (s, 2H); ^{19}F NMR of **1-OTf** (*in situ* generated) ($\text{DMSO}-d_6$, CFCl_3 as an external standard): δ -78.19 (s)

^1H NMR of **1-Cl** (*in situ* generated) ($\text{DMSO}-d_6$, 300 MHz): δ 1.30 (s, 18H), 1.54–1.60 (m, 2H), 1.72 (s, 18H), 1.85–2.10

(m, 4H), 3.02–3.11 (m, 2H), 3.56–3.70 (m, 2H), 7.42–7.47 (broad s, 4H), 7.77 (s, 2H).

2.3. Typical procedure for HKR reactions

In a 100 mL flask, a mixture of racemic epichlorohydrin (ECH) (9.2 g, 100 mmol), (*R,R*)-(*salen*)Co(II) **1** (64 mg, 0.1 mmol, 0.1 mol%) and $\text{Sc}(\text{OTf})_3$ (16.4 mg, 0.033 mmol, 0.033 mol%) was stirred at 20 °C for 1.5 h. Water (1.3 mL, 50 mmol) was then added to the reaction mixture, which was stirred until the resolution was completed. The reaction progress was checked periodically by chiral GC. (*S*)-ECH was isolated by vacuum transfer (50 °C, 10 mbar) from the reaction mixture into a cooled (-70 °C) receiving flask. The recovered epoxide was determined to be >99% ee by chiral GC analysis (GTA, 50 °C isothermal).

3. Results and discussion

3.1. *In situ* generation of Co(III)-X complexes by Lewis acid-promoted electron transfer

To investigate the promoting effect of Lewis acid for the oxidation of Co(II) complex **1** and identify the structure of the oxidation product, we first carried out the aerobic oxidation of Co(II) complex **1** in the presence of 0.33 equiv. $\text{Sc}(\text{OTf})_3$ in dichloromethane at room temperature under O_2 atmosphere and

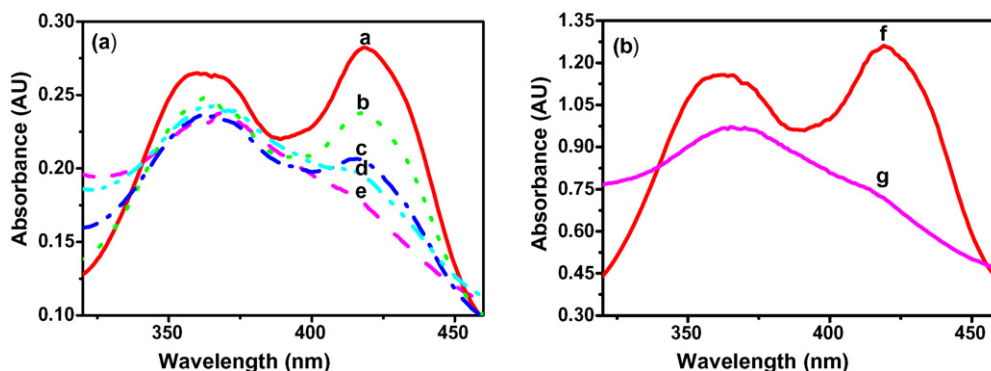


Fig. 1. (a) UV-vis absorption spectra of the mixture of **1** and Sc(OTf)₃ in a molar ratio of 3:1 which were continuously measured after mixing (curve a = UV spectrum after 1 min; b = after 15 min; c = after 30 min; d = after 50 min, e = after 80 min); (b) UV-vis absorption spectra of Co(II) complex **1** (curve f) and Co(III) complex **1**-OTf (curve g).

monitored the reaction progress by UV. As shown in Fig. 1, the oxidation reaction proceeded very fast and thus was completed within 80 min. The UV spectrum obtained after 80 min was the same as that of the Co(III) complex **1**-OTf (Compare curve e of Fig. 1a and curve g of Fig. 1b).

