A new dinuclear chiral salen complexes for asymmetric ring opening and closing reactions: Synthesis of valuable chiral intermediates

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Abstract

A new dinuclear chiral Co(salen) complexes bearing group 13 metals have been synthesized and characterized. The easily prepared complexes exhibited very high catalytic reactivity and enantioselectivity for the asymmetric ring opening of epoxides with H_2O, chloride ions and carboxylic acids and consequently provide enantiomerically enriched terminal epoxides (>99% ee). It also catalyzes the asymmetric cyclization of ring opened product, to prepare optically pure terminal epoxides in one step. The homogeneous dinuclear chiral Co(salen) have been covalently immobilized on MCM-41. The potential benefits of heterogenization include facilitation of catalyst separation and recyclability requiring very simple techniques. The system described is very efficient.
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Keywords: Asymmetric catalysis; Chiral dinuclear catalyst; Chiral intermediates; Asymmetric ring opening reactions; Kinetic resolution

1. Introduction

Design of simple and efficient chiral catalyst for asymmetric reactions is one of the most important tasks in organic synthesis [1]. Quite recently, several groups made significant progress towards the design and use of chiral homo- and heterodinuclear complex for asymmetric catalysis, with particularly important contributions reported by Shibasaki et al. [2], Trost et al. [3] and Belokon and Kagan et al. [4]. Homo- and heterodinuclear complexes have enormous potential to revolutionize asymmetric catalysis. They can activate both components of bimolecular reaction simultaneously, overcome entropy barriers associated with bringing the two reagents together, minimize the energy barrier that arises from solvent shell rearrangements during the reaction, and recognize prochiral faces or groups within the reagent through predetermination of the reaction trajectory. Very recently Kobayashi et al. [5] reported dinuclear chiral niobium complex for Lewis acid catalyzed enantioselective Mannich-type reaction of imines with silicon enolates. Zhu et al. [6] used heterodinuclear Ti–Ga salen in the enantioselective ring opening of *meso*-epoxides with aryl selenols. The stereoselective synthesis of chiral terminal epoxide is of immense academic and industrial interest due to their utility as versatile starting materials as well as chiral intermediates for the preparation of bioactive molecules [7–10]. Hydrolytic kinetic resolution (HKR) technology [11] is the very prominent way to prepare optically pure terminal epoxides among available methods [12].

In the asymmetric ring opening of epoxides catalyzed by chiral [(salen)Co] complexes [13] the reaction involved two separate chiral salen-metal species in the rate limiting step of the reaction and subsequently, very efficient oligomeric catalysts were developed based on this principle [14].

However, multistep and complicated synthesis method of oligomeric catalysts [14] and solubility problem during HKR make it less attractive strategy.

Pursuant to our own efforts directed towards the designing of the di- and multimeric chiral (salen)Co catalysts [15] herein we report the catalytic activity of new easily synthesized homogeneous and heterogeneous dinuclear chiral (salen)Co–MX_3 catalyst (Scheme 1) for the enantioselective kinetic resolution of terminal epoxides with H_2O and other nucleophiles and asymmetric cyclization reaction. The dinuclear catalysts **1b**–**9b** show remarkable enhanced reactivity and may be employed substantially lower loadings than its monomeric analogues **1a**–**9a** without suffering solubility problem and their deactivation.

2. Experimental

2.1. General

All ^1H NMR, ^{13}C NMR and ^{69}Ga NMR ($I = 3/2$) were recorded using 400 MHz FT NMR spectrophotometer (VARIANUNITYNOVA400) at ambient temperature. Optical rotation measurements were conducted using a Jasco DIP 370 digital polarimeter. Gas Chromatography analyses were performed on Hewlett-Packard 5890 Series II instruments equipped with FID detectors using chiral column (CHIRALDEX G-TA and A-TA, 20 m × 0.25 mm i.d. (Astec) and HP 3396 integrators with HP Chem Station software for data analysis. Chiral
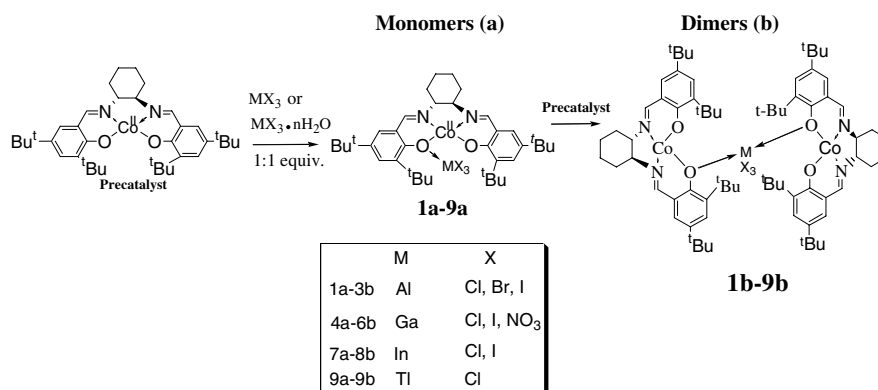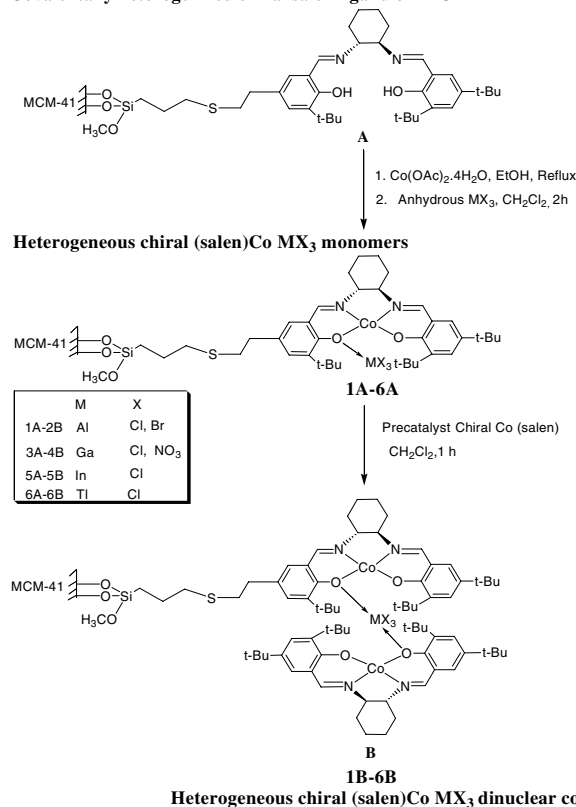
Scheme 1.

