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Synthesis and application of bimetallic chiral [Co(salen)]-type complexes: a new catalytic approach to synthesis of optically pure β-blockers via kinetic resolution of epichlorohydrin

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A series of bimetallic chiral [Co(salen)]-type complexes were successfully applied for the synthesis of optically pure β-blockers via phenolic kinetic resolution (PKR) of racemic epichlorohydrin [2-(chloromethyl)oxirane; (±)ECH]. The reaction proceeded readily at room temperature and consequently provided enantiomerically enriched corresponding α-aryloxy alcohols with excellent enantioselectivities of up to 98% ee. The PKR method described in this work is highly efficient and straightforward strategy for the synthesis of chiral building blocks.

Keywords: kinetic resolution; β-blockers; asymmetric catalysis; cobalt salen; α-aryloxy alcohols; ionic liquids; nonlinear effect

Introduction

The chirality of drugs is an important issue from pharmacological, pharmacokinetics, toxicological, and regulatory point of view.[1–4] Nowadays more research efforts have been focused on the production of optically pure products due to increasing demand for drugs that are administered in optically pure form.[5–7] The synthesis of optically pure β-blockers is a very important task in the asymmetric catalysis as well as being of pharmaceutical interest. The β-adrenergic blocking agents (β-blockers) are used for the treatment of various cardiovascular diseases such as hypertension, angina pectoris and cardiac arrhythmia.[8] In this category, atenolol and propranolol are the most important and widely prescribed drugs on the large scale.[9,10] In recent decades, numerous efforts have been devoted to the synthesis of β-blockers via lipase catalysis[11,12] or hydrolytic kinetic resolution (HKR),[13,14] or by a nitrile hydration catalytic method.[15] To the best of our knowledge, only a few synthetic methods of atenolol from racemic epichlorohydrin [2-(chloromethyl)oxirane; (±)-ECH] have been reported.[16] On the basis of these facts, the great utility of chiral oxiranes in stereoselective synthesis provided the motivation to develop a new method from which chiral atenolol could be prepared from racemic oxiranes. Among theses available methods, HKR provides a general protocol to achieve highly enantiomer-enriched chiral building blocks that are available from inexpensive racemic materials.[17,18] In our recent study, we have shown that [Co(salen)]-type complexes bearing transition-metal salts exhibited good enantioselectivity and reactivity for the HKR of racemic terminal oxiranes in the synthesis of chiral atenolol.[19] From a practical synthetic point of view, phenol derivatives are appealing candidates as nucleophiles for the ring opening of (±)-ECH, providing direct access to enantiopure α-aryloxy alcohols using chiral cobalt-salen complexes.[20,21] These chiral intermediates are valuable for the synthesis of β-blockers.

In continuation of our work, herein we report the synthesis and application of chiral [Co(salen)]-type complexes to the asymmetric phenolic kinetic resolution (PKR) of (±)-ECH. This method would allow an effective protocol for the synthesis of β-blockers via PKR reaction.

Experimental

Materials

All chemicals and reagents were purchased from Aldrich, Fluka and TCI (Tokyo Chemical Industry). The following abbreviations are used for the solvents: TBME, (*tert*-butyl methyl ether); CH_3CN (acetonitrile); $CHCl_3$, (chloroform); CH_2Cl_2, (dichloromethane); and THF (tetrahydrofuran).

IR spectroscopy

Infrared (IR) spectroscopy analysis was conducted using a Perkin–Elmer (Spectrum 2000 Explorer) spectrometer as thin films on KBr pellets. The spectra were obtained in the absorbance mode in a wave number range of 500–4000 cm^{-1} and analyzed using commercial software.

NMR spectroscopy

All ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova 400 MHz spectrometer (Varian Inc., Palo Alto, CA,

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USA) at ambient temperature. ^{1}H NMR chemical shifts (δ) were referenced to tetramethylsilane (TMS) as an internal standard and ^{13}C NMR chemical shifts (δ) were referenced to the internal solvent resonance. Signals are quoted in parts per million (ppm) as δ downfield from TMS as an internal reference. Coupling constants (J values) are given in hertz. $CDCl_3$, DMSO-d_6 and D_2O solvents were used for sample preparation. The following abbreviations were used to designate chemical shift multiplicities: s = singlet; d = doublet; t = triplet; m = multiplate signal.

GC analyses

Gas chromatographic (GC) analyses were conducted on Hewlett-Packard HP5890 Series II instrument equipped with a flame ionization detector (FID) using a following commercially available capillary columns: Chiraldex γ-TA (20 m $\times$ 0.25 mm i.d.; Advanced Separation Technologies Inc.) and Chiraldex α-TA (20 m $\times$ 0.25 mm i.d.; Advanced Separation Technologies Inc.). The HP 3396 integrator with HP Chem Station software was used for data analysis.

HPLC analyses

Chiral high-performance liquid chromatographic (HPLC) analyses were performed on a Younglin instrument (Younglin Co. Ltd, Seoul, Korea) using either a Chiralcel®-OD column (24 $\times$ 0.46 cm i.d.; Chiral Technologies Inc.) or (*R*, *R*)-Whelk-O1/(*S*, *S*) Whelk-O1 column (24 $\times$ 0.46 cm i.d.; Regis) at 254 nm. Autochro-2000 software was used for data analysis.

Samples were prepared by following method for HPLC or GC analyses. The reaction mixture was filtered through a pad of silica and washed with mixture of EtOAc–hexanes. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (60, particle size 0.043–0.065 mm, RStech Corporation, Korea) with 20% EtOAc–hexanes. The enantiomeric purity was determined by HPLC or GC.

TLC analyses

The reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck silica gel-coated glass plates (60F-254) using UV light to visualize the course of the reaction.

Column chromatography

Flash column chromatography was performed using silica (60, particle size 0.043–0.065 mm, RStech Corporation, Korea) packed in a glass column.

