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Article

속도론적 분할법을 통한 말단 에폭사이드로부터 고광학순도의 아렌술폰산 2-하이드록시 에스터의 합성

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Synthesis of Highly Enantiomerically Enriched Arenesulfonic Acid 2-Hydroxy Esters via Kinetic Resolution of Terminal Epoxides

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초 록

본 논문에서는 매우 효과적이고 고광학선택적으로 화합물 중의 말단기에 존재하는 에폭사이드기를 알킬 또는 아렌술폰산으로 여는 방법에 관하여 기고한다. Al, Ga 및 In과 같은 루이스산을 함유하는 이핵성 키랄 코발트살렌 착체는 염화테트라부틸암모늄 존재하에서 터샬리 부틸메틸에테르를 용매로 사용할 때, 이 반응에 대하여 광학선택적으로 높은 촉매활성을 나타내었다. 테트라부틸암모늄염 중의 음이온의 종류에 따라 페닐글리시딜 에테르의 에폭시 고리를 파라-톨루엔술폰산으로 여는 반응에서의 촉매활성과 선택도가 다르게 나타났다. 반응활성과 선택도는 $Cl^- > I^- > Br^- > OH^-$의 순서를 보였다. 서로 다른 루이스 산점을 갖는 Co-Al, Co-Ga 및 Co-In 착체는 촉매반응 중에 높은 상승효과를 나타내었다. $AlCl_3$를 함유한 이핵성 키랄 코발트살렌 착체 촉매가 가장 높은 활성과 91% ee에 이르는 높은 광학선택성을 보였다.

Abstract

This paper describes the very efficient and highly enantioselective ring opening of terminal epoxides with alkyl and arene sulfonic acid. The dinuclear chiral (salen) Co complexes bearing Lewis acids of Al, Ga and In catalyze the reaction enantioselectively in the presence of tetrabutylammonium chloride using *tert*-butyl methyl ether as a solvent. The variation of the anion of the tetra butyl ammonium salt has significant impact on the reactivity and selectivity of the asymmetric ring opening of phenyl glycidyl ether with *p*-toluenesulfonic acid. The order of reactivity and selectivity was found to be $Cl^- > I^- > Br^- > OH^-$. Strong synergistic effects of the different Lewis acid centers of Co-Al, Co-Ga and Co-In complexes were observed in the catalytic process. The dinuclear chiral salen catalyst containing $AlCl_3$ was found to be most active and highly enantioselective (91% ee).

Keywords: *enantioselective catalysis, chiral heterometallic salen catalyst, terminal epoxides, sulfonic acids*

1. Introduction

Chiral (salen) Co complexes catalyzed kinetic resolutions of terminal epoxides with various nucleophiles, have been established as a suitable approach in the synthesis of enantiomerically-enriched valuable epoxides and corresponding products[1-8]. It was reported recently that the heterometallic chiral salen complexes could be used as a multifunctional catalyst for the asymmetric ring opening reactions of epoxides [9-14]. Recently, heterometallic chiral salen complexes bearing Lewis acids of group 13 metals were reported to catalyze the ring opening of terminal epoxides with carboxylic acids[11]. As a part of ongoing studies, this paper reports the highly enantioselective kinetic resolution of terminal epoxides using various organic sulfonic acids as a nucleophile. However, the application of organic sulfonic acid for the enantioselective kinetic resolution of terminal epoxides in the presence of chiral Co salen catalysts has not been tried until now. We have used bimetallic catalysts successfully in the asymmetric ring opening reaction of terminal epoxides using various nuclephiles such as water, alcohols, and carboxylic acid. The desired monomer and dimer (salen) Co-MX_3 complexes were synthesized using a procedure reported elsewhere[10,12,13]. In this work, the enantioselective catalytic activities