HPLC analyses were performed on YOUNGLIN instrument using a Chiralcel® OD column (24 cm × 0.46 cm i.d.; Chiral Technologies, Inc.) and (R,R)-Whelk-O1/(S,S)-Whelk-O1 column (24 cm × 0.46 cm i.d.) (Regis) at 254 nm. 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 IR were measured in Chiralir™ ABB Bomem Inc using Bomem GRAMS-32 software. X-ray absorption spectroscopy (EXAFS) were measured by Rigaku Model R-XAS (Rigaku, Japan) applying Co K-edge energy (7708.9 eV), Ga K-edge energy (10,367.1 eV) radiation and data were simulated by using FEFF program. Solvents were used after distillation. TBME used as such obtained from Aldrich. All other reagents obtained from Aldrich, Fluka and TCI. The general procedure for the kinetic resolution was same as shown in published papers [11,15a].

2.2. Syntheses of dinuclear catalyst

To a solution of hydrated gallium nitrate $Ga(NO_3)_3 \cdot nH_2O$ (2.118 g, 8.28 mmol, 1.0 equiv.) in tetrahydrofuran (25 mL), precatalyst (R,R)-salenCo (5.0 g, 8.28 mmol, 1.0 equiv.) was added and stirred in at open atmosphere at room temperature. As soon as the chiral (salen)Co was added color of the solution changes from brick red to dark olive green. The solution was stirred at r.t. for 1 h. The resulting solution was concentrated under reduced pressure. The crude solid was worked up with H_2O and CH_2Cl_2. Yield = 98–99% as a dark green solid powder. ^{69}Ga NMR (solvent CDCl$_3$; $\delta = 78.2$ ppm) with reference to $[Ga(D_2O)_6]^{3+}$ for the catalyst **1a**. UV–Vis shows sharp absorbance on 375 nm. The characteristic absorption band of precatalyst Co(II) salen at 420 nm disappeared. In addition, anhydrous gallium (III) chloride, bromide or iodide (8.28 mmol, 1.0 equiv.) was added to a stirred solution of precatalyst chiral salen Co(II) in water and THF and synthesized in a similar manner, mentioned above. The crude solid was worked up with H_2O and CH_2Cl_2. Yield = 98–99% as a dark green solid powder. In case of anhydrous salt source, monomers of Co–MX$_3$ were prepared using methylene chloride (MC) as a solvent in place of THF and bimetallic complexes were prepared in a similar method except taking 2:1 equiv. of precatalyst chiral (salen)Co.

The heterogenized chiral salen **A** was prepared by earlier reported method [16]. Cobalt insertion into the MCM-41 bound salen ligand was accomplished by adding a equimolar solution of $Co(OAc)_2 \cdot 4H_2O$ in EtOH solvent and refluxed for 1 h. After 1 h the dark red complex was rinsed sequentially with EtOH and CH_2Cl_2 and dried in vacuo to yields a heterogenized Co(salen) complex. Subsequently heterogenized Co(salen)–MX$_3$ complex **1A–6A** and **1B–6B** were prepared by mixing stoichiometric amount of reacting partners in CH_2Cl_2 stirred for 1 h (Scheme 1).