With this promising results in hands, we next investigated the promoting effect of other Lewis acids, MX₃ (AlCl₃, GaCl₃, ScCl₃ and In(OTf)₃). In all cases, perfect oxidation from Co(II) to Co(III)-X was observed. As might be expected, the electron transfer promoting effect profile of various Lewis acids was consistent with the relative Lewis acidity scale. Thus, the oxidation of (salen)Co(II) complex **1** was completed within 20 h, 35 h or 41 h or 3 h, respectively, when ScCl₃, AlCl₃, GaCl₃ or In(OTf)₃ was used. After the corresponding reaction times, the reaction mixtures were concentrated under high vacuo and redissolved in d₆-DMSO for NMR analysis. In the ¹H and ¹⁹F NMR spectra of the mixture of **1** and MX₃ (AlCl₃, GaCl₃, ScCl₃, In(OTf)₃ and Sc(OTf)₃), all expected peaks were observed, which strongly confirmed the complete conversion of paramagnetic Co(II) complex **1** to diamagnetic Co(III) complex. Moreover, all NMR spectroscopic data were exactly same compared with those of (salen)Co(III)-X (**1**-X) which were prepared by conventional methods, i.e., by the reactions of (salen)Co(II) **1** and the corresponding Brønsted acids HX (HCl and HOTf). These results strongly indicate that the reactions of **1** and MX₃ afforded neither the mononuclear nor dinuclear heterobimetallic (salen)Co complexes **2** and **3** as proposed recently by Kim and co-workers [3], but rather the Jacobsen's complexes, (salen)Co(III)-X (**1**-X).

3.2. Catalytic efficiency of the *in situ* generated Co(III)-X complexes

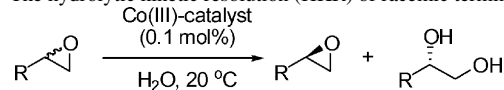
As described above, the Jacobsen's catalysts, (salen)Co(III)-X (**1**-X), can also be obtained in oxidatively pure form by Lewis acid-promoted electron transfer reactions. However, during aerobic oxidation of (salen)Co(II) **1** promoted by MX₃, MX₃ can be converted to metal oxide species which can exist as by-product in the reaction mixture (see Eq. (2)). Thus, to investigate whether these metal oxide species exert any negative influences on the HKR reactions, the catalytic efficiencies (activity, enantioselectivity and catalyst stability) of **1**-OTf generated *in situ* from the

reaction of **1** with Sc(OTf)₃ were examined and compared with those of the purified **1**-OTf which did not contain Sc-residue.

As shown from the results in Table 1, **1**-OTf, *in situ* generated by the aerobic oxidation of **1** in the presence of Sc(OTf)₃ (0.033 mol% based on epoxide, i.e., 33.3 mol% based on **1**), was shown to have exactly identical catalytic properties to those of the extra-purified **1**-OTf complex containing no Sc-residues, indicating the absence of any negative influences of the scandium residues remained in the *in situ* generated **1**-OTf on HKR reactions (see entries 1 and 3, 6 and 7, and 8 and 9). However, when the amount of the promoter (Sc(OTf)₃) was reduced (entry 2) or increased (entries 4 and 5), the HKR reactions of epichlorohydrin (ECH) after 20 h afforded only 75%, 65% and 14% ee, respectively. In the case using 0.02 mol% (i.e., 20 mol% respective to Co(II) complex) of Sc(OTf)₃, the catalytically inactive Co(II) complex **1** was imperfectly oxidized to **1**-X which increases the reaction time (entry 2). On the other hand, the use of an excess amount of Sc(OTf)₃ caused additional, non-enantioselective ring opening of epoxide, which affords the corresponding products with low ee values (entries 4 and 5). It should also here be noted that, as mentioned above, Kim and co-workers [3] proposed that mononuclear or dinuclear heterobimetallic (salen)Co complexes **2** or **3** are formed from the reaction of (salen)Co(II) (**1**) and Lewis acids (MX₃) and claimed that the higher catalytic enantioselectivity of **3** relative to **2** was due to the cooperative mechanism [1] of the dinuclear nature of **3**. However, in addition to our spectroscopic results, our above-described catalytic results indicate that the Lewis acid (MX₃)-promoted aerobic oxidation of (salen)Co(II) (**1**) afforded neither the mononuclear nor dinuclear heterobimetallic (salen)Co complexes such as **2** or **3**, but the Jacobsen's complexes **1**-X. The higher enantioselectivity of the 2:1 mixture of (salen)Co(II) and Lewis acids (MX₃), compared to that of the 1:1 mixture observed by Kim and co-workers [3], may be interpreted as being simply due to the less non-enantioselective ring opening of epoxide using 2:1 mixture compared to using 1:1 mixture, since the 2:1 mixture contains a lower level of excess Lewis acids than the 1:1 mixture does.