ESCA analyses

Electron spectroscopy for chemical analysis (ESCA) data was obtained with a Sigma–Probe (Thermo VG, UK) spectrometer using Mg $K\alpha$ radiation as an excitation source ($h\nu$ = 1253.6 eV). Binding energy was compared with a reference of cobalt salt such as Co(II) salen purchased from Aldrich.

UV analyses

UV spectra were recorded on UV–vis spectrophotometer (Optizen 2120 UV, available from Lab korea, Incheon, Korea) interfaced with a PC using Optizen view 3.1 software for data analysis.

General procedure for the preparation of bimetallic chiral [Co(salen)]-type complexes (a–f)

The bimetallic chiral Co (salen) complexes were synthesized by mixing in a 1 : 1.2 molar ratio of (*R*, *R*)-(−)-*N*, *N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (**A**) and transition-metal-salts in THF. The mixture was stirred in an open flask for 2 h. After the evaporation of the solvent, the obtained catalyst was collected by dissolution in CH_2Cl_2 to remove the unreacted metal salts. Evaporation of CH_2Cl_2 gave a dark green or dark brown solid powder; yield 95–98%.

General procedure for the kinetic resolution of (±)-ECH by using bimetallic chiral catalyst

A solution of (±)-ECH (0.98 g, 10.5 mmol, 2.22 equiv.), with (*R*, *R*) catalyst-**a** (0.156 g, 0.21 mmol, 2 mol%) dissolved in TBME was stirred for 15 min at room temperature, followed by the dropwise addition of butyl 2-(4-hydroxyphenyl)acetate (BHPA; 1 g, 4.8 mmol, 1.00 equiv.) in TBME for 5 min. The reaction mixture was slightly exothermic and it was kept under stirring for 10–12 h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography using silica gel (EtOAc–hexanes, 2 : 8), offering the colorless oily product in 1.15 g (82% yield). The enantiomeric excess (ee) of the product was determined by chiral HPLC.

Nonlinear effect studies

Catalyst (*R*, *R*)-**a** (32.5 mg, 4.4×10^{-5} M) was dissolved in a solution of (±)-ECH (2.00 M) in TBME (1.00 mL) and stirred for 8 h. An identical TBME solution of (*S*, *S*)-**a** (32.5 mg, 4.4×10^{-5} M) and (±)-ECH (2.00 M) was prepared and stirred for 8 h. Relative concentrations of the catalyst were confirmed by diluting aliquots (20 µL $\times$ 3) with THF and measuring the characteristics absorbance at 365 nm by UV–vis spectrophotometer. Reactions were carried out by mixing the solutions of enantiomeric catalysts in appropriate ratios and then adding a solution of BHPA in TBME (1.0 M) such that $[ECH]_0$ = 2.0 M, $[BHPA]_0$ = 1.00 M and [catalyst] = 0.01 M. All reactions approached completion within 12 h. The ee% of the ring opened product was determined by chiral HPLC.

*Dichloro{µ-{{2, 2′-{(1R, 2R)-cyclohexane-1,2-dilybis[(nitrilo-κN)methylidyne]}bis[4,6-bis(1,1-dimethylethyl)phenolato-κO:κO]}(2-)}}dicobalt (**a**)*

IR (KBr, cm^{-1}): 2954, 2866, 1637, 1611, 1525, 1465, 1369, 1249, 1202, 1165, 1023, 925, 835, 782, 754, 636, 595. ^{1}H 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). ^{13}C 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. Anal. calcd for $C_{36}H_{52}Cl_2Co_2N_2O_2$ (732): 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.

*{µ-{{2, 2′-{(1R, 2R)-cyclohexane-1,2-dilybis[(nitrilo-κN)methylidyne]}bis[4,6-bis(1,1-dimethylethyl)phenolato-κO:κO]}(2-)}}(dichlorozinc)cobalt (**b**)*

IR (KBr, cm^{-1}): 2950, 2866, 1604, 1523, 1461, 1388, 1361, 1249, 1203, 1033, 907, 866, 833, 788, 574. ^{1}H NMR (400 MHz, DMSO-d_6):

δ =1.29 (s, 18H), 1.50–1.58 (m, 2H), 1.73 (s, 18H), 1.80–1.95 (m, 4H), 1.96–1.98 (m, 2H), 3.0–3.1 (m, 2H), 3.5–3.6 (m, 2H), 7.42 (d, J = 2.4 Hz, 2H), 7.45 (d, J = 2.4 Hz, 2H), 7.79 (s, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ=24.2, 29.3, 30.3, 31.4, 33.5, 35.7, 66.9, 86.4, 118.4, 128.6, 141.6, 161.8, 164.4. Anal. calcd for $C_{36}H_{52}Cl_2CoN_2O_2$ (737): C, 59.19; H, 7.17; Cl, 9.71; Co, 8.07; 7.64; N, 3.83; O 4.38. Found: C, 59.15; H, 7.15; Cl, 9.69; Co, 8.00; 7.62; N, 3.79; O, 4.36.

*Trichloro(cobalt){μ-{{2, 2′-{(1R, 2R)-cyclohexane-1,2-dilybis[(nitrilo-κN)methylidyne]}bis[4,6-bis(1,1-dimethylethyl)phenolato-κO:κO]}(2-)}}iron (**c**)*

IR (KBr, cm^{-1}): 2954, 2866, 1634, 1609, 1511, 1459, 1365, 1251, 1208, 1169, 1035, 985, 834, 785, 734, 640, 597. ^{1}H 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), 1.9–2.20 (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). ^{13}C 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. Anal. calcd for $C_{36}H_{52}Cl_3CoFeN_2O_2$ (764): 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.