3. Results and discussion

In a representative example, the detailed characterization by ^{69}Ga ($I = 3/2$) NMR taking $[Ga(D_2O)_6]^{3+}$ as an external reference at 0 ppm shows the formation between Ga and Co salen unit for all chiral(salen)Co–GaCl$_3$ monomer and dimers. The monomeric chiral (salen)Co **4a** shows chemical shift on $\delta = 78.2$ ppm, while bimetallic chiral (salen)Co complex **4b** on $\delta = 52.4$ ppm. The chemical shift difference confirms the presence of the catalyst **4a** and **4b** as two distinct species. X-ray fine structure (EXAFS) data support the formation of Ga–O (**4a**) and Ga–O–Ga (**4b**) complex. For complex **4a** Ga–O bond length is 1.83 Å and Ga–O coordination number is 0.75 (~1) and for **4b** 1.75 Å and 1.50 (~2), respectively (see Supporting Information). The different vibrational circular dichroism (VCD) spectra for the catalyst **4a** and **4b** provide the configuration of monomeric and dinuclear forms (Fig. 1) as a distinct two species than that of precatalyst chiral Co(salen). The spectra of dimeric form shows that it is not a physical mixture of Co(II) ligand and monomeric form. Monomeric catalyst **4a** and dinuclear catalyst **4b** exhibit the new characteristic UV–Vis absorption band at 365 nm while band at 420 nm corresponding to the precatalyst Co(II) salen has disappeared. The FAB-mass spectra of monomer **4a** and dinuclear **4b** (Figs. 2 and 3) provide
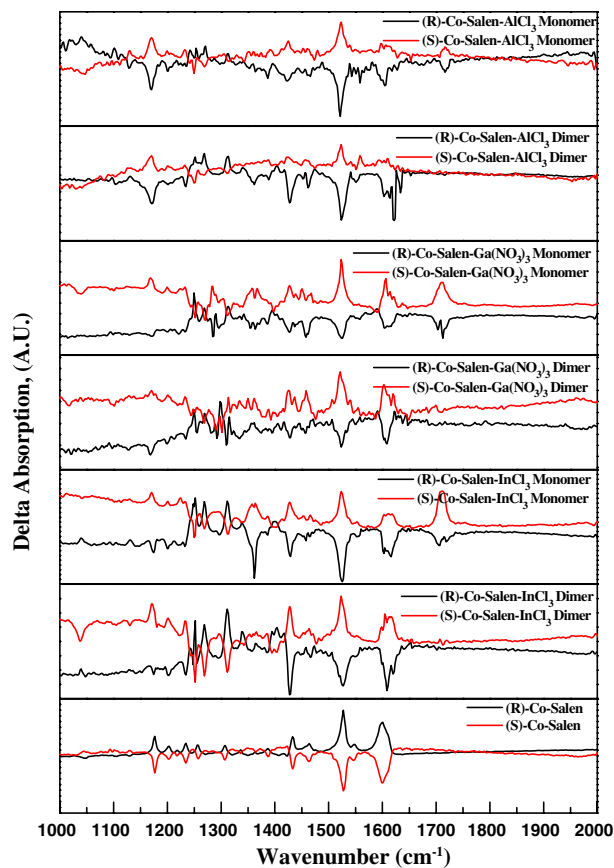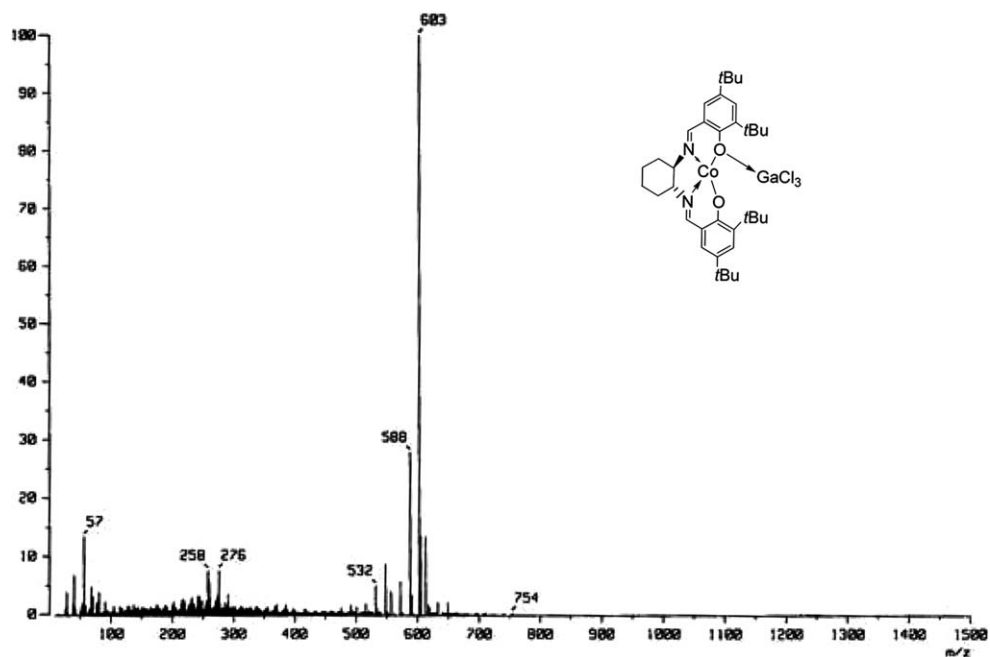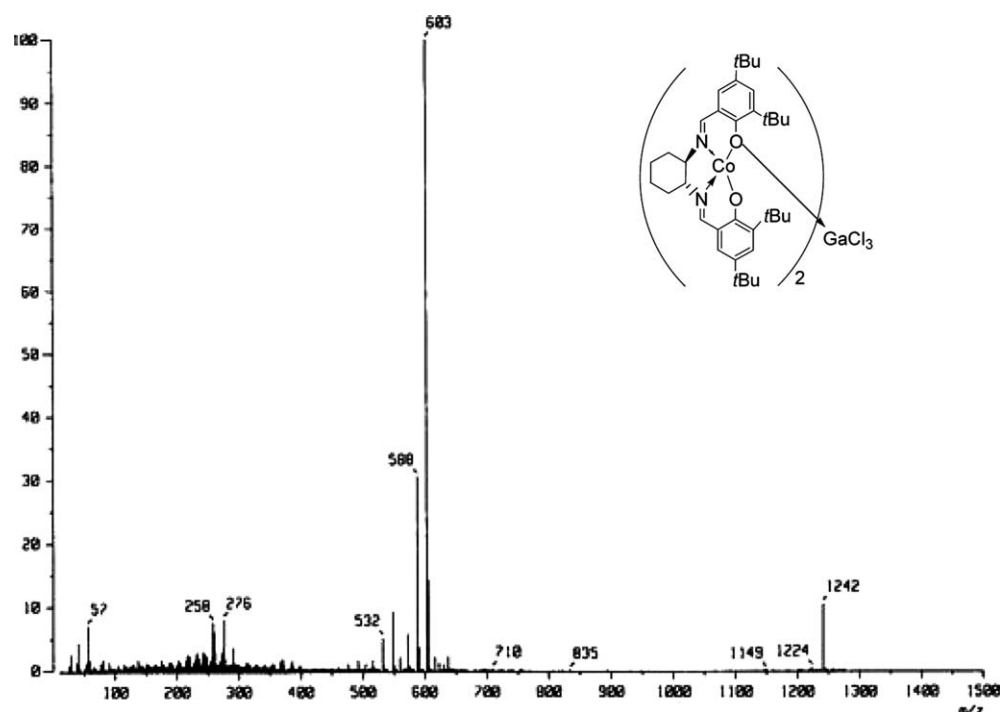

Fig. 1. Comparison of VCD spectra of mono- and dinuclear chiral catalysts.

Fig. 2. FAB-mass of Ga monomer catalyst **4a**.

Fig. 3. FAB-mass of Ga dinuclear catalyst **4b**.

direct evidence of formation of dinuclear complex. Dinuclear complex **4b** showed molecular mass over 1242 and monomer complex **4a** over 643. It has already been established that oxygen atoms of the metal complexes of the Schiff bases are able to coordinate to the transition and group 13 metals to form bi- and trinuclear complex [17]. On these bases possible structure of chiral (salen)Co–MX$_3$ complexes is depicted in Scheme 1.
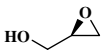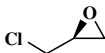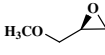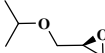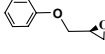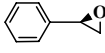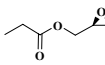
3.1. Syntheses of optically pure terminal epoxides via hydrolytic kinetic resolution (HKR)

The catalytic activities of the dinuclear catalyst **4b** for HKR of the diverse and valuable racemic terminal epoxides are shown in Table 1.