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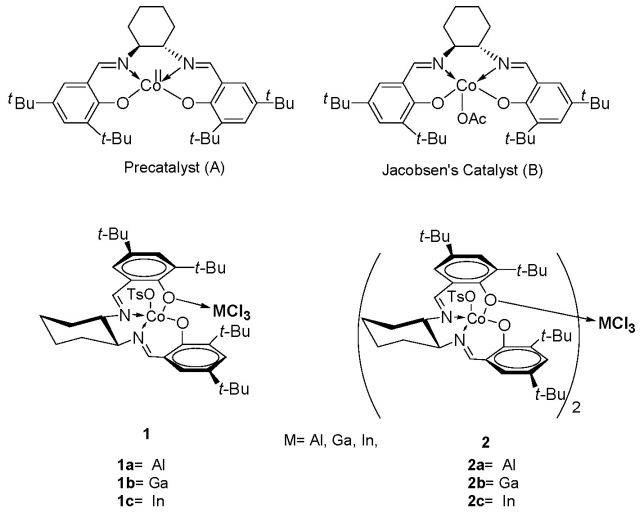


Scheme 1. Schematic diagrams of heterometallic chiral (salen) Co-MX_3 monomers and dimmers linked through Lewis acids.

of those catalysts were investigated for the synthesis of highly enantiomerically enriched arenesulfonic acid 2-hydroxy esters *via* kinetic resolution of terminal epoxides with various sulfonic acids such as methanesulfonic acid, 10-camporsulfonic acid, *p*-tolunenesulfonic acid, and 4-nitrobenzenesulfonic acid. Additionally the differences of catalytic activity depending on the structure of chiral salen complex were also compared in that reaction. Bimetallic catalysts showed remarkably enhanced reactivity and may be employed to reduce the loadings compared to its monomeric analogues without suffering from solubility problem and their deactivation. These catalysts would be capable for the synthesis of (*S*)-atenolol chiral drug *via* asymmetric ring opening reaction using organic sulfonic acid as a nucleophile.

2. Experimental

2.1. Catalyst Synthesis

The monomer and dimer type complexes of (salen) Co-$AlCl_3$/$GaCl_3$/$InCl_3$ were synthesized and characterized according to an earlier report[10,12,13], and the brief procedure for the synthesis of those complexes is shown in Scheme 1. Subsequently the following procedure was adopted for the synthesis of **1a-2c**. For **1a**, an oven dried 50 ml flask equipped with a stir bar was charged with *p*-toluenesulfonic acid (0.4666 g, 2.71 mmol, 1.0 equiv.) and stirred in THF (10 mL) in an open atmosphere and room temperature for 30 min. (salen) Co-$AlCl_3$ monomer (2.0 g, 2.71 mmol, 1.0 equiv.) was mixed into the *p*-toluenesulfonic acid solution and stirred for 1 h at room temperature. The resulting solution was concentrated under reduced pressure (yield = 99% as a dark brown solid powder). The oxidation sate of Co^{III} was checked by ESCA. For the synthesis of **1b-2b**, a similar procedure was adopted by taking 1 : 1 or 2 : 1 equivalent of *p*-toluenesulfonic acid and corresponding Co-$AlCl_3$/Co-$GaCl_3$/Co-$InCl_3$ monomer and dimer, respectively. In the case of catalyst B, the precatalyst (*R,R*)-(-)-N, N'-bis (3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diamino cobalt (II) was activated by mixing a 1.0 equivalent of *p*-toluenesulfonic acid (based on Co unit) in THF and stirred for 1 h.

