

Asymmetric Ring Opening of Epoxides Catalyzed by Novel Heterobimetallic Schiff-Bases Containing Transition Metal Salts

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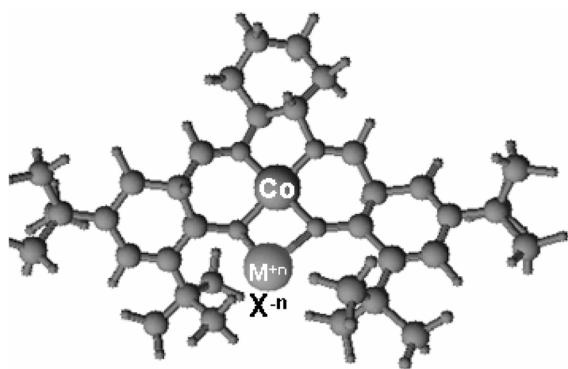
An enantioselective ring opening of racemic terminal epoxides has been achieved by using heterobimetallic cobalt salen complexes with variety of nucleophiles. They were proven to be highly enantioselective and reactive for the synthesis of valuable chiral building blocks in enantio-riched forms up to 98% ee.

Key Words : Kinetic resolution, Ring opening reactions, Heterobimetallic catalyst, Chiral intermediate

Introduction

Asymmetric catalysis is an attractive strategy for the production of valuable chiral building blocks as an academic and pharmaceutical interest. Specifically, hydrolytic kinetic resolution (HKR) is one of the most important reactions to synthesize an enantiomerically enriched terminal epoxides.¹ In our previous research, we have introduced that, dimeric chiral salens having 13 group metal salts such as AlCl_3 or GaCl_3 displayed good enantioselectivity and reactivity for the asymmetric kinetic resolution (AKR) of terminal epoxides.² More recently, Shibasaki *et al.* reported the heterobimetallic asymmetric catalysis in which the two different metal plays different role to enhance the reactivity of both reacting partners.³ In 1968, Gruber's group demonstrated that the preparation of both homo- and heterodinuclear complexes contained similar or dissimilar transition metal salts.⁴ On the basis of this report our idea was to design of chiral Co (salen) catalyst that contained transition metal salts as remarkably efficient catalyst.

In this paper, addition of nucleophiles, such as water, phenols and CO_2 to several terminal epoxides was examined using novel heterobimetallic Co (salen) catalysts (Scheme 1)



M=a=Co, b=Ni, c=Zn, d=Fe; X= Cl_2

M=e=Fe; X= Cl_3

M=f=Zn, g=Ni, h=Co; X=(NO_3)₂

Scheme 1. Cobalt salen catalyst with similar and dissimilar metals.

to obtain chiral building blocks. However, these types of catalysts have never been explored in the asymmetric synthesis; especially in enantioselective ring opening of terminal racemic epoxides to obtain the variety of chiral intermediates.

Wide ranges of synthetic application of our catalysts in AKR are readily envisaged. Surprisingly, very high catalytic activity and enantioselectivity were obtained not only for the special reaction but also for many other AKR reactions applied in this study, and were dependent on the type of transition metal salts combined to the cobalt-salens with the different nucleophiles. It has been already established that oxygen atoms of the metal complexes of the Schiff bases are able to coordinate to the transition metals to form bi- and trinuclear complex.⁵

Results and Discussion

A series of chiral Co (salen) complexes were screened in order to evaluate the reactivity and performance of chiral catalysts in HKR of epichlorohydrin (ECH) with H_2O as a model reaction and the results are summarized in Table 1. From this comparison, the catalyst **a**, **e**, **f**, and **h** exhibited high enantioselectivity with good yield in HKR reaction (Table 1, entries 1, 5, 6, and 8). As expected, the HKR of racemic styrene oxide, phenyl glycidyl ether, and methyl glycidyl ether underwent resolution with 96-99% ee of corresponding products under solvent-free condition (Table 1, entries 9-11). In each instance, the reactions carried out at ambient temperature were completed within 3-12 h. Furthermore, catalyst **a** and **e** were identified as the most effective among those evaluated although **f** and **h** were useful. Kinetic studies in HKR reaction using complex **a** revealed the reaction pathway involving the cooperative, intramolecular bimetallic catalysis.