Due to high selectivity factor (k_{rel} values) every epoxide underwent resolution in excellent yield and high ee% employ-

Table 1
HKR of terminal epoxides catalyzed by the dinuclear catalyst
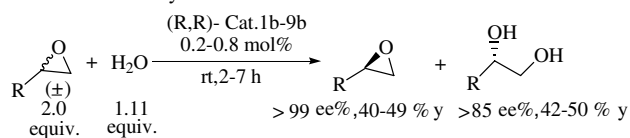
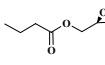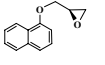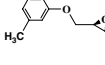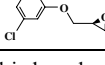| Entry	Recovered epoxides[a]	Catalyst	Catalyst loading (mol%)[b]	Time (h)	%Yield (ee)[c]	k_{rel}
1		4b	0.2	2	43 (99.3)	480
2		4b	0.2	3	45 (99.7)	510
3[d]		4b	0.5	7	43 (98.7)	110
4		4b	0.2	3	45 (99.8)	205
5		4b	0.4	3	49 (99.6)	167
6		4b	0.4	4	40 (99.3)	173
7		4b	0.5	2	42 (99.3)	145
8[d]		4b	0.8	6	40 (98.2)	135
9		4b	0.5	3	44 (99.4)	151
10		4b	0.5	4	43 (99.8)	92
11[e]		4b	0.5	6	43 (96.8)	290
12[e]		4b	0.5	2	42 (99.3)	120
13[e]		4b	0.5	2	42 (99.3)	125

[a] Isolated yield is based on racemic epoxides (theoretical maximum = 50%).
[b] Loading on a per [Co] basis w.r.t. racemic epoxides.
[c] ee % was determined by chiral GC or chiral HPLC.
[d] THF was used as a solvent.
[e] Solvents CH$_2$Cl$_2$:THF = 2:1. The selectivity factor (k_{rel}) was calculated using the equation = ln[1 − c(1 − ee)]/ln [1 − c(1 + ee)] where the conversion c was set to equal the isolated yield of the recovered epoxide.

ing 0.2–0.8 mol% of catalyst in solvent free condition in most of the cases. In a similar condition, catalyst 4a loading per [Co] basis gives <50% ee and <30% isolated products (see Supporting Information). The order of reactivity for dinuclear complexes were found to be Co–In > Co–Tl > Co–Ga > Co–Al and for the counter ions I > Cl > Br > NO$_3$ (see Figs. 4 and 5).
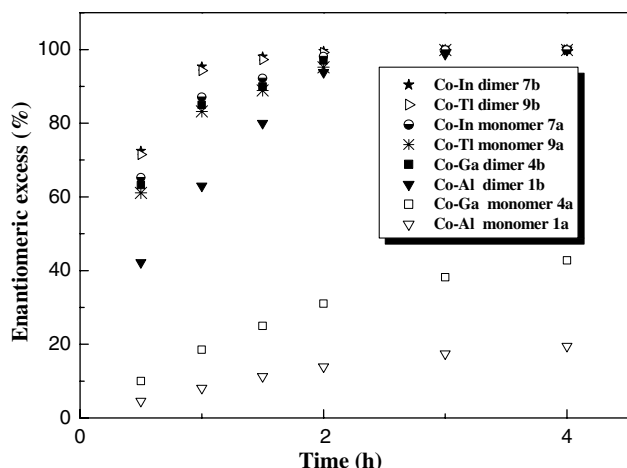
Fig. 4. Comparison of reactivity and enantioselectivity of catalysts Co–MX$_3$ for the HKR reaction of epichlorohydrin at r.t. using 0.2 mol % of the catalyst per [Co] basis w.r.t. substrate.
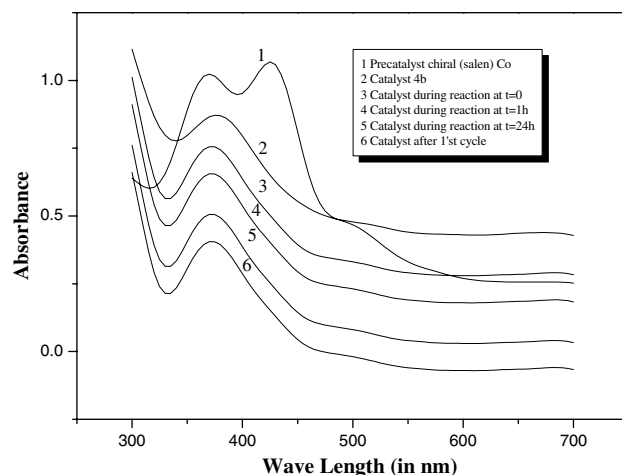

Fig. 6. The UV–Vis spectral analysis of the catalyst during and after the HKR of racemate methyl glycidyl ether at r.t.
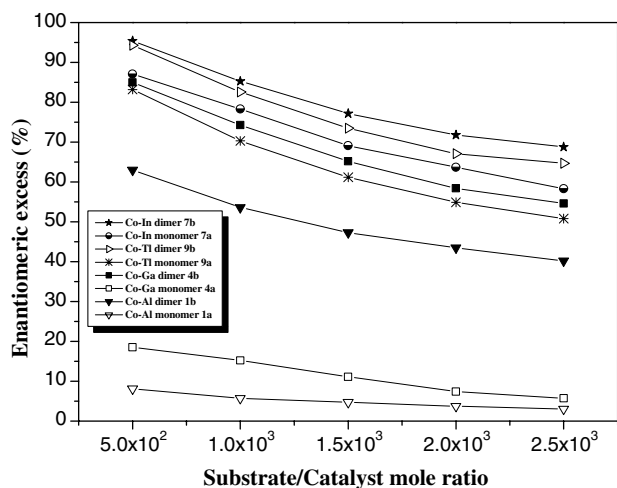
Fig. 5. The effect of substrate/catalyst mole ratio on the enantiosectivity of the HKR of epichlorohydrin at r.t. in 1 h.

Fig. 7. Comparison of reactivity and enantioselectivity of heterogeneous catalysts Co–MX$_3$/MCM-41 for the HKR reaction of epichlorohydrin at r.t. using 0.2 mol% of the catalyst per [Co] basis w.r.t. substrate.

Scheme 2. Stability of the catalyst under control experiment.

In a control experiment, the dinuclear complexes treated with excess of water and worked up are found to have the similar reactivity and selectivity (Scheme 2). The catalyst prepared from hydrated MX$_3$ · nH$_2$O exhibited similar activity and enantioselectivity for the present study. EXAFS data of the water treated Co–Ga dimer reveal that there is no dissociation of Co–Ga complex during HKR reaction (see supporting information). However, catalyst could be generated in situ by suspension of the precatalyst in epoxide or epoxide/solvent and addition of MX$_3$. The continuous monitoring of UV–Vis spectra of dinuclear catalyst **4b** during the HKR reaction of methyl glycidyl ether (Fig. 6) revealed that there is no

Fig. 8. Recyclability of the heterogeneous catalyst **3B** in the asymmetric HKR of (±) ECH using 0.2 mol% catalyst at r.t.