2.2. Asymmetric catalytic reaction using chiral Co(III) salen complex

In a representative reaction of phenyl glycidyl ether (PGE) and *p*-toluenesulfonic acid (entry 14 in Table 1), an oven dried 25 mL flask equipped with a stir bar was charged with (*R, R*)-**2a** (0.7559 g, 0.5 mmol, 5 mol%,) and (±)-phenyl glycidyl ether (PGE) (1.5017 g, 10 mmol) and stirred in the open atmosphere. The resulting mixture was dissolved in 5 ml of *tert*-butyl methyl ether as the solvent at ambient temperature. *p*-Toluenesulfonic acid (0.861 g, 5.0 mmol, 0.5 equiv.) was added after complete dissolution of the catalyst and PGE. Finally, tetra butyl ammonium chloride (TBACl, 0.4169 g, 1.5 mmol, 0.3 equiv.) was mixed into the reaction mixture. The resulting solution was heated under reflux for up to 1 hour and stirred for a further 1 hour at room temperature. The conversions of epoxides were monitored by Gas Chromatography (GC; Hewlett-Packard 5890 Series II), and enantiomeric excess% (ee%) values of the ring opened product were determined by capillary GC equipped with FID detectors using a chiral column (CHIRALDEX (gamma-cyclodextrin trifluroacetyl (G-TA) and alpha-cyclodextrin trifluroacetyl (A-TA), Astec Co.), 20 m × 0.25 mm I.D.) and by HPLC using a Chiralcel® OD-H column (Regis Co., 24 cm × 0.46 cm I.D., diluent; hexane:*i*-propylalcohol = 95 : 5 (vol%), flow rate; 5 mL/min, UV detector; 254 nm). The purification of the products were performed by flash column chromatography and recrystallized three times by CH_2Cl_2/*n*-hepatane to afford almost colorless crystals. The products were confirmed by FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy, and found to be similar to the reported value [17,18]. In the case of epoxy butane (entry 1, 4, 7, 17, 20 in Table 1), the reaction was performed at ambient temperature.

2.3. Characterization of catalysts and analysis

All ^{1}H nuclear magnetic resonance (NMR), ^{13}C-NMR data were recorded using a 400 MHz FT-NMR spectrophotometer (VARIAN UNITYNOVA 400) at ambient temperatures. Optical rotation measurements were conducted using a Jasco DIP 370 digital polarimeter. The UV spectra were recorded on UV-Vis spectrophotometer (Optizen 2120 UV) interfaced with PC using Optizen view 3.1 software for data analysis. Vibrational Circular Dichroism (VCD) and Fourier transform infrared (FT-IR) spectroscopy were performed on a Chiralir TM-ABB Bomem Inc. using Bomem GRAMS-32 software. The solvents were used after distillation. TBME was used as obtained from Aldrich. All reagents were purchased from Aldrich, Fluka, TCI, and Lancaster.

3. Results and Discussion

A series of chiral (salen) Co complexes (Scheme 1) were screened to identify the most enantioselective and reactive catalyst for the asymmetric ring opening (ARO) of PGE with *p*-toluenesulfonic acid. Figure 1 shows that the dimeric catalyst **2a-2c** are more reactive and enantioselective than their monomeric analogue. The catalyst **2a** in the present study was found to be most effective and highly enantioselective (91%

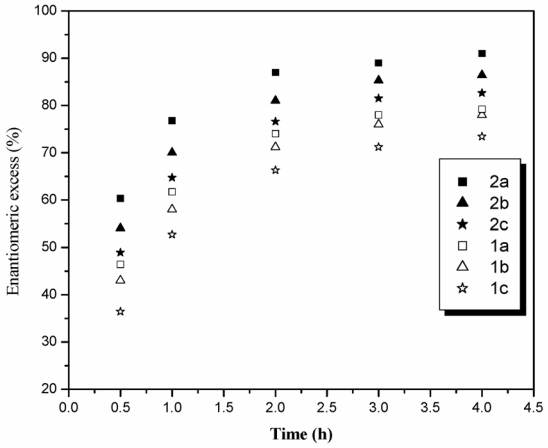


Figure 1. Comparisons of the catalytic activity and selectivity of heterometallic (salen) Co-MX_3 mononuclear and dinuclear complexes for the enantioselective ring opening of PGE with *p*-toluenesulfonic acid. The catalyst amount was 5 mol% for 2a-2c and 10 mol% for 1a-1c.

ee, 4 h). For the choice of additive, such as quaternary ammonium salts, to enhance the reaction rate and enantioselectivity, the tetra butyl ammonium chloride was found to be quite useful for the enantioselective ring opening of PGE with *p*-toluenesulfonic acid.