(S)- β -Hydroxy- γ -butyrolactone is known as a satiety agent as well as a potential intermediate for variety of neuroleptic drugs.⁶ Encouraged with the initial success in the HKR reaction, the synthesis of (S)-(-)- β -hydroxy- γ -butyrolactone has been accomplished by employing HKR of methyl-4-oxobutanoate using 0.5 mol% of catalyst **a** to get chiral 3,4-

Table 1. Hydrolytic kinetic resolution (HKR) of terminal epoxides

Entry ^a	Catalyst	Mol% ^b	Time (h)	%ee ^c
1	a	0.3	3	99
2	a	0.05	12	98
3	e	0.3	5	97
4	e	0.5	2	99
5	e	0.05	12	97
6	f	0.3	3	99
7	f	0.5	1	99
8	f	0.05	12	99
9 ^d	a	0.3	5	94
10 ^e	a	1.0	7	96
11 ^f	a	0.3	3	99

^aEpichlorohydrine used as a reactant from entry 1 to 8. ^bCatalyst loading on a per Co basis relative to racemic epoxides. ^cee % was determined by chiral GC. ^dPhenyl glycidyl ether is used as a reactant. ^eStyrene oxide used as a reactant. ^fMethyl glycidyl ether is used as a reactant.

dihydroxy butanoate with 99% ee. Further, the cyclization of 3,4-dihydroxy butanoate was performed by using catalytic amount trifluoroacetic acid in methylene chloride (MC) as

shown in Scheme 2.

To widen the scope, catalyst **a** was tested in the HKR of (±) 1-[*p*-(cyanomethyl) phenoxy]-2,3-epoxypropane to obtain chiral epoxides. In this case, the nitrile substituted epoxides at para position displayed a high ee of chiral epoxides, which are vital intermediates for the synthesis of *S*(-)-atenolol.⁷⁻⁹ Transformation to chiral atenolol was simply achieved by asymmetric ring opening (ARO) of chiral 1-[*p*-(cyanomethyl) phenoxy]-2,3-epoxypropane with isopropyl amine, followed by hydration of nitrile groups as shown in Scheme 3. This is one of the promising strategies using chiral catalyst in our current study.

Spurred with the success of HKR of aromatic epoxides, another important reaction, and direct ring opening of terminal epoxides with phenols as nucleophile catalyzed by chiral cobalt complexes and the results are summarized in Table 2. As can be seen from Table 2, a series of terminal epoxides reacts with various phenol derivatives to offer corresponding optically enriched α-aryloxy alcohols with 84-99% ee in 38-43% yields. To further explore the utility of chiral cobalt salen catalysts for the enantioselective ring opening of terminal epoxides by phenols, 1-[*p*-(butoxycarbonyl) methyl] phenoxy]-2,3-epoxypropane was evaluated as a substrate for the synthesis of atenolol using catalyst **a** through kinetic resolutions. The ARO of racemic ECH proceeded perfectly both in terms of enantioselectivity and reactivity. The reaction was completed within 8 h to afford corresponding enantiopure α-aryloxy alcohols with 98% ee

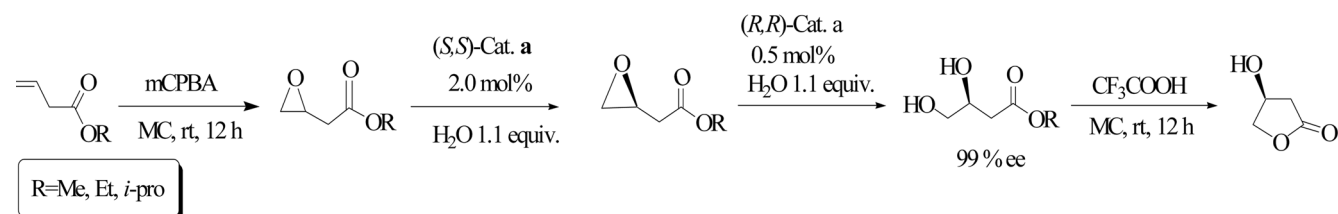
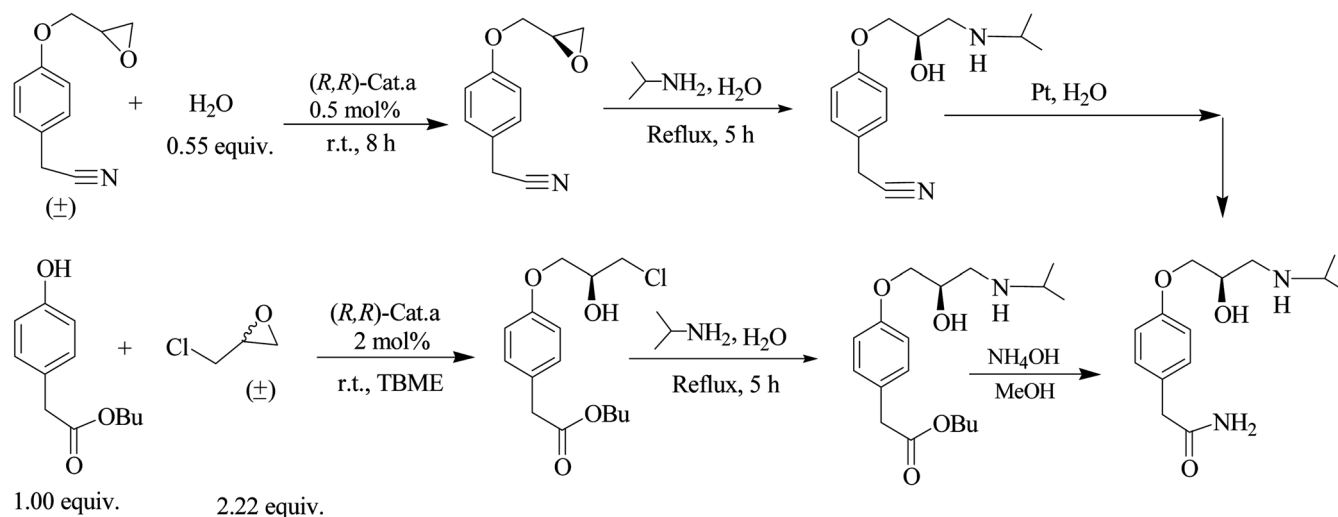
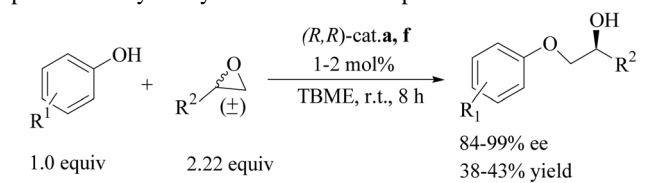
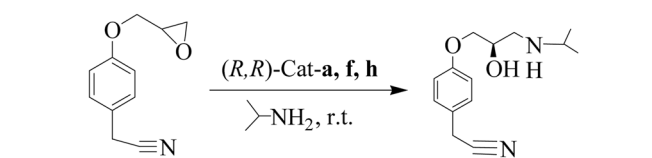
**Scheme 2.** Synthesis of *S*(-)-β-Hydroxy-γ-butyrolactone.**Scheme 3.** Synthesis of *S*(-)-Atenolol using cobalt salen **a** via kinetic resolution.