Fig. 9. The calculated and observed VCD and IR spectra of optical isomers of epichlorohydrin (A) and styrene oxide (B) obtained after the HKR reaction.

Table 2
Kinetic data for the HKR of racemic ECH catalyzed by monomers and dimers

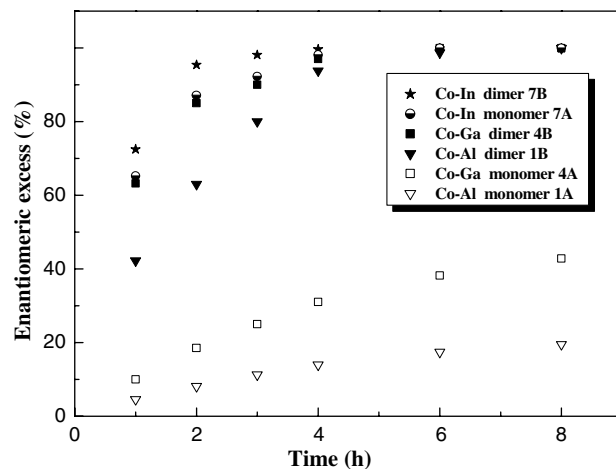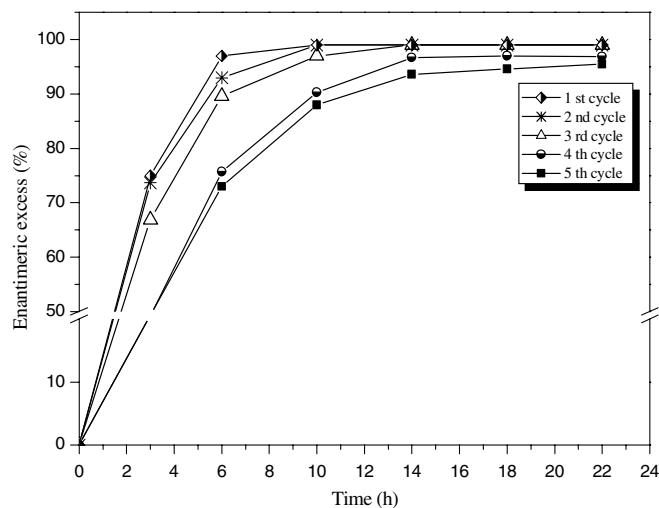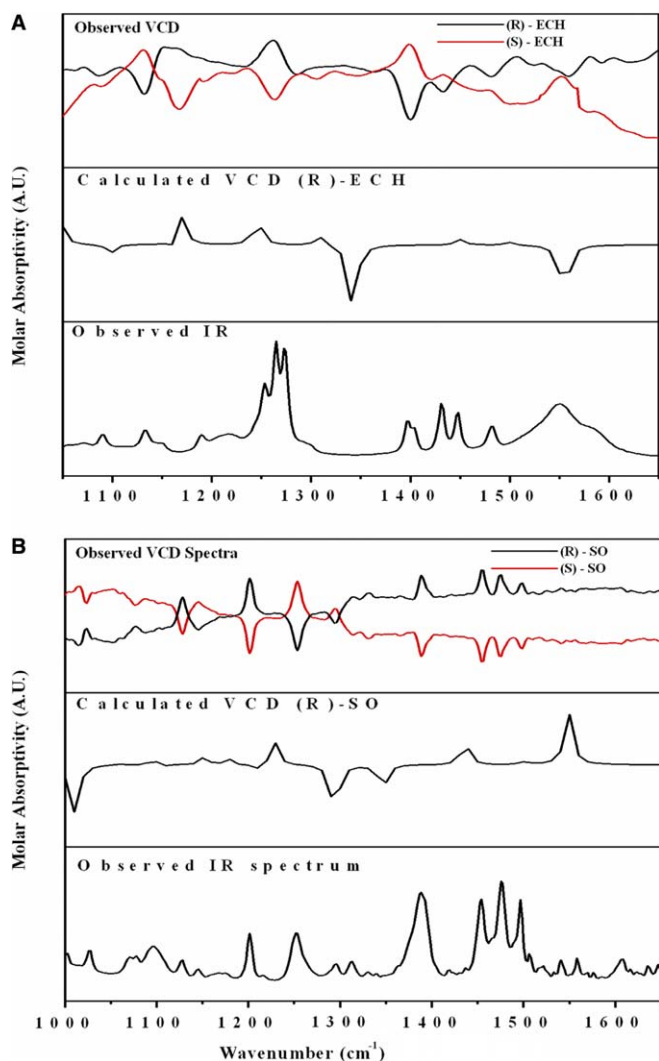| Catalyst	No. of (salen)Co unit	k_{intra} $(\text{min}^{-1} \times 10^{-2})^{\text{a}}$	k_{inter} $(\text{M}^{-1}\ \text{min}^{-1})^{\text{a}}$
1a	1		1.0
1b	2	44.4	10.2
4a	1		5.07
4b	2	47.8	11.4
7a	1	49.8	15.2
7b	2	66.0	22.0
9a	1	49.3	12.1
9b	2	61.3	21.0

^a Calculated from Fig. 10 using Eq. (1).

Vibrational circular dichroism (VCD) spectroscopy has been applied to elucidate the stereochemistries of chiral molecules, including the accurate estimation of enantiomeric excess and their absolute configurations [19]. In the present study VCD spectra was used to elucidate the stereochemistries of chiral mono- and dinuclear catalyst and optically pure chiral intermediates (Fig. 9), including the accurate estimation of enantiomeric excess and their absolute configurations. Optically pure samples as well as racemic samples were used as a reference to compare the VCD spectra. The VCD spectra of opposite configuration, such as *R* and *S* exhibited the reverse absorption peaks. The theoretical VCD spectra of optically pure epichlorohydrin and styrene oxide were calculated using DFT/6-31G(d)/B3LYP program. The observed VCD and IR spectra were obtained for 1.0 M solution of (*R*)-(−) epichlorohydrin and (*R*)-(+)-styrene oxide each in CDCl$_3$ using Chiral IR FT VCD ABB Bomem (Bio Tools) spectrometer, with a path length 94 μm set at 8 cm^{-1} resolution and a spectral collection time of 1 h. The comparison of observed and calculated spectra shows very high level fidelity and clearly establish the absolute configuration of these two chiral intermediates. The

dissociation and equilibrium of **4b** to their monomeric form. The dinuclear catalyst is very stable even after HKR reaction.