The variation of the anion of the tetrabutylammonium salt has significant impact on the reactivity and selectivity of the ARO of PGE. The order of reactivity and selectivity was found to be $Cl^- > I^- > Br^- > OH^-$ (Figure 2).

Surprisingly, in the absence of tetrabutylammonium salts but with the other conditions kept constant, the reaction afforded low enantioselectivity (67.7% ee vs. 99.0% ee) and low yield (32% vs. 47%). It was clearly found that the organic solvent played a crucial role on the reactivity and selectivity of the enantioselective ring opening of PGE with *p*-toluenesulfonic acid. Interestingly, the use of a non-polar solvent such as *tert*-butyl methyl ether (TBME) increases the reactivity and enantioselectivity dramatically (Figure 3). Other solvents, such as 1,4-dioxane, acetonitrile, methylene chloride, and tetrahydrofuran, showed less reactivity and enantioselectivity, as can be seen in the result of Figure 3.

Table 1 shows the catalytic activity of catalyst **2a** for the ring opening reaction of the representative racemic terminal epoxides. In a representative example of ARO of PGE with *p*-toluenesulfonic acid, the catalytic activity and enantioselectivity of **1a-2c** were observed and are listed in Table 1. The order of reactivity and enantioselectivity was **2a** > **2b** > **2c**, whereas it was **1a** > **1b** > **1c** for the monomeric complex. The optimized reaction conditions for various terminal epoxides with methanesulfonic acid, 10-camporsulfonic acid, *p*-tolunenesulfonic acid and 4-nitrobenzenesulfonic acid were listed in Table 1. A change in the counter ion of **1a-1c** from tosylate to camphor sulfonate did not result in any improvement in the reactivity and enantioselectivity on this reaction. The catalyst **1a** and **2a** prepared from hydrated $AlCl_3$ and $Al(NO_3)_3 \cdot 9H_2O$ displayed similar reactivity to anhydrous $AlCl_3$. Table 1 shows that PGE (entry 3, 14, 19 and 22) is more reactive and enantioselective than epoxy butane (entry 1, 4, 7, 17 and 20) and epichlorohydrin (entry 2, 5, 8, 18 and 21). The *p*-toluenesulfonic acid showed considerable nucleophilicity than those evaluated in Table 1. This might be because the *p*-position CH_3 electron releasing group increases the electron density on the oxygen and increases the nucleophilicity. All entries afforded high regioisomeric arylsulfonyloxy secondary alcohols except for epoxy butane (entry 1, 4, 7, 17 and 20). In the case of epoxy butane with methanesulfonic acid and arenesulfonic acid at room temperature it afforded the corresponding sulfonoxy secondary alcohols, and under reflux conditions, it provided a 1 : 1 mixture of the regioisomeric primary and secondary sulfonoxy alcohol with low ee% (< 50%).

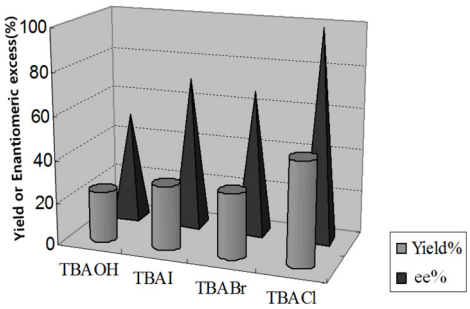


Figure 2. Effects of the various counter ions of tetrabutyl ammonium salts on the asymmetric ring opening of PGE with *p*-toluenesulfonic acid catalyst 2a with the other reaction condition kept the same as listed in Table 1.

