Catalysis Science & Technology

Accepted Manuscript

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ARTICLE

Asymmetric hydrolytic kinetic resolution with recyclable polymeric Co(III)-salen complexes: A practical strategy in the preparation of (*S*)-Metoprolol, (*S*)-Toliprolol and (*S*)-Alprenolol: Computational rationale for enantioselectivity

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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A series of chiral polymeric Co(III) salen complexes based on a number of achiral and chiral linkers were synthesized and their catalytic performances were assessed in asymmetric hydrolytic kinetic resolution of terminal epoxides. The effect of the linker were judiciously studied and it was found that in case of chiral BINOL based polymeric salen complex **1**, there was certain enrichment in catalyst reactivity and enantioselectivity of the unreacted epoxide particularly in the case of short as well as long chain aliphatic epoxides. Good isolated yield of the unreacted epoxide (up to 46% out of 50% theoretical yield) along with high enantioselectivity (up to >99%) were obtained in most of the cases using catalyst **1**. Further studies exhibited that the catalyst **1** could retain its catalytic activity for six cycles under the present reaction conditions without any significant loss in activity and enantioselectivity. To show the practical applicability of the above synthesized catalyst we have carried out synthesis of some potent chiral β-blockers using complex **1** in moderate yield and high enantioselectivity. The DFT (M06-L/6-31+G**//ONIOM(B3LYP/6-31G*:STO-3G)) calculations revealed that the chiral BINOL linker influences the enantioselectivity with Co(III)salen complexes. Further, the transition state calculations show that the *R*-BINOL linker with (*S*,*S*)-(salen)Co(III) complex is energetically preferred over the corresponding *S*-BINOL linker with (*S*,*S*)-(salen)Co(III) complex for HKR of 1,2-epoxyhexane. The role of non-covalent C-H... π interaction and steric effects has been discussed to control the HKR reaction of 1,2-epoxyhexane.