The reactivity and enantioselectivity of hydrolytic kinetic resolution of epichlorohydrin by covalently immobilized chiral Co(salen) MX$_3$ monomer and dimer over MCM-41 is outlined in Fig. 7. The heterogenized catalysts **1A**–**6A** and **1B**–**6B** activity is found to be similar to the homogeneous catalyst **1a**–**9a** and **1b**–**9b**, except taking longer reaction time. The recylability of the heterogenized catalyst is shown in Fig. 8.

The supported catalysts **1B**–**6B** were removed by simple filtration and repeated for recycling with no loss of reactivity and enantioselectivity up to three cycle. The potential benefits of heterogenization include facilitation of catalyst separation from reagents and reaction products, simplification of methods for catalyst recycle, and possible adaptation of immobilized catalyst to continuous-flow process [18].
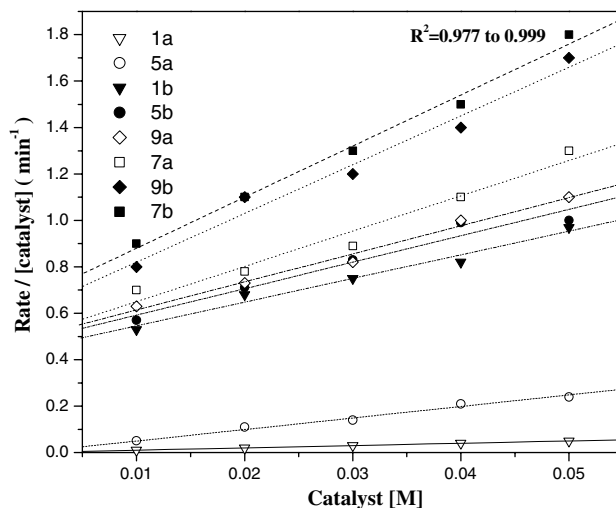

Fig. 10. Initial rate kinetics for the asymmetric HKR of the ECH catalyzed by the monomer and dimmer catalysts.

shift in peak position between observed and calculated VCD spectra might be due to solute–solvent interactions [20]. The ee% determined by the VCD and those measured by GC were found to be good agreement within 2% ee.

Kinetic studies of the HKR of epichlorohydrin (ECH) were carried out studied as a model reaction (Table 2). Considering the two-term rate equation involving both intra- and intermolecular components (Eq. (1)) [15a,21,22].

$$\text{rate} \propto k_{\text{intra}}[\text{catalyst}] + k_{\text{inter}}[\text{catalyst}]^2 \qquad (1)$$

Plots of rate/[catalyst] vs. [catalyst] should be linear with slopes equal to k_{inter} and y-intercepts corresponding to k_{intra}.

Analysis of such plots with rate data obtained with dinuclear catalysts **1b–9b** and monomeric catalysts **7a–9a** depicted linear correlations with positive slopes and non zero y-intercepts, consistent with participation of both inter- and intramolecular pathway for the HKR (Fig. 10). Similar analysis of rate data obtained with monomeric catalysts **1a** and **4a** revealed y-intercepts of zero, reflecting the absence of any first-order pathway for these complexes. With dinuclear catalyst **7b**, a maximum value for intra- and intermolecular rate constants was obtained showing highest reactivity and enantioselectivity. Thus, the dinuclear catalyst provides appropriate relative proximity and orientation, which eventually reinforces the reactivity and selectivity relative to monomeric complex.

The HKR reactions follow the cooperative bimetallic catalysis where epoxide and nucleophile activate simultaneously by two different (salen)Co–Ga catalyst molecules. The active intermediate during HKR may be a Co^{III}–OH complex [8a]. The linking of two (salen)Co unit through the Al and Ga induces the cooperative mechanism, albeit through a far less enantio-discriminating transition state than that attained with the catalyst **1a** and **4a**. The reaction mechanism for **4b** is similar to **1b** [15a]. Although the HKR reaction is easily carried out with Co(II) complexes, but it appears that the reactive species is in fact Co(III). Unlikely to dinuclear complex of Co–Al and Co–Ga, the monomers
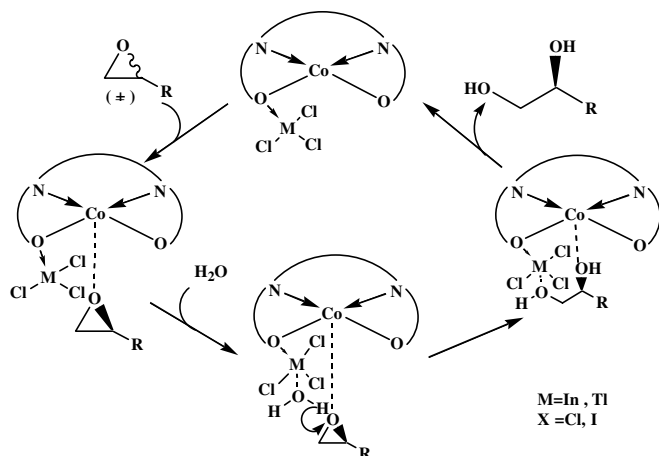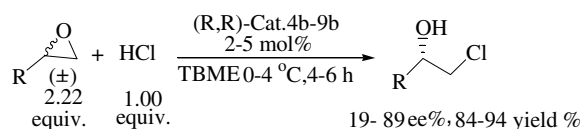
of Co–In **7a** and Co–Tl **9a** show the intramolecular pathway which is quite obvious from kinetic analysis. It seems, Co–In **7a** and Co–Tl **9a** act as heterometallic complexes exhibiting two different Lewis acid centers Co and In [23a,23b] and Co and Tl [23c] and show strong synergistic effect. However, dinuclear complex of Co–In **7b** and Co–Tl **9b** show two fold more reactive than corresponding monomeric analogy **7a** and **9a**. The central metal atom Co appears to activate and control the orientation of epoxide and stereoselectively bind only one enantiomer and the latter seems to activate and control the orientation of nucleophlie H_2O by enabling an enantioselective ring opening of epoxides with nucleophiles. The proposed model for HKR catalyzed by Co–In and Co–Tl complex is given in Scheme 3 which may be a similar to enantioselective ring opening of epoxides with 4-methoxyphenol catalyzed by gallium heterobimetallic complexes as reported by Shibasaki et al. [2c]. The intra- and inter-molecular mechanism for the **7a–9b** may be a similar to earlier report [15a,21,22].