Next we investigated the influence of scandium residues on the stabilization of oxidation state of the *in situ* generated catalyst **1**-OTf during HKR reactions. It is well recognized that

Table 1

The hydrolytic kinetic resolution (HKR) of racemic terminal epoxides catalyzed by (*R,R*)-(salen)Co(III)-OTf^a

Entry	R	Catalyst type (0.1 mol%)	Sc(OTf) ₃ (mol%)	Time (h)	Yield (%) ^b	% ee of recovered epoxide ^c
1	CH ₂ Cl	1-OTf (extra-purified) ^d	–	20	39	>99
2	CH ₂ Cl	1-OTf (<i>in situ</i> generated)	0.02 ^e (20) ^f	20	26	75
3	CH ₂ Cl	1-OTf (<i>in situ</i> generated)	0.033 ^e (33.3) ^f	20	38	>99
4	CH ₂ Cl	1-OTf (<i>in situ</i> generated)	0.04 ^e (40) ^f	20	38	65
5	CH ₂ Cl	1-OTf (<i>in situ</i> generated)	0.1 ^e (100) ^f	20	39	14
6	Me	1-OTf (extra-purified) ^d	–	3	40	>99
7	Me	1-OTf (<i>in situ</i> generated)	0.033 ^e (33.3) ^f	3	40	>99
8	<i>n</i> -Bu	1-OTf (extra-purified) ^d	–	11	42	>99
9	<i>n</i> -Bu	1-OTf (<i>in situ</i> generated)	0.033 ^e (33.3) ^f	11	42	>99

^a The reactions were carried out on 25 mmol scale of epoxides in the presence of 0.5 equiv. of H₂O based on epoxides without additional organic solvent.^b Isolated yields.^c Determined by chiral GC using γ -cyclodextrin trifluoroacetyl column, 40 m \times 0.25 mm i.d. (Astec).^d Sc residue was nearly 0 ppm (ICP analysis).^e Based on epoxides.^f Based on Co(II) complex **1**.

the typical catalyst for HKR of racemic epoxides, **1**-OAc, is reduced to catalytically inactive (salen)Co(II) complex **1** during the HKR reactions, which consequently results in low activity [1]. Fortunately, the UV–vis spectra (curves b and c in Fig. 2) of two types of catalysts (**1**-OTf (*in situ* generated) and **1**-OTf (extra-purified)) recovered after the reactions of entries 3 and 1 in Table 1, respectively, exhibited the same absorption curves for (salen)Co(III)-OTf complex, confirming the absence of any negative influences of scandium residues on the catalyst stability.

Finally, we also investigated whether or not scandium residues present in the *in situ* generated catalyst **1**-OTf can cause the non-enantioselective ring-opening of resolved ECH. It is well recognized that when **1**-OAc is used as the catalyst, the resolved ECH can be easily racemized during the isolation step which renders the large-scale production of (*R*)- or (*S*)-ECH difficult and uneconomical [4,5]. Fortunately, as shown in Fig. 3,