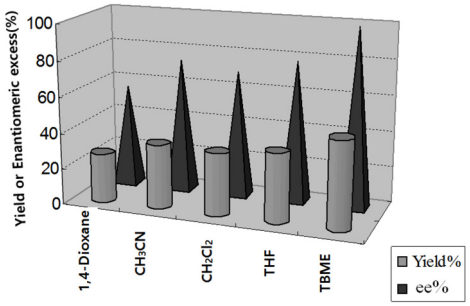
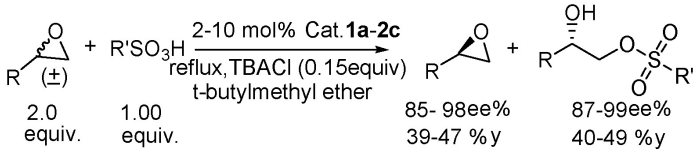


Figure 3. Effects of the diverse solvents on the asymmetric ring opening of PGE with *p*-toluenesulfonic acid catalyst 2a keeping other reaction conditions kept the same as listed in Table 1.

The effects of the catalyst amount on the activity and enantioselectivity of PGE with *p*-toluenesulfonic acid is given in Figure 4. The data show that the reaction obeys the cooperatives bimetallic mechanism. The central metal atom Co activates and controls the orientation of epoxide, activating stereoselectively only one enantiomer, but Al, Ga and In appear to bind and control the orientation of arenesulfonic acid by enabling the enantioselective ring opening of epoxides with nucleophiles (Scheme 2). The proposed mechanism may follow according to the recently published enantioselective ring opening of terminal epoxides with carboxylic acid catalyzed by heterometallic chiral (salen) Co complex[11]. The intermolecular mechanism for the mono- and dimeric complex may follow an earlier report[15].

Table 1. Asymmetric Ring Opening of Terminal Epoxides with Sulfonic Acids Catalyzed by Heterometallic Chiral (Salen) Co Complex



Entry	(R) in Epoxide	Sulfonic Acid (R′)	Cat. Type	Catalyst Amount[a]	Time (h)	Product[b] Ee% (Yield)[c]
1	C_2H_5	CH_3	2a	5.0	2.0	60.2 (41)
2	CH_2Cl	CH_3	2a	5.0	2.0	53.7 (37)
3	$PhOCH_2$	CH_3	2a	5.0	2.0	94.6 (45)
4	C_2H_5		2a	5.0	6.0	60.3 (16)
5	CH_2Cl		2a	5.0	6.0	54.7 (24)
6	$PhOCH_2$		2a	5.0	6.0	88.1 (43)
7	C_2H_5		2a	5.0	3.0	61.5 (42)
8	CH_2Cl		2a	5.0	6.0	55.8 (39)
9	$PhOCH_2$		A	10.0	2.0	47.3 (17)
10	$PhOCH_2$		B	10.0	2.0	63.5 (26)
11	$PhOCH_2$		1a	10.0	2.0	75.3 (32)
12	$PhOCH_2$		1b	10.0	2.0	67.5 (40)
13	$PhOCH_2$		1c	10.0	4.0	61.8 (43)
14	$PhOCH_2$		2a	5.0	2.0	99.3 (49)
15	$PhOCH_2$		2b	5.0	5.0	93.5 (46)
16	$PhOCH_2$		2c	5.0	3.0	91.2 (40)
17	C_2H_5		2a	5.0	3.5	67.5 (41)
18	CH_2Cl		2a	5.0	4.0	69.3 (40)
19	$PhOCH_2$		2a	5.0	6.0	99.5 (43)
20	C_2H_5		2a	5.0	5.0	53.2 (39)
21	CH_2Cl		2a	5.0	3.0	65.6 (42)
22	$PhOCH_2$		2a	5.0	2.0	93.1 (45)

[a]In mol% loading on a per [Co] basis w.r.t. racemic epoxides [b]The products obtained were characterized by ^1H, ^{13}C and elemental analyses. [c]Isolated yield is based on racemic epoxides (theoretical maximum = 50%). [c]ee% was determined by chiral GC or chiral HPLC.