Table 2. Asymmetric ring opening of terminal epoxides with phenols catalyzed by heterometallic complexes

Entry	R ¹	R ²	Catalyst	Mol% ^a	Time [h]	ee% ^b (yield, % ^c)
1	H	CH ₂ Cl	a	1	8	98(41)
2	H	CH ₂ Cl	f	1	8	96(41)
3	3-Cl	CH ₂ Cl	f	1	9	98(40)
4	3-Cl	CH ₂ Cl	f	2	9	99(42)
5	3-Cl	C ₆ H ₅ -O-CH ₂	a	2	12	84(38)
6	3-Cl	C ₆ H ₅ -O-CH ₂	f	2	12	85(39)
7	3-CH ₃	CH ₂ Cl	a	2	8	92(43)
8	3-CH ₃	CH ₂ Cl	f	2	8	94(42)
9	3-CH ₃	CH ₂ Cl	f	1	8	94(41)

^aCatalyst loading on a per Co basis relative to racemic epoxides. ^bee % of ring opened product was determined by chiral HPLC/GC. ^cIsolated yield of ring opened product on the basis of racemic epoxides.

Table 3. Asymmetric ring opening of (±) 1-[*p*-(cyanomethyl) phenoxy]-2,3-epoxy propane with isopropyl amine catalyzed by heterometallic complexes

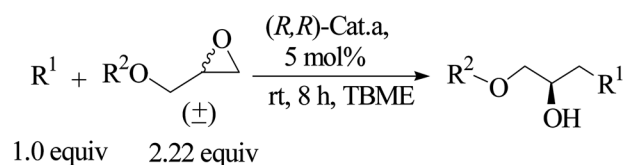
Entry	Catalyst	Mol% ^a	Solvent	Conv %	ee % ^b
1	a	5	TBME	30	96
2	f	5	TBME	34	95
3	f	5	MeCN	26	95
4	h	5	TBME	26	89

^aCatalyst loading on a per Co basis w.r.t to racemic epoxides. ^bee % of product was determined by chiral HPLC.

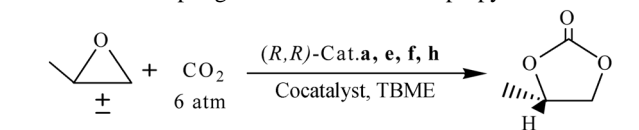
in 40% yields as shown in Scheme 3. To the best of our knowledge, we have first evaluated the direct opening of epoxides in case of chiral atenolol.