3.2. Kinetic resolution with other nucleophiles and asymmetric ring closing reaction

3.2.1. Kinetic resolution with hydrochloride

Among the myriad of nucleophiles that have been employed in epoxide ring openings, halide ions (which afford the corresponding halohydrins) have been received considerable attention [24,25]. Methods for the asymmetric synthesis of chlorohydrins by enantioselective ring opening of epoxides have relied upon the use of stoichiometric amounts of chiral Lewis acid halides [26]. Garrett et al. [27a], Denmark et al. [27b] and quite recently Wang et al. [27c] disclosed the enantioselective ring opening of epoxides with TMSCl and $SiCl_4$ to afford optically active chlorohydrins. To our knowledge, we have observed first time enantioselective ring opening of terminal epoxides with HCl [15a]. We report herein one step synthesis of optically pure chlorohydrins using new chiral catalyst **4b–9b** dimer via kinetic resolution of terminal epoxides with HCl at 0–4 °C in *tert*-butyl methyl ether (TBME) solvent. Before starting the reaction the catalyst **4b–9b** were treated

Scheme 3. Possible working model for the HKR of terminal epoxides catalyzed by Co–In and Co–Tl heterometallic complex.

Scheme 4. Asymmetric ring opening of terminal epoxides with HCl catalyzed by **4b** and **9b** (yield based on HCl).
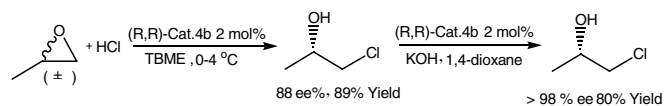
Scheme 5. Kinetic resolution/cyclization sequence in the presence of catalyst **4b**.
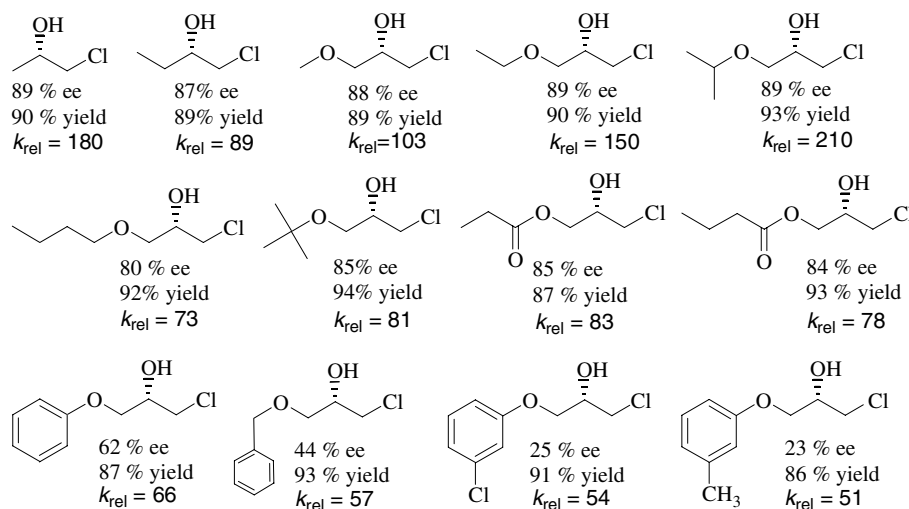
Fig. 11. Kinetic resolution products obtained using HCl and catalyst Co–In. Conditions are shown in Scheme 2. Yields correspond to the isolated product based on HCl 5. The selectivity factor (k_{rel}) was calculated using the equation $= \ln [1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$ where the conversion c was set to equal the isolated yield of the ring opened products.

in situ with HCl by taking 2:1 equiv. of HCl:4b in TBME for 1 h at 0–4 °C. The optimum condition for the kinetic resolution of terminal epoxides with HCl is illustrated in Scheme 4. TBME demonstrated the highest reactivity amongst various solvents like CH_2Cl_2, CH_3CN, THF and *n*-hexane at 0–4 °C. The reaction time and catalyst loading amount depend upon the individual terminal epoxides.

In a representative example, *rac*-propylene oxide and HCl were catalyzed by 2 mol% of 4b with major regioselectivity to afford 1-chloro-propan-2-ol in 88% ee within 1 h at 0–4 °C in TBME solvent. The ring opened 1-chloro-propan-2-ol in the presence of equimolar base and 2 mol% of catalyst 4b (with respect to substrate) minor enantiomer selectively ring closed to provide optically pure propylene oxide along with higher optically pure 1-chloro-propan-2-ol (Scheme 5) in 1,4-dioxane solvent at room temperature within 4 h. Moreover, HKR technology is the direct way to prepare enantiomerically enriched terminal epoxides but this method has benefit in terms of easy separation.

Terminal epoxides containing halide, ether, ester and aliphatic substituents underwent resolution to 89% ee of the corresponding products with good yields (Fig. 11).

However, phenyl glycidyl ether and their 3-chloro, 3-methyl derivatives, and benzyl glycidyl ether proved to be problematic substrates and resolved with relatively low ee%, even after high catalyst loading (3–10 mol%) and prolonged time (6 h). It appears that aromatic group might be plagued by conflicting steric and electronic factors influencing regioselectivity in the epoxide ring opening with HCl. In all present studied epoxides afforded with major regioselectivity 2-ol chlorohydrins and very few amount (<2%) regioisomer was experienced.

The reactivity and selectivity for kinetic resolution of terminal epoxides with HCl catalyzed by monomers and dimers of Co–Ga, Co–In, Co–Tl have not shown great differences, however, the order of reactivity is Co–In > Co–

Tl > Co–Ga and for the counter ion Cl > I > NO_3. The enantioselective ring opening of epoxides with HCl catalyzed by Co–Ga, Co–In and Co–Tl complex may occur similar to Scheme 3 where Ga, In and Tl also play an important role to activate the attacking reagent regio- and stereoselectively.