*{μ-{{2, 2′-{(1R, 2R)-cyclohexane-1,2-dilybis[(nitrilo-κN)methylidyne]}bis[4,6-bis(1,1-dimethylethyl)phenolato-κO:κO]}(2-)}}[di(nitrato-κN)nickel]cobalt (**d**)*

IR (KBr, cm^{-1}): 2950, 2866, 1616, 1527, 1434, 1384, 1253, 1203, 1172, 871, 833, 783, 574, 543. ^{1}H NMR (400 MHz, DMSO-d_6): δ=1.27 (s, 18H), 1.54–1.58 (m, 2H), 1.73 (s, 18H), 1.80–1.85 (m, 4H), 1.96–1.97 (m, 2H), 3.0–3.1 (m, 2H), 3.5–3.6 (m, 2H), 7.41 (d, J = 2.4 Hz, 2H), 7.43 (d, J = 2.4 Hz, 2H), 7.77 (s, 2H). Anal. calcd for $C_{36}H_{52}CoN_4NiO_8$, (786): C, 54.98; H, 6.66; Co, 7.49; N, 7.12; Ni, 7.46; O, 16.28. Found: C, 54.95; H, 6.54; Co, 7.45; N, 7.09; Ni, 7.45; O, 16.25.

*{μ-{{2, 2′-{(1R, 2R)-cyclohexane-1,2-dilybis[(nitrilo-κN)methylidyne]}bis[4,6-bis(1,1-dimethylethyl)phenolato-κO:κO]}(2-)}}[di(nitrato-κN)zinc]cobalt (**f**)*

IR (KBr, cm^{-1}): 2950, 2863, 1635, 1608, 1523, 1461, 1361, 1253, 1200, 1172, 1026, 926, 833, 783, 744, 640, 597. ^{1}H 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). ^{13}C 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. Anal. calcd for $C_{36}H_{52}CoN_4O_8Zn$, (793): 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)-butyl 2-[4-(3-chloro-2-hydroxypropoxy)phenyl]acetate (Table 2, entry 1)

IR (neat): 3430, 1730 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ=0.96 (t, J = 14.8 Hz, 3H, $-CH_3$), 1.22–1.80 [m, 4H, $(-CH_2)_2$], 2.6 (d, J = 6.0 Hz, 1H, –OH), 3.51 (s, 2H, Ph–CH_2), 3.71 (d, J = 6.0 Hz, 2H, $-CH_2Cl$), 4.0–4.4 [m, 5H, $(-OCH_2)_2$, –CH], 6.85 (d, J = 8.8 Hz, 2H, Ph–H); 7.17 (d, J = 8.8 Hz, 2H, Ph–H). ^{13}C NMR (400 MHz, $CDCl_3$): 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.

(S)-butyl 2-{4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl} acetate

IR (KBr): 3290, 3210, 1724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.96 (t, J = 14.8 Hz, 3H, $-CH_3$), 1.1 [d, J = 6.4 Hz, 6H, $(-CH_3)_2$], 1.22–1.80 [m, 4H, $(-CH_2)_2$], 2.4 (br, s, 1H, –OH), 2.7–2.9 (m, 3H, $-CH_2N-$, –CHN–), 3.51 (s, 2H, Ph–CH_2), 3.9–4.2 [m, 5H, $(-OCH_2)_2$, –CH], 6.85 (d, J = 8.8 Hz, 2H, Ph–H); 7.17 (d, J = 8.8 Hz, 2H, Ph–H). ^{13}C NMR ($CDCl_3$): 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.

(R)-methyl 2-[4-(3-chloro-2-hydroxypropoxy)phenyl]acetate (Table 2, entry 4)

^{1}H NMR (400 MHz, $CDCl_3$): δ=3.58 (s, 2H, Ph–CH_2), 3.69 (s, 3H, $-OCH_3$), 3.73–3.77 (m, 2H, $-CH_2Cl$), 4.08–4.2 = (m, 3H, $-OCH_2$, –CH), 6.87–6.89 (d, J = 8.8 Hz, 2H, Ph–H), 7.20–7.22 (d, J = 8.4 Hz, 2H, Ph–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ=40.2, 45.7, 52.0, 68.7, 69.8, 114.5, 126.7, 130.3, 157.2, 172.1.

(S)-methyl 2-{4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl} acetate

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.07 (d, J = 6.0 Hz, 6H, $(-CH_3)_2$), 2.6 (br, s, 1H, –OH), 2.72–2.74 (m, 2H, $-CH_2N-$), 2.82–2.87 (m, 1H, –CHN–), 3.55 (s, 2H, Ph–CH_2), 3.67 (s, 3 H, $-OCH_3$), 3.94–3.98 (m, 2H, $-OCH_2$), 4.10–4.18 (m, 1H, –CH), 6.85–6.88 (d, J = 4.4 Hz, 2H, Ph–H), 7.17–7.19 (m, 2H, Ph–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ=22.6, 22.7, 40.0, 49.2, 49.7, 51.9, 70.4, 72.1, 114.5, 126.8, 130.3, 157.3, 174.1.

(R)-ethyl 2-[4-(3-chloro-2-hydroxypropoxy)phenyl]acetate (Table 2, entry 7)

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (t, J = 14.4 Hz, 3H, $-CH_3$), 2.65 (br, s, 1H, –OH), 3.56 (s, 2H, Ph–CH_2), 3.77–3.82 (m, 2H, $-CH_2Cl$), 4.06–4.08(m, 3H, $-OCH_2$, –CH), 4.12–4.17 (m, 2H, $-OCH_2$), 6.86–6.89 (d, J = 8.8 Hz, 2H, Ph–H), 7.20–7.22 (d, J = 8.0 Hz, 2H, Ph–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ=14.2, 40.5, 45.9, 60.8, 68.5, 69.8, 114.5, 126.9, 130.2, 157.1, 171.7.