Interestingly, the kinetic resolution of (±) 1-[*p*-(cyanomethyl) phenoxy]-2,3-epoxypropane (Table 3) and (±)-glycidyl 1-naphthyl ether with isopropyl amine led to highly enriched atenolol or propranolol in presence of **a** in a one-pot reaction. As a special case, catalyst **a** was also effective in the ARO reaction of epoxide with NH₂-Boc as shown in Scheme 4. The practical utility of AKR of naphthyl glycidyl ether with NH₂-Boc may be focused on the synthesis of propranolol as reported by Bartoli *et al.*¹⁰

In recent year, the coupling reaction of carbon dioxide and epoxides to form chiral cyclic carbonates has received much attention.^{11,12} The chiral propylene carbonate is the crucial intermediate in the synthesis of Tenofovir as anti HIV/AIDS drugs.¹⁴ Chiral propylene carbonates are prepared by cyclization of chiral diols with triphosgene or by enzyme-



R¹ = NH₂-BOC, Isopropyl amine,
R² = Ph, Glycidyl-1-naphthyl ether

Scheme 4. Aminolytic kinetic resolution by using (*R,R*)-catalyst **a**.**Table 4.** CO₂ coupling reaction with racemic propylene oxide

Entry ^a	Catalyst	Cocatalyst	PC [ee%]	Yield, %
1 ^b	a	None	89	25
2 ^c	a	TBACl	54	19
3	a	TBACl	80	40
4 ^d	a	[EMIm]OH	63	32
5	a	TBAOH	79	39
6	a	K ₂ CO ₃	88	23
7 ^e	a	[BMIm]Br	60	25
8 ^f	h	TBACl	78	33
9	h	TBACl	83	43
10 ^g	h	TBACl	73	26
11	e	TBACl	68	19
12	e	TBAOH	46	14
13 ^h	f	None	90	29
14	f	TBACl	83	45
15 ⁱ	f	TBACl	85	44
16 ^j	f	[BMIm]OH	77	33
17	f	K ₂ CO ₃	89	23
18	f	[BMIm]Br	65	25

^aThe molar ratio used for reaction is PO:Cat:Co-cat 1:0.001:0.0005, ^{b,h}The reaction performed without co-catalyst. ^cReaction performed under solvent-free condition. ^gReaction performed using 0.4 and 0.2 mol% catalyst respectively. ^d[EMIm]OH = 1-ethyl-3-methylimidazolium hydroxide. ^e[BMIm]Br = 1-Ethyl-3-methylimidazolium bromide. ^f[BMIm]-OH = 1-Bu-3-methylimidazolium hydroxide.

mediated enantioselective hydrolysis of racemic cyclic carbonates.^{13,14} To avoid the use of toxic triphosgene in synthesis, the chemical fixation of CO₂ onto epoxides using bimetallic asymmetric catalysis is the most promising alternatives to prepare the corresponding five-member chiral propylene carbonates.¹³⁻¹⁶ The bimetallic catalytic addition of epoxides to CO₂ represents nontoxic, nonflammable and commercially useful methodology in this study. As a part of ongoing development of Co (salen) catalytic system, we had much interest in the possibility of employing the newly synthesized Co (salen) complexes for direct synthesis of optically active cyclic carbonates from the racemic terminal epoxides. As can be seen from Table 4, we have found **a**, **h** and **f** to be much more active and selective than the

analogous Co^{II}(salen) or Co^{III}(salen) complex^{12,13} in the binary catalytic system. Decreasing the loading amount of catalyst and the addition of quaternary ammonium salts as an additive increased the enantiomeric purity of product. The reaction without quaternary ammonium halide exhibited higher enantioselectivity but less in yield. However, the activity was greatly enhanced with addition of catalytic amount of quaternary ammonium halides. To the best of our knowledge, our catalytic system showed the highest enantioselectivity for the cycloaddition of CO₂ to epoxides under mild conditions among the reported catalysts.¹²

Conclusion

We have explored the new chiral Co (salen) complexes efficient for HKR, ARO of terminal epoxides by various nucleophiles, and the enantioselective cycloaddition of CO₂ to epoxypropane. New salen complexes applied in this work has displayed a high enantioselective inducing ability in each reaction, providing more than 98% ee in high product yields. We have developed new route to optically pure atenolol synthesis *via* AKR of racemic ECH with *p*-hydroxyphenyl acetic acid as nucleophiles, and in addition *via* HKR of (±) 1-[*p*-(cynomethyl)phenoxy]-2,3-epoxypropane. Our salen catalysts also showed a very unique activity in the kinetic resolution of epoxides with amine compounds such as isopropyl amine and NH₂-Boc. Efforts are underway to elucidate the mechanistic details and to explore other applications of the catalyst systems.

Experimental

All ¹H-NMR and ¹³C-NMR were recorded using OXFERD-400 MHz-NMR instrument. Chemical shifts for proton were reported in part per million downfield from tetramethyl silane (TMS) as an internal reference at ambient temperature. DMSO-*d*₆, CDCl₃ and D₂O solvents were used for NMR analysis. Infrared spectra (IR) were measured with a Perkin-Elmer Spectrum 2000 Explorer FT-IR spectrometer. Optical rotation measurements were conducted using a JASCO DIP 370 digital polarimeter. Chiral HPLC analyses were performed on a YOUNGLIN instrument using a Chiralcel[®] OD column (24 cm × 0.46 cm i.d. Chiral Technologies, Inc.) and Regis (*S,S*) Whelk-O1 at 254 nm. Chiral Gas chromatographic analyses were performed on Hewlett-Packard 5890 Series II instrument equipped with a FID detector using a chiral column (CHIRALDEX γ -TA and α -TA, 20 m × 0.25 mm i.d. (Astec) and a HP 3396 integrator with HP Chem Station software for data analysis.