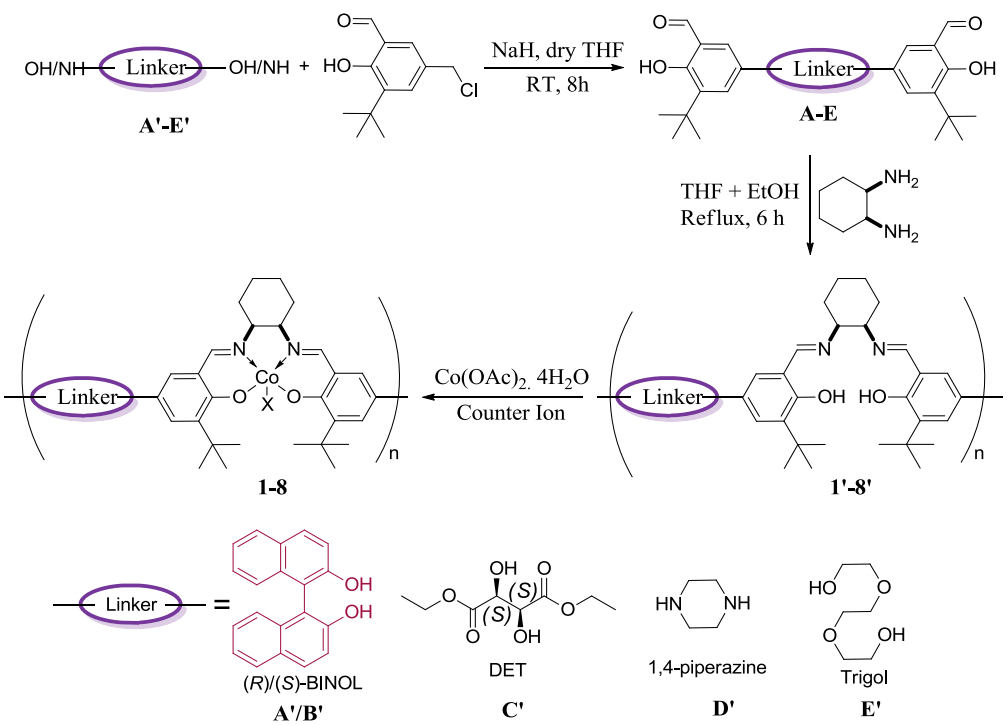
Introduction

Presence of strained three member ring unit makes epoxides a unique and one of the most significant molecule in synthetic organic chemistry.[1] Additionally, stereospecific ring opening of epoxides, in particular chiral epoxides, leads to several biologically and medicinally active compounds together with some of the most important building block in asymmetric synthesis.[2] Over the last three decades methodologies to synthesize epoxides in high optical purity has become a prime area of interest amongst the scientific community worldwide. Most significant breakthrough was achieved by Sharpless *et al.*[3] for the synthesis of enantio-enriched epoxy alcohols from allylic alcohol, followed by pivotal work of Jacobsen[4] and Katsuki[5] to develop manganese-salen complex for the asymmetric epoxidation of non-functionalized olefins. Besides numerous exciting developments have been made in the area of organo-catalytic asymmetric epoxidation reaction.[6] Nevertheless it is the seminal work of Jacobsen *et al.* on asymmetric hydrolytic kinetic resolution (HKR) of terminal epoxides that makes the synthesis of enantiopure 1,2-epoxides convenient, which was otherwise difficult to obtain by the earlier methods.[7] Good yield, high enantioselectivity for both the unreacted epoxide and product 1,2-diol, high atom efficiency and extraordinary K_{rel} value makes the process of particular interest mainly in total synthesis of bioactive compounds and in pharmaceutical industry.[8] A number of works have been reported afterwards to improve on the reaction

parameters such as catalyst loading, reaction time, enantioselectivity of the products and catalyst recyclability as well as to understand the mechanistic behaviour of the reaction.[9] In quest of synthesizing highly recyclable catalyst, immobilization of the chiral Co(III) salen complex was achieved by means of solid support such as mesoporous silica,[9e,10] zeolites,[11] polymers,[9e,12] gold colloids.[13] Fluorous biphasic catalytic system[14] and ionic liquid[15] have also been explored in the asymmetric HKR of terminal epoxides. Alternatively, with the advent of dimeric,[16] oligomeric[7,9b] and polymeric[17] ligands, the catalyst recyclability was significantly improved even in homogeneous reaction condition along with additional benefit of improved reactivity than their monomeric counter parts, as mechanistically it is evident that HKR reaction proceeds via a bimetallic pathway. Our constant interest in the field of HKR[16b-d] as well as in development of recyclable salen based complexes in several other asymmetric organic transformations,[18] on the basis of high molecular weight and less solubility of these catalysts in non-polar solvents, led us to the synthesis of a series of polymeric Co(III)-salen complexes based on some chiral (*S*-BINOL, *R*-BINOL, diethyl tartrate) and achiral (trigol, piperazine) linkers. Subsequently we have tested the synthesized catalysts for asymmetric hydrolytic kinetic resolution of terminal epoxides. Preliminary results showed that in case of catalyst **1**, i.e. catalyst with chiral BINOL linker, there was some additive effect of auxiliary chirality of BINOL particularly in the case of short as well as long chained aliphatic 1,2-epoxides. Good isolated yield (up to 46%) and high enantioselectivity (up to >99%) of the unreacted epoxides were obtained with most of the 1,2-epoxides used in the present reaction condition sparing a very little amount of catalyst **1**. Furthermore the catalyst **1** was highly recyclable in the present reaction conditions and could be reused for six successive cycles just by performing regeneration of the catalyst once with acetic acid. To show general applicability of complex **1**, we have checked its efficacy in the synthesis of three potent chiral *β*- blockers namely (*S*)-Metoprolol, (*S*)-Toliprolol and (*S*)-Alprenolol in moderate yield (up to 44% w.r.t starting phenol) and high enantioselectivity (99%).

Results and Discussion

An extra element of chirality together with multiple catalytically active sites often increases the catalyst performance in asymmetric catalysis. Further, salen ligand has proven role in numerous asymmetric transformations including HKR.[19-22] Keeping these simple facts in mind achiral/chiral linker based polymeric salen ligands **1'-8'** were synthesized in two steps; i.e. initial formation of bis-aldehydes by interaction of 5-chloromethyl-3-*tert*-butyl salicylaldehyde with diamines[18b]/ diols[19-21] followed by condensation using chiral trans 1,2-diaminocyclohexane as per earlier reported procedure.[22] In turn metalation of these ligands was furnished with $Co(OAC)_2.4H_2O$ under anaerobic condition followed by auto-oxidation in air with the help of an appropriate counter ion source (Scheme 1) to achieve polymeric cobalt salen complexes **1-8** (Figure 1).



Scheme 1. Synthetic steps for the preparation of chiral polymeric Co(III) salen complexes.