(S)-ethyl 2-{4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl} acetate

IR (KBr): 3301, 3150, 1731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.06–1.08 (d, J = 6.0 Hz, 6H, $(-CH_3)_2$), 1.22 (t, J = 7.2 Hz, 3H, CH_3), 2.66–2.88 (m, 3H, $-CH_2N-$, –CHN–), 3.52 (s, 2H, Ph–CH_2), 3.92–4.01 (m, 3H, $-OCH_2$, –CH), 4.08–4.16 (m, 2H, $-OCH_2$), 6.83–6.85 (d, J = 8.4 Hz, 2H, Ph–H), 7.16–7.18 (d, J = 8.4 Hz, 2H, Ph–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ=14.2, 22.9, 23.0, 40.5, 48.8, 49.3, 60.7, 68.4, 70.5, 114.5, 126.4, 130.1, 157.5, 171.7.

(R)-2-[4-(3-chloro-2-hydroxypropoxy)phenyl]acetonitrile (Table 2, entry 10)

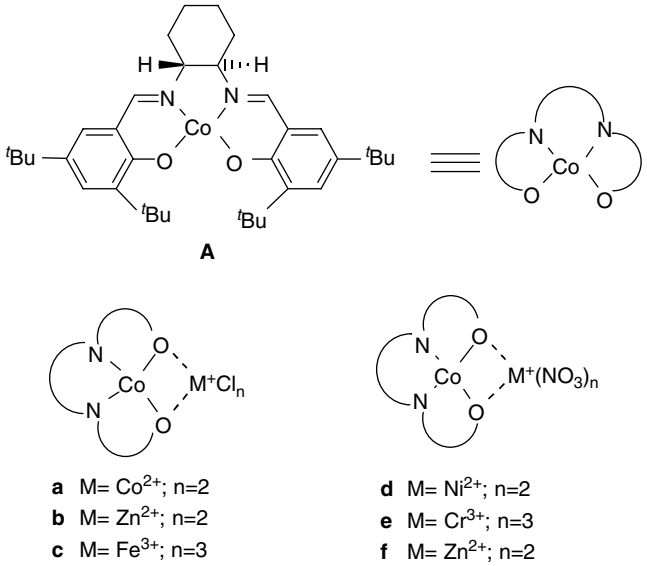
^{1}H NMR (400 MHz, $CDCl_3$): δ=2.58 (br, s, 1H, –OH), 3.66 (s, 2H, Ph–CH_2), 3.70–3.74 (m, 2H, $-CH_2Cl$), 4.04–4.20 (m, 3H, $-OCH_2$, –CH), 6.88 (d, J = 8.8 Hz, 2H, Ph–H), 7.22 (d, J = 6.4 Hz, 2H, Ph–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ=22.8, 45.9, 68.6, 69.7, 115.1, 117.9, 122.5, 129.1, 157.8.

(S)-2-{4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl}acetonitrile

IR (KBr, cm^{-1}): 3305, 3150, 2252, 1512, 1245 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=1.07–1.08 (d, J = 6.4 Hz, 6H, $(-CH_3)_2$), 2.55 (br, s, 1H, –OH), 2.7–2.9 (m, 3H, $-CH_2N-$, –CHN–), 3.67 (s, 2H, Ph–CH_2), 3.9–4.2 (m, 3H, $-OCH_2$, –CH), 6.92 (d, J = 8.8 Hz, 2H, Ph–H), 7.23 (d, J = 8.4 Hz, 2H, Ph–H). ^{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)-2-{4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl}acetamide (S-atenolol) (Scheme 1)

IR (KBr, cm^{-1}): 3352, 3174, 1639, 1242 cm^{-1}. ^1H-NMR (400 MHz, D_2O): δ=1.1 [d, J = 2 Hz, 6 H, $(-CH_3)_2$], 2.81–2.96 (m, 3H, $-CH_2N-$, –CHN–), 3.58 (s, 2H, Ph–CH_2), 4.04–4.14 [m, 3 H, $-OCH_2$, –CH], 7.04 (d, J = 8.4 Hz, 2H, Ph–H_2); 7.30 (d, J = 8.4 Hz, 2H, Ph–H). ^{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, 127.8, 130.4, 130.6, 157.4, 178.0.

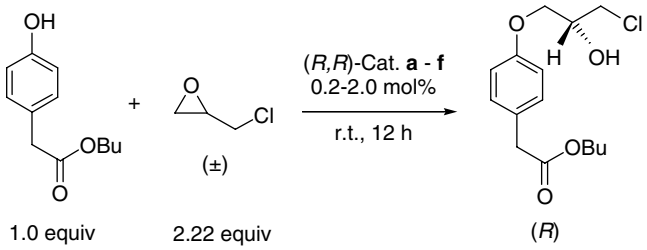


Scheme 1. Bimetallic chiral cobalt-salen-type complexes.

Results and Discussion

The catalytic activities of chiral cobalt salen complexes (Scheme 1) were screened in the PKR of (±)-ECH with BHPA under solvent-free conditions at room temperature, and the results are summarized in Table 1. The loading amount of catalyst was varied in the range of 0.2–2.0 mol% (Table 1, entries 1–4) to investigate the effect on the enantioselectivity in the asymmetric kinetic resolution. As shown in Table 1, the enantioselectivity of the product was rapidly increased at 2 mol% of catalyst up to 98% ee in the case of **a** or **f** (Table 1, entries 4 and 9). However, with the low catalyst amount to 0.2 mol%, a moderate enantioselectivity (65% ee) was observed, even after prolonged reaction periods (Table 1, entry 1). The catalysts **a, c** and **f** (Table 1, entries 4, 6 and 9) were particularly efficient in terms of both enantioselectivity and fast reaction rate as compared with those of the catalysts **b,d** and **e** (Table 1, entries 5, 7, and 8). Furthermore, the catalysts **a, c** and **f** were identified as the most active and enantioselective among the catalytic series and they were selected for further study. It is obvious from Table 1 that the best results were obtained using 2.0 mol% of catalysts and afforded highly valuable optically pure α-aryloxy alcohols with mostly high %ee within 12 h. Therefore, we decided to use 2 mol% of catalyst for further experiments. Importantly, the introduction of second transition-metal in the bimetallic catalyst was an essential factor for the enhancement of catalytic activity

Table 1. Screening of chiral cobalt salen complexes in the kinetic resolutions of (±)-ECH with butyl 2-(4-hydroxyphenyl)acetate



Entry	Catalyst	Mol%[a]	Yield (%)[b]	ee (%)[c]
1	**a**	0.2	70	65
2	**a**	0.5	77	87
3	**a**	1.0	81	92
4	**a**	2.0	82	98
5	**b**	2.0	74	83
6	**c**	2.0	78	86
7	**d**	2.0	71	79
8	**e**	2.0	73	82
9	**f**	2.0	71	98

[a] The catalyst loading based on per [Co] unit relative to (±)-ECH.
[b] Yield of product on the basis of phenol.
[c] Enantiomeric excess was determined by HPLC or chiral GC.