(*R,R*)-*N,N*-Bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexanediamine Co-CoCl₂ (a). To a solution of (*R,R*)-*N,N*-bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexanediamine Co^{II} salen complex (1.00 g, 0.0016 mole, 1 equiv.) in 15 mL THF was added CoCl₂·6H₂O (0.473 g, 0.0019 mole, 1.2 equiv.) in 5 mL THF. The solution was stirred in open atmosphere at room temperature for 2 h and the solvent was removed in *vacuo*. The residue was dissolved in MC and the solution

was only collected to remove unreacted excess metal salts: The product **a** was obtained as a dark brown solid after removal of solvent in *vacuo* (1.19 g, 0.00162 mole, 98% yield).

¹H-NMR (400 MHz, DMSO-*d*₆): δ 1.28 (s, 18H), 1.50-1.62 (m, 2H), 1.72 (s, 18H), 1.80-1.95 (m, 4H), 1.96-1.98 (m, 2H), 3.1-3.2 (m, 2H), 3.5-3.7 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 2H), 7.45 (d, *J* = 2.4 Hz, 2H), 7.78 (s, 2H). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ 25.8, 31.1, 32.2, 36.4, 67.6, 69.9, 119.2, 129.3, 136.4, 142.3, 162.5. FT-IR (KBr): [cm⁻¹] = 2954, 2866, 1637, 1611, 1525, 1465, 1369, 1249, 1202, 1165, 1023, 925, 835, 782, 754, 636, 595. Anal. Cal. For C₃₆H₅₂Cl₂Co₂N₂O₂: C, 58.94; H, 7.14; Cl, 9.67; Co, 16.07; N, 3.82; O, 4.36 Found: C, 59.03; H, 7.00; Cl, 9.52; Co, 16.00; N, 3.79; O, 4.45.

(*R,R*)-*N,N*-Bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexanediamine Co-FeCl₃ (e). To a solution of (*R,R*)-*N,N*-bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexanediamine salen Co^{II} complex (1.00 g, 0.0016 mole, 1.0 equiv.) in 15 mL THF was added FeCl₃ (0.322 g, 0.0019 mole, 1.2 equiv.) in 5 mL THF. The residue was dissolved in MC and the solution was filtered to remove excess metal salts: The product **e** was obtained as a dark brown solid after removal of solvent in *vacuo* (1.20 g, 0.00150 mole, 95% yield). ¹H-NMR (400 MHz, DMSO-*d*₆): δ 1.27 (s, 18H), 1.55-1.68 (m, 2H), 1.71 (s, 18H), 1.86-1.95 (m, 4H), 1.96-2.20 (m, 2H), 3.0-3.2 (m, 2H), 3.5-3.8 (m, 2H), 7.41 (d, *J* = 2.4 Hz, 2H), 7.59 (d, *J* = 2.4 Hz, 2H), 7.76 (s, 2H). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ , 24.5, 25.8, 29.3, 30.9, 31.5, 35.7, 69.21, 119.3, 128.4, 134.1, 142.3, 158.5, 162.1.164.8. FT-IR (KBr): [cm⁻¹] = 2954, 2866, 1634, 1609, 1511, 1459, 1365, 1251, 1208, 1169, 1035, 985, 834, 785, 734, 640, 597. Anal. Cal. For C₃₆H₅₂Cl₃CoFeN₂O₂: C, 56.90; H, 7.10; Cl, 13.62; Co, 7.55; Fe, 7.15; N, 3.59; O, 4.10 Found: C, 56.85; H, 7.13; Cl, 13.66; Co, 7.60; Fe, 7.20; N, 3.62; O, 4.09.

(*R,R*)-*N,N*-Bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexanediamine Co-Zn(NO₃)₂ (f). To a solution of (*R,R*)-*N,N*-bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexanediamine salen Co^{II} complex (1.00 g, 0.0016 mole, 1.0 equiv.) in 15 mL THF was added Zn(NO₃)₂·6H₂O (0.591 g, 0.0019 mole, 1.2 equiv.) in 5 mL THF. The solution was stirred at open atmosphere at room temperature for 2 h, and the solvent was removed in *vacuo*. The residue was dissolved in MC and filtered to remove unreacted metal salts: The product **f** was obtained as a dark brown solid after removal of solvent in *vacuo* (1.26 g, 0.00160 mole, 96% yield).