Both polymeric ligands and their corresponding metal complexes were characterized by dint of suitable physico-chemical techniques like IR-, ^{1}H- and ^{13}C NMR, UV-Vis spectroscopy, elemental analysis, GPC and optical rotation (See supporting information). Once the above synthesized metal complexes are aptly characterized these are employed for asymmetric hydrolytic kinetic resolution of 1,2-epoxyhexane as a test substrate.

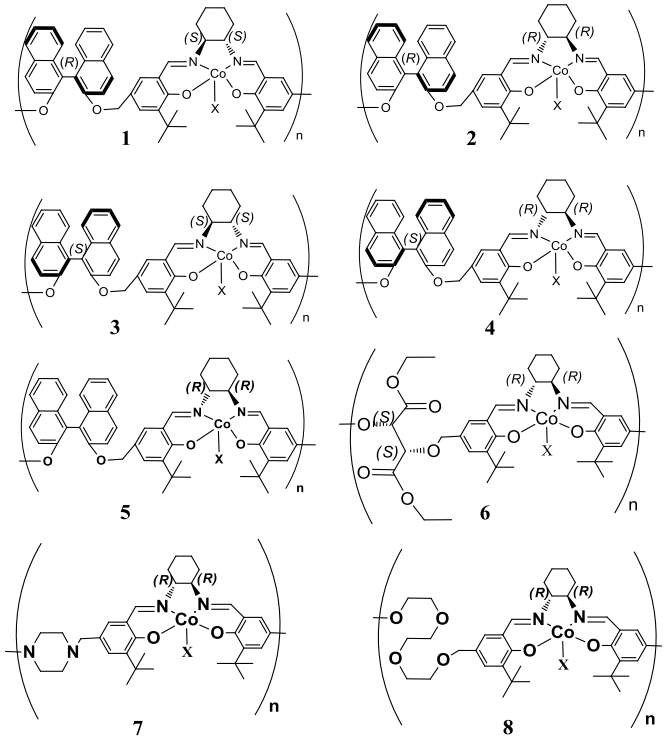


Figure 1. Structures of the polymeric Co(III) salen complexes **1**-**8**.

To check the influence of counter ion in HKR of 1,2-epoxyhexane, polymeric Co(III) salen complexes with diverse counter ions were prepared *via* treatment of the Co(II) salen complex of ligand **1'** with a suitable source such as, acetic acid, trichloroacetic acid, trifluoroacetic acid, para-nitro benzoic acid, lutidine 2,6-dimethyl pyridiniumtosylate (LPTS) ferroceniumhexafluorophosphate and ferroceniumtetrafluoro borate in an appropriate solvent. No general trend in terms of activity and enantioselectivity, was obtained from this study, however it has been found that Co(III) salen complex obtained with the use of acetic acid was most suitable (Figure 2), reason for which is not clearly known but are in tandem with some of the earlier literature reports.[7a,b] Besides the data obtained from above study clearly suggest that counter ions having a covalent bond with the metal centre were better performed in terms of reactivity in HKR compare to those where there is an ionic interaction between metal centre and the counter ion.

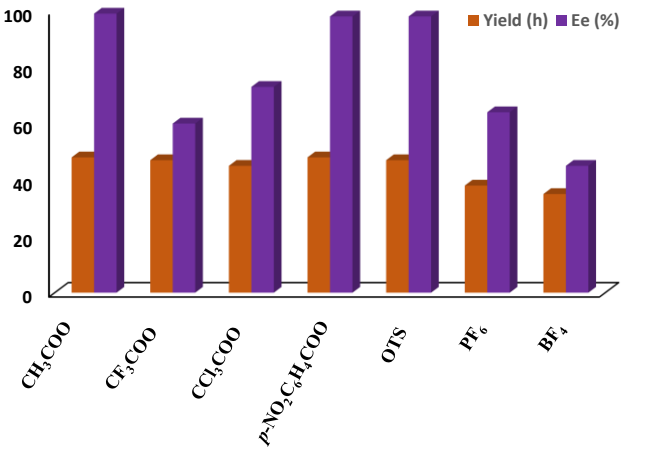
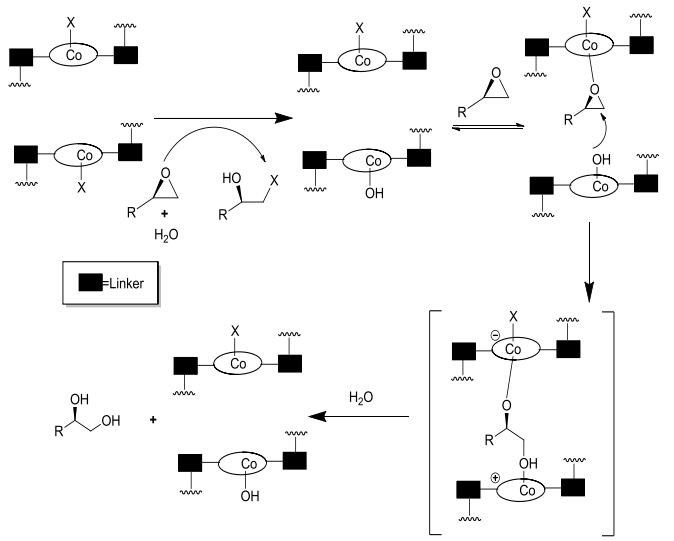