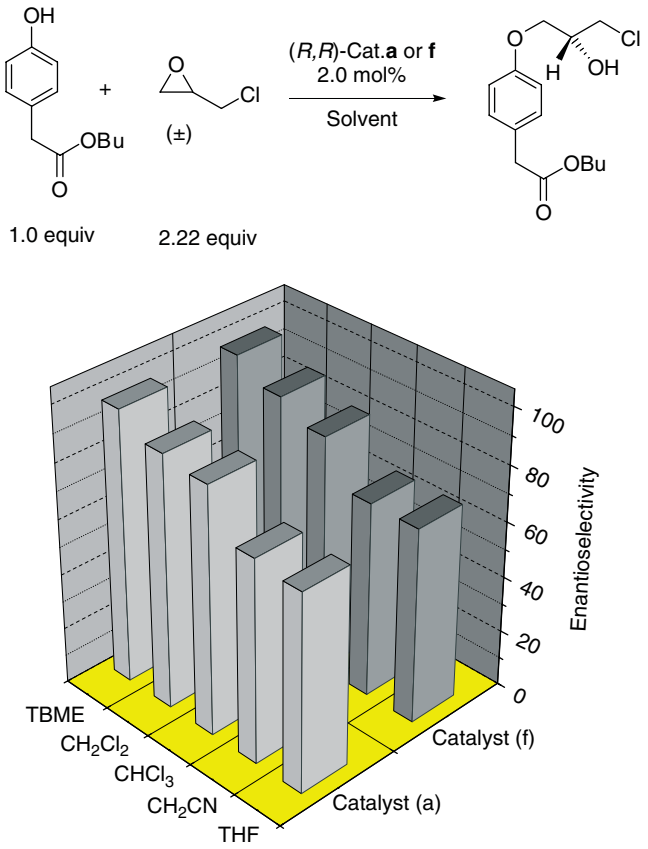


Figure 1. Effect of various solvents in the PKR reaction using chiral cobalt-salen-type complexes **a** and **f**.

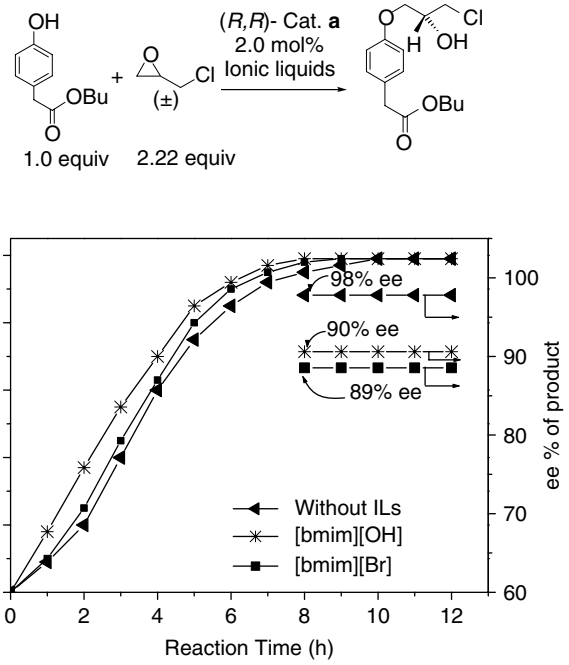


Figure 2. Effect of ILs on the enantioselectivity and conversion of the product using cobalt-salen-type catalyst **a** in PKR reaction.

and enantioselectivity. These salen-based catalysts showed unique catalytic property to accelerate the kinetic resolutions in highly efficient manner.

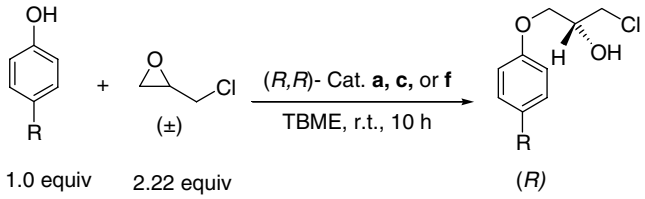
It was observed that the solvent plays crucial role in this reaction. In the typical example during the reaction of (±) ECH with BHPA, the effect of polar and non-polar solvents were examined and non-polar solvents such as TBME was proved to be the most suitable solvents, as illustrated in Fig. 1.

The effect of ionic liquids (ILs) such as l-butyl-3-methylimidazolium hydroxide [bmim][OH] and 1-butyl-3-methylimidazolium bromide [bmim][Br] on the catalytic reactivity and enantioselectivity through PKR of (±)-ECH has been investigated briefly (Fig. 2). Only a moderate improvement in catalytic reactivity (conversion of phenol) was obtained when ILs were introduced as co-catalysts; however, no significant effect was observed on the enantioselectivity of the products. In contrast, the enantiomeric purity was greatly enhanced without addition of ILs (Fig. 2). Generally, better results were obtained when the reaction was performed in the absence of ILs. It seems that the presence of ILs is unfavorable in terms of enantioselectivity at the current stage of the study.