¹H-NMR (400 MHz, DMSO-*d*₆): δ = 1.25 (s, 18H), 1.54-1.64 (m, 2H), 1.71 (s, 18H), 1.80-1.90 (m, 4H), 1.95-1.97 (m, 2H), 3.1-3.2 (m, 2H), 3.5-3.6 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 2H), 7.42 (d, *J* = 2.4 Hz, 2H), 7.74 (s, 2H). ¹³C-NMR (400 MHz, DMSO-*d*₆): δ = 24.3, 25.1, 29.5, 30.5, 31.5, 33.5, 67.0, 69.2, 118.5, 128.6, 129.0, 135.8, 141.7, 161.8, 164.4. FT-IR (KBr): [cm⁻¹] = 2950, 2863, 1635, 1608, 1523, 1461, 1361, 1253, 1200, 1172, 1026, 926, 833, 783, 744, 640, 597. Anal. Cal. For C₃₆H₅₂CoN₄O₈Zn: C, 54.52; H, 6.61; Co, 7.43; N, 7.06; O, 16.14; Zn, 8.24 Found: C, 54.50; H, 6.65; Co, 7.39; N, 7.10; O, 16.20; Zn, 8.20.

(*R,R*)-*N,N*-Bis(3,5-*tert*-butylsalicylidene)-1,2-cyclohexane-diamine Co-Co(NO₃)₂ (h**).** The catalyst was synthesized as a similar procedure of the complex **f** only with the substitution of Co(NO₃)₂·6H₂O for Zn(NO₃)₂·6H₂O. The product **h** was obtained as a dark green solid. ¹H-NMR (400 MHz, DMSO-*d*₆): δ = 1.24 (s, 18H), 1.55-1.68 (m, 2H), 1.69 (s, 18H), 1.86-1.95 (m, 2H), 1.96-2.20 (m, 2H), 3.0-3.2 (m, 2H), 3.5-3.8 (m, 2H), 7.40 (d, *J* = 2.4 Hz, 2H), 7.59 (d, *J* = 2.4 Hz, 2H), 7.74 (s, 2H). ¹³C-NMR (400 MHz, DMSO-*d*₆) δ = 24.3, 25.1, 29.5, 30.4, 31.5, 33.5, 35.7, 66.9, 69.2, 118.5, 128.6, 129.0, 135.8, 141.6, 161.8, 164.4. FT-IR (KBr): [cm⁻¹] = 2950, 2863, 1635, 1608, 1523, 1461, 1361, 1253, 1200, 1172, 1026, 926, 833, 783, 744, 640, 597. Anal. Cal. for C₃₆H₅₂Co₂N₄O₈: C, 54.96; H, 6.66; Co, 14.98; N, 7.12; O, 16.27. Found C, 54.55; H, 6.67; Co, 15.00; N, 7.15; O, 16.30.

(*S*)-ECH (Entry 1, Table 1). An oven dried 25 mL flask equipped with a stir bar was charged with (*R,R*) catalysts **a** (0.3 mol %) and (±)-ECH (3.7 g, 40 mmol, 1.0 equiv.) was stirred at open atmosphere at room temperature water bath. H₂O (0.396 g, 22 mmol, 0.55 equiv.) was added slowly. The reaction was mildly exothermic. The reaction mixture was allowed to stir for 5 h. The optically pure product was isolated on Kugelrohr distillation (seal less tube oven Eyela KRD100, Tokyo Rikakikai Co. Ltd.) into a 0 °C receiving flask. The recovered epoxide was followed filtration through a pad of MgSO₄ to remove excess H₂O. An ee value (> 99%) of the recovered epoxide was determined to be Chiral GC (*γ*-TA, 50 °C, isothermal, [*α*]_D²⁰ + 33.5 (c = 1, CH₃OH) and compared with commercially available standard product. ¹H, ¹³C NMR and elemental analysis confirmed the recovered epoxides.

(*S*)-Phenyl glycidyl ether (Entry 9, Table 1) & (*S*)-Styrene Oxide (Entry 10, Table 1). Synthesis procedure and analysis conditions followed by as mentioned above.

(*S*)-Glycidyl methyl ether (Entry 11, Table 1). An oven dried 25 mL flask equipped with a stir bar was charged with (*R,R*) catalysts **a** (0.3 mol %) and (±)-glycidyl methyl ether (3.524 g, 40 mmol, 1.0 equiv.) was stirred under open atmosphere at room temperature water bath. H₂O (0.396 g, 22 mmol, 0.55 equiv.) was added drop wise. The reaction was mildly exothermic. The reaction mixture was allowed to stir for 3 h. After reaction the recovered epoxide was treated with excess of aq. HCl (35%) and ring opened epoxide (1-Chloro-3-phenoxy-propane-2-ol) was analyzed by Chiral GC analysis product obtained in > 99% ee (Chiraldex *γ*-TA, 60 °C isothermal). The structure of products was confirmed by ¹H, ¹³C NMR and elemental analysis.