Figure 2. Study of effect of counter ion in asymmetric HKR of 1,2-epoxyhexane. Reaction Condition: 1,2-epoxyhexane (10 mmol), Catalyst (0.05 mol %), H_2O (5 mmol), Room temperature.

This phenomenon could possibly be explained by considering the mechanistic aspects of asymmetric HKR reaction as proposed by Jacobsen *et al.*[9k] where the reaction is believed to proceed in a bimetallic pathway with *in situ* generation of an active Co(III)-OH species (Scheme 2).

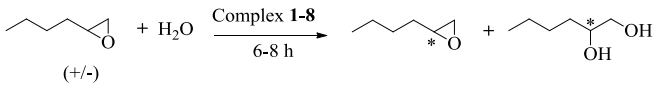


Scheme 2. Proposed bimetallic mechanism of Co(III) salen complex catalyzed asymmetric HKR of terminal epoxides.

So it would be fair to expect that the counter ions that are attached to the metal centre via an ionic interaction are non-transferable and could not generate the active Co(III)-OH species as faster compare to the formers. Moreover, strong acidic counter ions increased the Lewis acidity of the metal centre to such an extent that a majority of the reaction proceeded in a non-chiral pathway to give less enantioselectivity of the unreacted 1,2-epoxyhexane.

With optimization of the counter ion, next to better understand the effect of the linker connecting two salen units, we have employed all the above synthesized polymeric Co(III) salen complexes **1**-**8** in asymmetric HKR reaction of (+/-)-1,2-epoxyhexane (Table 1).

Table 1. Catalyst screening in asymmetric HKR of 1,2-epoxyhexane at room temperature under solvent free condition.[a]



Co(III)salen complex	Catalyst loading (mol %)	Time (h)	Unreacted epoxide Yield (%)	ee (%)
1	0.05	6	42	99[b]
2	0.05	6	42	86[c]
3	0.05	6	41	86[b]
4	0.05	6	42	99[c]
5	0.05	6	40	72[c]
6	0.1	8	41	95[c]
7	0.1	8	42	89[c]
8	0.1	6	43	90[c]

[a]Reaction conditions: 1,2-epoxyhexane (10 mmol), Catalyst (0.05 to 0.1 mol%), H_2O (5 mmol), Room temperature. [b]Epoxide configuration (*S*), [b]Epoxide configuration (*R*).

From the mechanism proposed for the reaction it can be anticipated that the linker might have some role on the outcome of the reaction due to their ability to provide the necessary arrangement to the two metal centres involved in the reaction pathway. Preliminary results suggested that all these complexes except complex **5** (ee, 72%) were showing good activity and moderate to good enantioselectivity in asymmetric HKR of 1,2-epoxyhexane. A possible explanation for less reactivity of complex **5** was provided by us in an earlier report,[22] as the distortions (random twists) in the structure of the polymeric salen ligand in case of ligand **5'** prepared from racemic BINOL where both *R*- and *S*-BINOL motifs may perhaps present randomly in a single polymeric chain.

Straight chain aliphatic epoxides are particularly important class of compounds and have their occurrence in many biologically active compounds. These epoxides are hard to get in good yield and high enantioselectivity and often requires either higher catalyst loading or use of an extra volume of water (0.6-0.7 equivalent) under HKR condition, which results in diminishing enantioselectivity for the corresponding 1,2-diol. When employed in asymmetric HKR of 1,2-epoxyhexane (with 0.5 equivalent of water), we found best activities (Table 1, Figure 3) with complexes **1** and **4** (ee of unreacted epoxide is 99% in both cases), having different absolute configuration of the linker and of the diamine collar [(*R*,*S*,*S*) or (*S*,*R*,*R*)]. Enantioselectivity values obtained with these two catalysts were significantly higher than the other catalysts, where there is incompatible chirality at those two points (ee 86% in both cases).