The PKR of (±)-ECH was found to have a broad substrate scope with respect to phenol derivatives. A series of *para*-substituted ester and nitrile containing phenols were evaluated in the ring-opening of (±)-ECH using most active and enantioselective bimetallic chiral cobalt-salen-type complexes **a, c** or **f** in TBME at room temperature within 10 h (Table 2). As expected, all the reactions afforded corresponding α-aryloxy alcohols in relatively good-to-excellent enantioselectivity and the decrease in reaction time was occurred in the presence of TBME. The PKR of (±)-ECH with BHPA was proved to be a highly efficient reaction, providing the synthetically important (*R*)-butyl 2-[4-(3-chloro-2-hydroxypropoxy)phenyl]acetate with high optical purity in excellent yield within 10 h (Table 2, entry 1). The PKR of (±)-ECH with methyl 2-(4-hydroxyphenyl)acetate and ethyl 2-(4-hydroxyphenyl)acetate were also performed in efficient manner, requiring 2.0 mol% of catalysts **a** or **f** to obtain the high enantioselectivity in 77–80% yield (Table 2, entries 4, 6, 7 and 9). Moreover, the above-described PKR method was found to be applicable for the phenol containing a *Lewis* base functionality such as 2-(4-hydroxyphenyl)acetonitrile, and transformed into (*R*)-2-[4-(3-chloro-2-hydroxypropoxy)phenyl]acetonitrile but to some extent lower enantioselectivity was obtained as compared with ester containing phenols (Table 2, entries 10 and 12). In each instance, the reactions proceeded smoothly in the presence of bimetallic chiral catalysts. Considering the enantioselectivity and yields, BHPA was evaluated to be the best substrate for the kinetic resolution of (±)-ECH, which is the best result of the present reactions in terms of both enantioselectivity and yield (Table 2, entry 1). These results shows an importance to the asymmetric ring-opening of (±)-ECH, because the highly enantio-enriched β-blockers could be easily synthesized in high yields by using bimetallic chiral cobalt-salen-type complexes. Further transformation into (*S*)-atenolol was accomplished by well-known simple methods (i.e. by addition of excess *i*PrNH$_2$ in the presence of H$_2$O at reflux temperature, followed by treatment with aqueous NH$_4$OH). This straightforward transformation is a useful alternative to existing methods as outlined in Scheme 2.

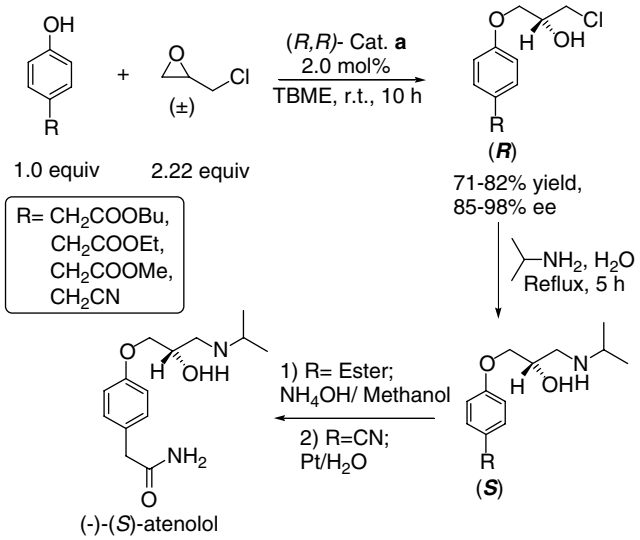
To broaden the substrate scope of PKR reaction, asymmetric ring-opening of (±)-ECH with 2-chloro-5-methyl phenol was examined in the presence of newly synthesized bimetallic chiral catalysts (Table 3, entries 1–4). It is evident from Table 3 that, moderate-to-excellent levels of enantioselectivities were obtained to afford (*R*)-1-chloro-3-(2-chloro-5-methyl-phenoxy)-propan-2-ol

Table 2. Kinetic resolution of (±)-ECH with various substrates using chiral cobalt-salen-type complexes



Entry	R	Catalyst[a]	Yield (%)[b]	ee (%)[c]
1	CH_2COOBu	**a**	82	98
2	CH_2COOBu	**c**	78	87
3	CH_2COOBu	**f**	71	98
4	CH_2COOMe	**a**	78	97
5	CH_2COOMe	**c**	76	85
6	CH_2COOMe	**f**	80	96
7	CH_2COOEt	**a**	78	96
8	CH_2COOEt	**c**	75	88
9	CH_2COOEt	**f**	77	96
10	CH_2CN	**a**	79	94
11	CH_2CN	**c**	80	89
12	CH_2CN	**f**	76	93

[a] The catalyst loading based on per [Co] unit relative to (±)-ECH; 2.0 mol%.
[b] Yield of product based on the phenols.
[c] Enantiomeric excess was determined by HPLC or chiral GC.



Scheme 2. Synthesis of (−)-(*S*)−atenolol using bimetallic chiral cobalt-salen-type complex **a**.

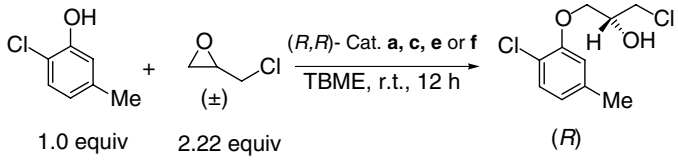
within 12 h. This interesting chiral building block has particular potential for the synthesis of (*S*)-bupranolol,[22] as depicted in Scheme 3.