General procedure for phenolic kinetic resolution (Table 2). In a representative reaction of ECH and phenol, with (*R,R*) catalysts **a** (1-2 mol %), *tert*-butyl methyl ether (TBME) and (±)-ECH (2.22 equiv.) were charged in an oven dried 25 mL flask and the reaction mixture was stirred in open atmosphere at ambient temperature. Phenol (1.0 equiv.) was added after complete dissolution of the catalyst. The resultant solution was stirred for 8 h and monitored by chiral GC and HPLC. The purification of the products was

performed by flash column chromatography.

Butyl-*p*-hydroxyphenyl acetate. *p*-Hydroxyphenyl acetic acid (5 g, 0.03 mol) and NaHSO₄ (0.2 g) was dissolved in butyl alcohol (50 mL) at room temperature. A solution was refluxed and water removed through dean stark apparatus by azeotropic distillation. After completion of reaction, excess butyl alcohol was removed under reduced pressure offered oily turbid liquid purified by means of liquid column chromatography. Purification offered a colorless oily liquid 6.5 g (95% yields).

¹H-NMR (400 MHz, CDCl₃): δ = 0.96 (t, 3H), 1.22-1.68 (m, 4H), 3.51 (s, 2H), 4.1 (t, 2H), 6.72-7.20 (q, 4H). ¹³C-NMR (400 MHz, CDCl₃) δ = 13.6, 13.7, 18.8, 19.0, 30.4, 34.6, 40.5, 62.7, 64.8, 115.4, 125.5, 130.2, 155.2, 172.7. FT-IR (neat): [cm⁻¹] = 1740, 3450.

(*S*)-1-[*p*-[(Butoxycarbonyl) methyl] phenoxy]-3-chloropropane-2-ol. A solution of (±)-ECH (0.98 g, 0.01 mol, 2.22 equiv.), with (*R,R*) catalysts **a** (0.156 g, 2 mol%) dissolved in TBME and stirred for 15 min at room temperature followed by the drop wise addition of Butyl-*p*-hydroxyphenyl acetate (1 g, 0.004 mol) in TBME for 5 min. The reaction mixture was slightly warm and left for 8 h at room temperature under stirring. The reaction was monitored by TLC and the product was purified by flash column chromatography using silica gel to offer the colorless oil 1.25 g. The enantiomeric excess (*ee*) of the product is monitored by HPLC (OD-H- column). ¹H-NMR (400 MHz, CDCl₃): δ = 0.96 (t, 3H), 1.22-1.80 (m, 4H), 2.6 (d, 1H), 3.51 (s, 2H), 3.71 (d, 2H), 4.0-4.4 (m, 5H), 6.80-7.40 (q, 4H). ¹³C-NMR (400 MHz, CDCl₃) δ = 13.6, 19.0, 30.5, 40.4, 45.9, 64.7, 68.5, 69.8, 79.5, 114.6, 127.1, 130.3, 157.2, 171.8. FT-IR (neat): [cm⁻¹] = 1730, 3430.

(*S*)-1-[*p*-[(Butoxycarbonyl) methyl] phenoxy]-3-(isopropylamino) propane-2-ol. The mixture of optically pure (*S*)-1-[*p*-[(Butoxycarbonyl) methyl] phenoxy]-3-chloropropane-2-ol (1.0 g, 0.0033 mol), isopropyl amine (6 mL) and water (1 mL) was refluxed for 3 h. The reaction was monitored by TLC. Excess isopropyl amine was removed under reduced pressure. Residue was extracted by ethyl acetate, followed by the addition of water. The solvent was evaporated and crude product was recrystallized from hexane to give white crystals 0.80 g (74 % yield).

¹H-NMR (400 MHz, CDCl₃): δ = 0.96 (t, 3H), 1.1 (d, 6H), 1.22-1.80 (m, 4H), 2.4 (s, 2H), 2.7-2.9 (m, 3H), 3.51 (s, 2H), 3.9-4.2 (m, 5H), 6.80-7.40 (q, 4H). ¹³C-NMR (400 MHz, CDCl₃) δ = 13.6, 19.0, 30.6, 48.9, 49.2, 64.6, 68.4, 70.5, 114.6, 126.6, 130.2, 157.7, 171.9.

(*S*)-Atenolol. An optically pure (*S*)-1-[*p*-[(Butoxycarbonyl) methyl] phenoxy]-3-(isopropyl amino) propane-2-ol (0.5 g, 0.0015 mol) dissolved in cold methanol (3 mL) and NH₄OH (1 mL) was stirred at room temperature until TLC showed completion of reaction. The solvent was removed under reduced pressure to offer the crude atenolol, and it was purified by recrystallization from ethyl acetate to give a pure atenolol 0.30 g (73% yield).

¹H-NMR (400 MHz, D₂O): δ = 1.1 (d, 6H, *J* = 2 Hz), 2.81-2.96 (m, 3H), 3.58 (s, 2H), 4.04-4.14 (m, 3H), 7.01-7.30 (q,

4H). ^{13}C -NMR (400 MHz, D_2O) δ = 20.95, 20.97, 41.0, 48.2, 48.6, 68.4, 70.6, 114.9, 115.2, 130.4, 130.6, 157.4, 178.0.