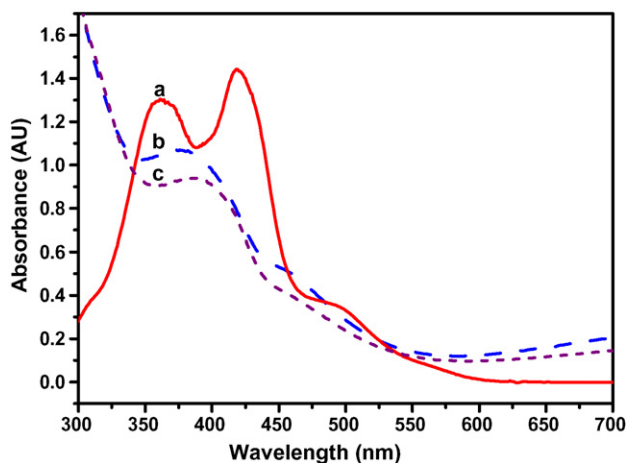


Fig. 2. UV–vis spectra of the catalyst **1**-OTf (*in situ* generated; curve c) and **1**-OTf (extra-purified; curve b) recovered after the reactions of entries 3 and 1 in Table 1, respectively. The absorption curve of (salen)Co(II) (**1**) is also given for comparison (curve a).

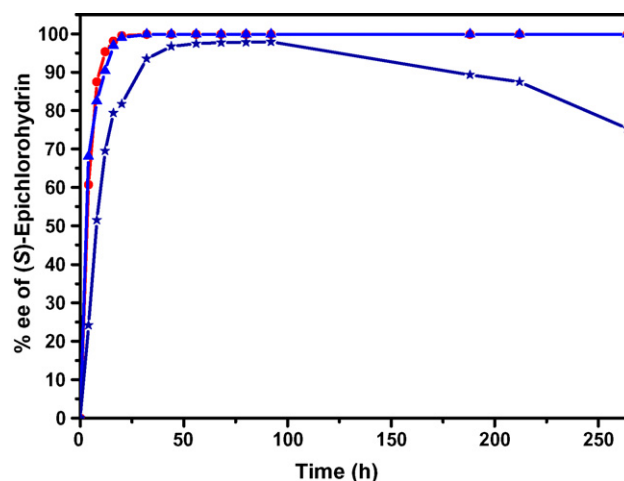


Fig. 3. Plot of ee value (%) vs. reaction time (h) during the HKR reaction of ECH catalyzed by **1**-OTf (*in situ* generated; the dashed line with ●) or **1**-OTf (extra-purified; the dashed line with ▲). The plot obtained using **1**-OAc as the catalyst is also given for comparison (the dashed line with ★).

in the HKR of ECH catalyzed by **1**-OTf (*in situ* generated) or **1**-OTf (extra-purified), no decrease in ee values was observed even after 250 h. All above-described results presented in this paper clearly indicate that (i) aerobic oxidation of Co(II) complex **1** promoted by Lewis acid afforded not heterobimetallic (salen)Co complexes such as **2** or **3**, but the Jacobsen's complexes **1**-X and (ii) the metal oxide residues present in the *in situ* generated complexes **1**-X do not exert any negative influence on the catalytic efficiencies in the HKR reactions of racemic epoxides.

4. Conclusion

In summary, the Lewis acid (MX₃)-promoted oxidation of catalytically inactive (salen)Co(II) afforded neither the mononuclear nor dinuclear heterobimetallic (salen)Co complexes, such as [(salen)Co(III)-X]·MX₃ or [(salen)Co(III)-X]₂·MX₃, as

reported in the literatures, but rather selectively the Jacobsen's complexes, (salen)Co(III)-X. The (salen)Co(III)-X catalysts *in situ* generated by the reaction of MX_3 and (salen)Co(II) in molar ratio of 1:3 were shown to have identical catalytic properties, in terms of activity, enantioselectivity and stability, to those of the extra-purified (salen)Co(III)-X complex, which strongly indicate that metallic residues of Lewis acids (e.g., metal oxides) remained in the reaction mixture did not display any influence on the catalytic efficiencies in the HKR reactions of racemic epoxides. Thus, the present *in situ* method for catalyst activation will be applicable for large scale process for HKR reactions.

Acknowledgements

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