As noted above, both the ester and nitrile functionalized phenols were evaluated as effective nucleophiles for the bimetallic chiral cobalt-salen catalyzed kinetic resolution of (±)-ECH. While water is also attractive nucleophile for kinetic resolution if epoxide recovery is desired,[18] the phenolic ring-opening provides direct access to α-aryloxy alcohols, which are valuable synthetic intermediates that are otherwise not easily accessible.[20] The PKR displays more attractive features with regards to the substrates of HKR.[19] In addition, the nucleophilic components can be varied, and phenols with a wide range of electronic properties are effective substrates. This raises the interesting possibility of applying this methodology to enantioselective catalytic synthesis of β-blockers through PKR. An efficient strategy for providing very high enantioselectivity could be achieved in the synthesis of valuable chiral building blocks via our catalytic system. As a result, the PKR of (±)-ECH was established as an efficient, synthetically useful enantiomer-separation method applicable to a broad range of substrates and suggesting a great potential of this strategy for product generation on an industrial scale, as shown in Scheme 3.

Nonlinear effects in asymmetric synthesis have become a tool of choice to understand molecular behavior developed by Kagan *et al*.[23] The enhanced reactivity of the bimetallic catalyst indicates that PKR with catalyst **a** takes place via cooperative action of two different metal sites present in the intra-framework. Consistent with the mechanism involving bimetallic catalysis, simultaneous activation of both phenol and epoxides by different metal sites within one salen unit happens in the bimetallic structure. A significant nonlinear effects was observed with regards to catalysts enantiomeric composition on reaction enantioselectivity in the presence of catalysts **a** or **f** (Fig. 3). However, a linear relationship was observed between the ee of product and catalyst, when the catalyst concentration was below the experimental value. The remarkable nonlinearity indicates that participation of highly selective intramolecular and cooperative bimetallic pathway dominates within one salen unit.

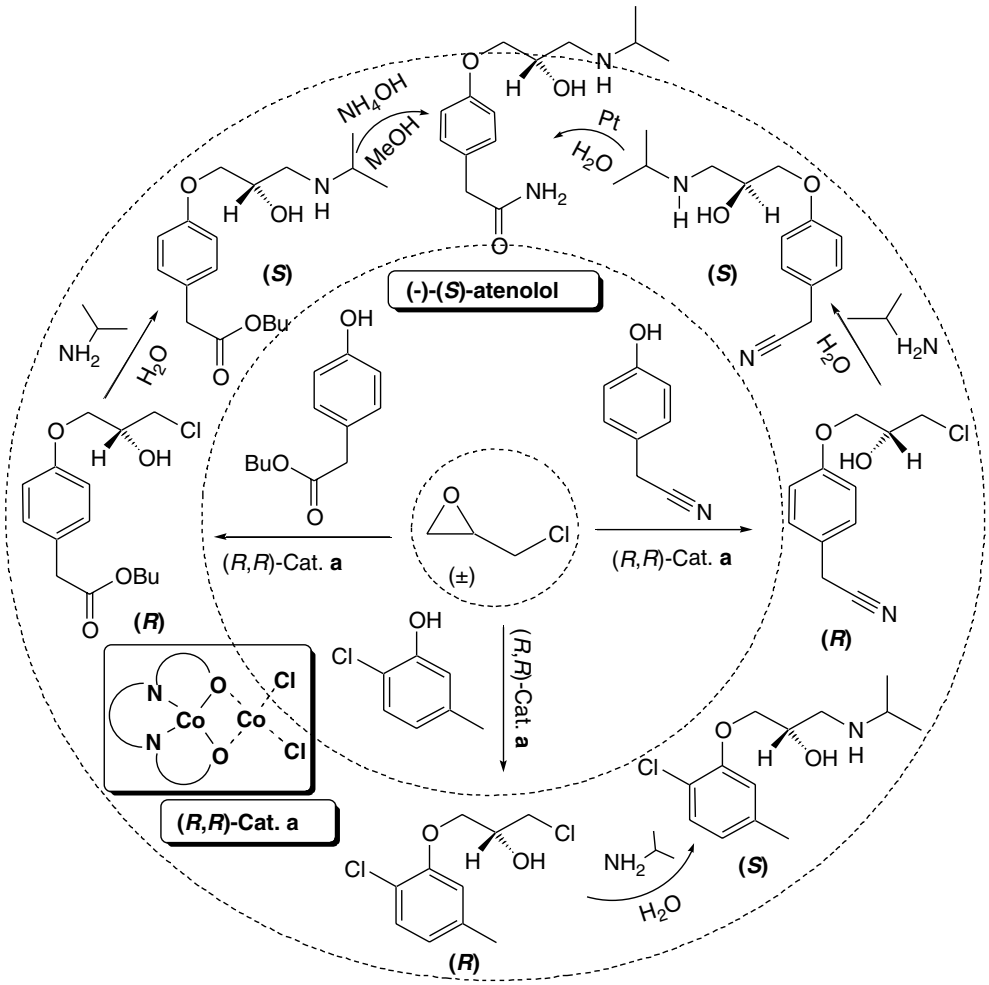
ESCA technique was used to characterize newly synthesized chiral Co(salen) complexes and the results are summarized in Fig. 4. ESCA Spectra can provide unique evidence about the chemical composition, the element's oxidation state and the environment created by the attachment of a transition-metal to

Table 3. Kinetic resolution of (±)-ECH with 2-chloro-5-methyl phenol using chiral cobalt-salen-type complexes



Entry	Catalyst[a]	Yield (%)[b]	ee (%)[c]
1	**a**	82	93
2	**c**	76	85
3	**e**	71	79
4	**f**	84	93

[a] The catalyst loading based on per [Co] unit relative to (±)-ECH; 2.0 mol%.
[b] Yield of product based on the phenol.
[c] Enantiomeric excess was determined by HPLC.