(S)-1-[p-(Cyanomethyl) phenoxy]-2,3-epoxypropane. A mixture of (\pm)-1-[p-(cyanomethyl) phenoxy]-2,3-epoxypropane (1.0 g, 0.0053 mol, 1 equiv.), (**R,R**)-catalyst **a** (0.5 mol%) dissolved in THF and the mixture were stirred at room temperature. H_2O (0.052 g, 0.55 equiv.) was added drop wise. The reaction was mildly exothermic. The reaction mixture was stirred up to occurrence of optically terminal epoxides and was checked periodically by HPLC using OD-H Chiral column as well as TLC. After completion of reaction, the solvent was removed under reduced pressure, and epoxide was extracted by MC followed by addition of water. Yield of product was 45% (98% ee) on the basis of racemic epoxide. H-NMR (400 MHz, CDCl_3): δ = 2.71 (dd, 1H, J = 1.6, 3.6 Hz), 2.87 (t, 1H, J = 4.4 Hz), 3.32 (m, 1H), 3.65 (s, 2H), 3.92 (dd, 1H, J = 5.6 Hz), 4.22 (dd, 1H, J = 2.4, 2.8 Hz), 6.89 (d, 2H J = 8 Hz), 7.21 (d, 2H J = 8 Hz). ^{13}C -NMR (400 MHz, CDCl_3) δ = 22.8, 44.6, 50.0, 68.8, 115.1, 118.0, 122.3, 129.0, 158.0.

(S)-1-[p-(Cyanomethyl) phenoxy]-3-(isopropylamino) propane-2-ol. The mixture of an optically pure (*S*)-1-[p-(cyanomethyl) phenoxy]-3-chloropropane-2-ol (0.8 g, 0.0035 mol, 1equiv.), isopropyl amine (6 mL) and water (1 mL) was refluxed for 3 h. The reaction was monitored by TLC. Excess isopropyl amine was removed under reduced pressure. Residue was extracted by ethyl acetate, followed by the addition of water. The solvent was evaporated and the crude product was recrystallized from hexane to give yellowish white crystals 0.62 g (70% yield). H-NMR (400 MHz, CDCl_3): δ = 1.1 (s, 6H), 2.7 (m, 1H), 2.9 (d, 2H), 3.67 (s, 2H), 3.9-4.2 (m, 3H), 6.80-7.40 (q, 4H). ^{13}C -NMR (400 MHz, CDCl_3) δ = 22.8, 23.0, 23.1, 48.8, 49.2, 68.3, 68.9, 70.6, 115.0, 118.0, 121.9, 128.9, 129, 158.3.

(S)-(-)-3,4-Dihydroxybutanoate methyl ester. A solution of (\pm)-methyl-4-oxobutanoate (1 g, 0.0086 mol, 1 equiv.) in 2 mL THF and (*S,S*)-catalyst **a** (2.54 mg, 0 mol%) was stirred for 10 min at room temperature in 25 mL round bottom flask. The flask was cooled to 5 °C and H_2O (0.09 g, 0.55 equiv.) was added in one portion. The reaction was allowed to warm up room temperature and stirred for 12 h. The reaction monitored by GC indicated that diol was presented in 50% yield. Hexane was added and filtered to remove the catalyst. The residue was stirred with the mixture of water and ethyl acetate (1:1 vol. ratio). The ethyl acetate layer was collected and dried with Na_2SO_4 , and then concentrated in *vacuo*. The residue was purified by flash column with MC:Methanol (80:20). The optical purity determined with chiral γ -TA column was 99% ee. H-NMR (400 MHz, CDCl_3): δ = 2.50 (dd, 2H, J = 12, 8 Hz), 3.52 (m, 1H), 3.63-3.76 (m, 1H) overlapping with 3.70 (s, 3H), 4.10 (m, 1H). ^{13}C -NMR (400 MHz, CDCl_3) δ = 35.9, 37.5, 51.9, 52.5, 65.6, 68.5, 172.7.

(S)- β -Hydroxy- γ -butyrolactone. An optically pure (*S*)-

(-)-3,4-dihydroxybutanoate methyl ester was dissolved in 5 mL MC and catalytic amount of CF_3COOH was added, and it was refluxed for 12 h. After completion of reaction, the solvent was removed under reduced pressure and the product was purified through column chromatography. The optical purity determined by chiral γ -TA column indicated 98% ee. H-NMR (400 MHz, CDCl_3): δ = 2.28 (dd, 1H, J = 16.4, 1.2 Hz), 2.59-2.65 (dd, 1H, J = 6.0, 6.0 Hz), 4.11-4.14 (dd, 1H) 4.25-4.29 (dd, 1H), 4.5 (dd, 1H). ^{13}C -NMR (400 MHz, CDCl_3) δ = 37.4, 66.9, 76.2, 177.3.

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