3.2.2. Catalytic asymmetric ring closing reactions

In an important and interesting reaction the optically pure epichlorohydrin and glycidol were obtained in good ee with over 70% ee and 43% yield, respectively, catalyzed by the catalyst 1b–4b in the presence of equivalent amount base with respect to substrate (Scheme 6). The asymmetric cyclization of 1,3-dichloro-2-propanol involves asymmetric elimination of hydrogen chloride with base potassium phosphate. The asymmetric cyclization of 1,3-dichloro-2-propanol could proceed significantly only in the presence of the catalyst.
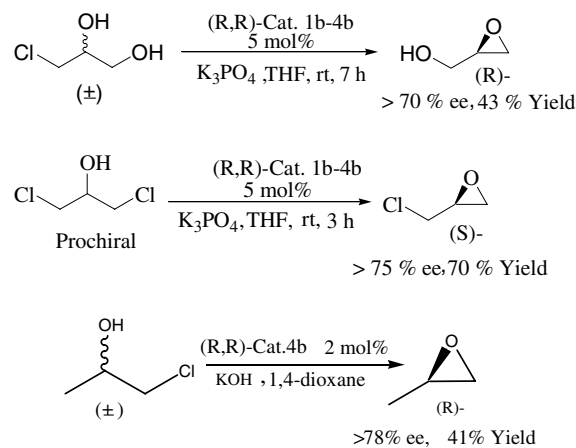
Scheme 6. Asymmetric cyclization of chlorohydrin catalyzed by dinuclear complex 1b–4b.

Table 3
Asymmetric ring opening of terminal epoxides with carboxylic acids catalyzed by 4b

Entry[A]	R	R′	Catalyst	Catalyst loading[a]	Time (h)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl	(O=, OH)	4b	2.0	3.0	42	61
2	CH_2Cl	(O=, OH)	4b	2.0	4.0	41	63
3	CH_2Cl	(O=, OH)	4b	3.0	3.0	43	76
4	CH_2Cl	(O=, OH)	4b	3.0	5.0	41	75

[A] For entry 1–2, 1,4-dioxane and 3–4 TBME was taken as solvent.
[a] In mol% loading on a per [Co] basis w.r.t. racemic epoxide.
[b] Isolated yield is based on racemic epoxides (theoretical maximum = 45%).
[c] ee% was determined by chiral GC or chiral HPLC.
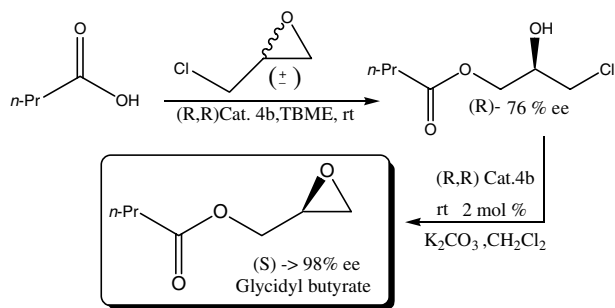
Scheme 7.

In the absence of catalyst reaction underwent slowly and formed racemic mixture. Similarly optically active glycidol was synthesized from asymmetric cyclization of 3-chloro-propane-1,2-diol via kinetic resolution. The result shows that (S)-3-chloro-propane-1,2-diol is preferentially cyclized to give (S)-glycidol. The mechanism of asymmetric cyclization may follow the similar mechanism reported by Takeichi et al. [28].

### 3.2.3. Asymmetric ring opening of terminal epoxides with carboxylic acids

The moderate to high enantioselectivity displayed by these catalysts for asymmetric ring opening of terminal epoxides with H_2O and HCl led us to extend the possible use of other nucleophiles. Carboxylic acids are interesting candidates (Table 3) because of their low cost, ease of handling and reaction of epoxides provides a direct and appealing route to 1,2-diol monoesters [29]. In an important and model reaction, butyric acid and (±) epichlorohydrin was catalyzed by 4b with complete regioselectivity along with 75% ee and in a 43% yield (45% theoretical yield). The resolved ring opened product followed by ring closing in the presence of base and catalyst afforded glycidyl butyrate in high 98% ee and quantitative yield (see Scheme 7).

(R)-glycidyl butyrate is very important compound and has been used to introduce a stereogenic center in the synthesis of Linezolid [30] which is currently marketed for the treatment of multidrug resistant Gram-positive infections such as nosocomial, community-acquired pneumonia, and skin infections.

4. Conclusion

In summary, we have synthesized homogeneous and heterogeneous chiral dinuclear complex and demonstrated their catalytic activity and selectivity for the asymmetric ring opening (ARO) of terminal epoxides with variety of nucleophiles and for asymmetric cyclization to prepare optically pure terminal epoxides in one step. The ARO reactions are summarized in Scheme 8. Yields and enantioselectivities are good to excellent. The resolved ring opened product combined with ring closing in the presence of base and catalyst afforded terminal epoxides in high ee and quantitative yield. The catalyst can be easily synthesized by readily commercially available precatalyst Co(salen) in both enantiomeric forms. Potentially, the catalyst may be used on an industrial scale. Further studies concerning the mechanism and scope of binuclear catalysts,
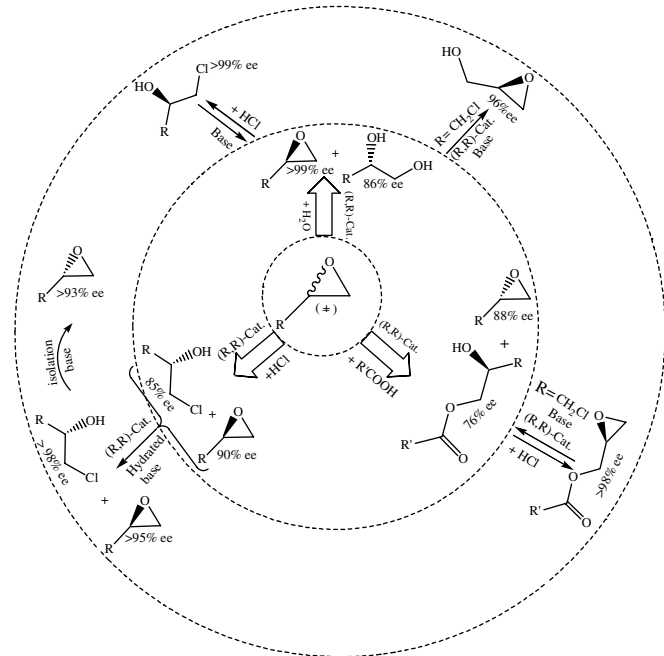
Scheme 8. Coupled route for the synthesis of chiral intermediates catalyzed by dinuclear salen complex.

for asymmetric catalytic reactions are currently under investigation for a broad applicability as a general catalyst.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.12.044.

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