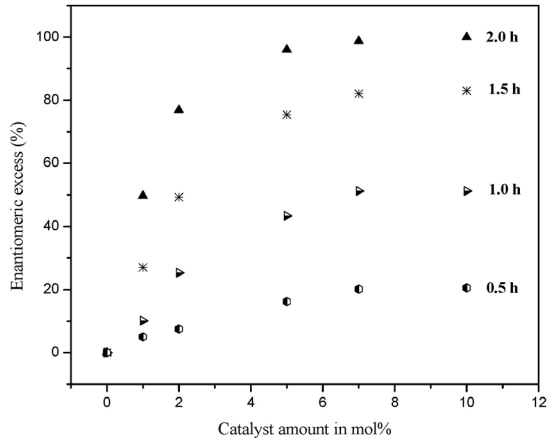
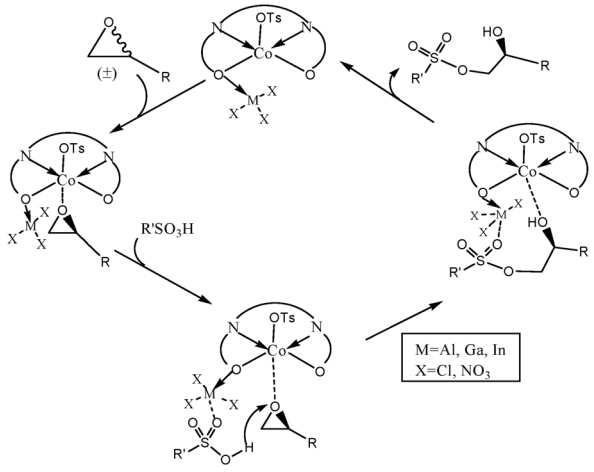
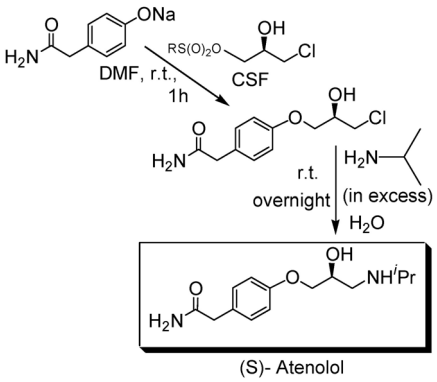


Figure 4. Effects of the varying amount of catalyst on the asymmetric ring opening of PGE with *p*-toluenesulfonic acid catalyst 2a keeping other reaction condition identical with Table 1.



Scheme 2. Proposed mechanism for a cooperative catalysis during the reaction.



Scheme 3. Application of the present study for the synthesis of (*S*)-atenolol chiral drugs.

Scheme 3 shows the practical utility of the present study for the synthesis of optically pure (*S*)-atenolol. Racemic atenolol is one of the top five best-selling drugs in the world today for the treatment of hypertension, angina and post-myocardial infarction, but the (*S*)-isomer has been found to avoid the occasional side effects of a lower heart rate encountered with racemate[16]. The use of these catalysts for the synthesis of (*S*)-atenolol chiral drug via Scheme 3 remains an important goal for the further study.

4. Conclusions

The enantioselective catalysis of reactions between nucleophiles and electrophiles is of synthetic interest because such processes can provide practical access to valuable chiral materials. Because the reactions of epoxides with nucleophiles containing oxygen are rather difficult, the ring opening of epoxides with oxygen-containing nucleophiles is quite challenging. The challenge was overcome and the good results are obtained in this work through successful use of organic sulfonic acid as a nucleophile to open terminal epoxide rings. The dinuclear chiral (salen) Co complexes bearing Lewis acids of Al, Ga and In catalyze the reaction enantioselectively in the presence of tetrabutylammonium chloride using *tert*-butyl methyl ether as a solvent. Strong synergistic effects of the different Lewis acid centers of Co-Al, Co-Ga and Co-In complex were found in the catalytic ring opening reactions. The dinuclear chiral salen catalyst containing $AlCl_3$ was found to be most active and highly enantioselective. However, the new application of these catalysts in the enantioselective ring opening of epoxides using various organic sulfonic acids would open the unique routes for a synthesis of valuable block compounds for the production of chiral drugs.

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