Scheme 3. Schematic representation of PKR reaction using chiral cobalt-salen-type catalyst.

salen complex. In an ESCA spectrum, the binding energies of the peaks are characteristic of each element. Atoms in altered environments result in the shift of absorption peak to different binding energies. Therefore, the binding energy of O_{1s} of Co(salen) complexes in ESCA spectra was determined to investigate whether the transition-metal salt is attached to the oxygens of salen molecules. Figure 4 shows the ESCA spectra for several typical Co(salen) containing transition-metal samples. The [Co^{II}(salen)] complex **A** exhibited O_{1s} core level peak at a binding energy of *ca* 531 eV, while the transition-metal-containing cobalt-salen-type complexes showed a binding energy at higher value of *ca* 532 eV, and are in accordance with the earlier literature.[19] The observed

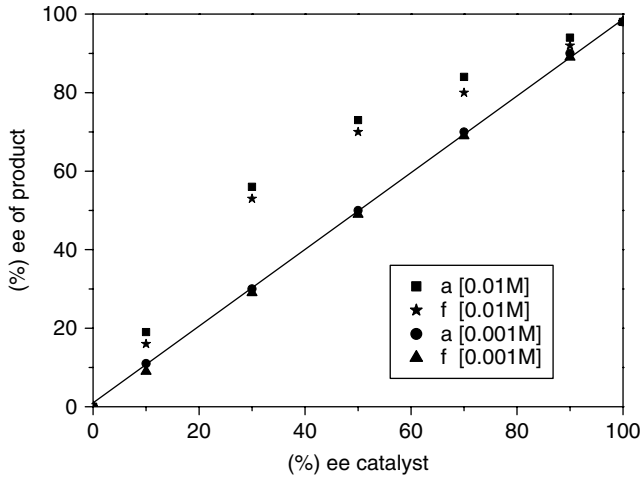


Figure 3. Nonlinear effects in the kinetic resolution of (±)-ECH with butyl 2-(4-hydroxyphenyl)acetate using cobalt-salen-type complexes **a** and **f**.

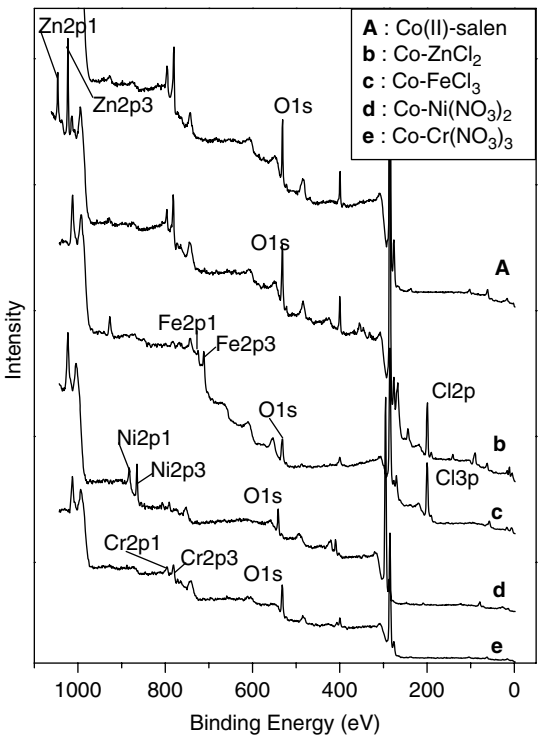


Figure 4. ESCA Spectra of [Co(Salen)]-type catalyst **A**, $Co^{II}-ZnCl_2$ catalyst **b**, $Co^{II}-FeCl_3$ catalyst **c,** $Co^{II}-Ni(NO_3)_2$ catalyst **d,** and $Co^{II}-Cr(NO_3)_3$ catalyst **e**.

change in binding energy of 1 eV (i.e. from *ca* 531 to 532 eV) for the Co(salen) containing transition-metal sample could be attributed to the differences in the coordination environments of transition metal and confirms the interaction with oxygen of cobalt salen. These differences in core binding energies have been related to structural changes in the cobalt-salen-type complexes. In the case of a Jacobsen-type catalyst [$Co^{III}-OAc$], the $AcO^{(-)}$ anion[17] is present to balance the positive charge of the Co-center, which is +3, but there is no interaction between such an anion and the O-atom of the salen-type ligand. Therefore, the binding energies of O_{1s} did not vary between **A** and Jacobsen-type catalyst [$Co^{III}-OAc$].

Thus, the change in binding energy (O_{1s}) of salen complex **b, c, d** and **e** was generated by the anchoring of the transition-metal species to the O-atoms in ligand by the Lewis – acid interaction.

As can be seen from Fig. 4, ESCA spectrum shows the absorption peaks for Zn, Fe, Ni, Cr and Cl which are directly correlated to the complexes **b, c, d** and **e**. Such peaks can be generated only by the attachment of their corresponding transition metal salts [i.e. $ZnCl_2$, $FeCl_3$, $Ni(NO_3)_2$, and $Cr(NO_3)_3$] to the O-atoms of the salen-type ligand, and it is suggested that the transition-metal cation attached to these O-atoms adopts a stable coordination. Because such transition-metal salts are fully soluble in water, we could purify the catalysts by water-workup. After sufficient washing with water, the presence of metal salts in ESCA spectra may provide the data for the formation bimetallic structure of salen catalysts. Also the peaks are identical to that of **A**, which was used as a starting compound. This result means that the Co(II) oxidation state was retained during the formation of the transition-metal-salt-containing complexes **b, c, d** and **e** from **A**. Thus, these results provided direct evidence for the coordination of transition-metal-salt to O-atom of the salen-type complexes in order to form the bimetallic chiral cobalt salen complexes. On the basis of this experimental evidence as well as previous reports of related heterobimetallic Schiff base complexes,[24] we assumed that a bimetallic (salen)$Co-M^+$ complex would be the active species. At the moment, we believe that the bimetallic (salen)$Co-M^+$ system would play a crucial role for high enantioselectivity. Further studies to clarify the role of each metal and reaction mechanism are underway.

Conclusion

In summary, we have established the bimetallic chiral [Co(salen)]-type catalyst systems for the kinetic resolution of epoxides with various *para*-substituted phenol derivatives. This methodology affords simple and effective protocol for the synthesis of pharmaceutically useful β-blockers. Further mechanistic studies as well as applications of the present bimetallic catalyst to other asymmetric reactions are in progress.

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