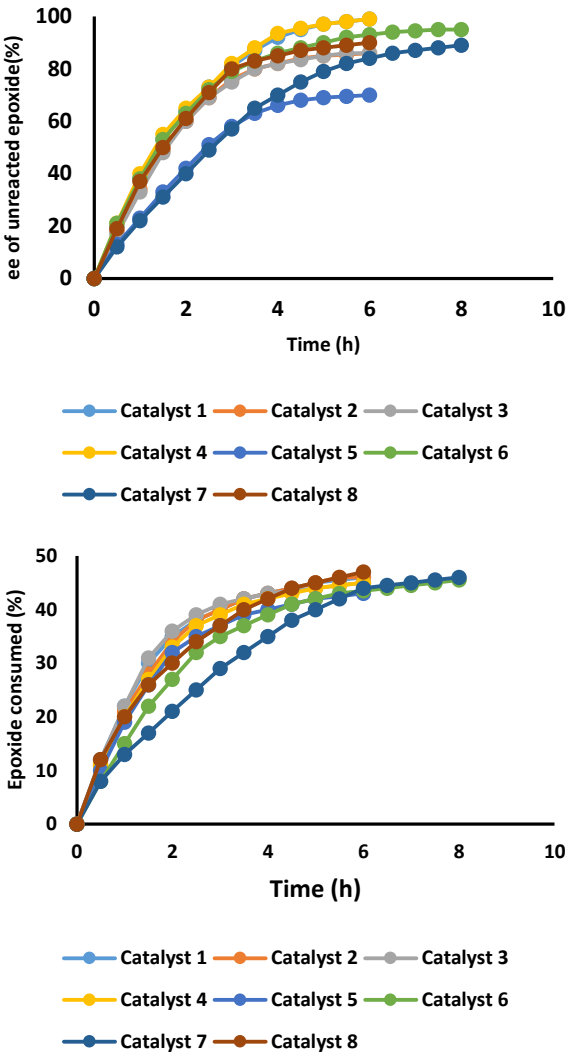


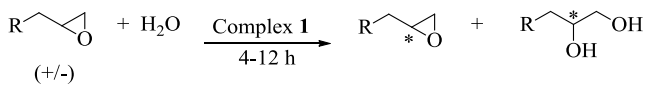
Figure 3. The catalytic activity of Co(III)salen complexes **1**-**8** in the asymmetric HKR 1,2-epoxyehxane at RT a) ee value of the epoxide versus time (above); and b) epoxide consumed in percentage versus time (below). Reaction conditions: 1,2-epoxyhexane=10 mmol, H_2O=5 mmol, catalyst=0.05-0.1 mol%.

Besides the complexes **7** and **8** with an achiral linker joining the salen units gave comparatively inferior results (ee 89% and 90% respectively) when employed in HKR of 1,2-epoxy hexane. An intermediate result (ee 95% of unreacted epoxide) was obtained under similar reaction condition with complex **6** having diethyl tartrate as a chiral linker (Table 1, Figure 3). The enantioselectivity of the unreacted 1,2-epoxyhexane could be increased up to 99% with the use of extra equivalent of water (0.7 equivalent) in case of complex **7** and **8** as reported earlier by Jacobsen et al., at the cost of reduced ee of the corresponding diol (78%).

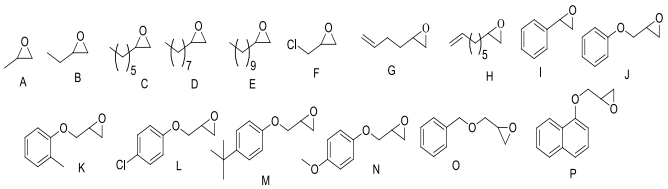
From the results obtained in HKR of 1,2-epoxyhexane it could be concluded that though the diamine collar in the salen motif was mainly responsible for governing the enantioselectivity in products, still the distance and the orientation between the two salen units as provided by the achiral/chiral linkers also played

an important role. In an earlier work by us where we have used the above set of complexes, we have recorded CD spectra of complexes **1-3** in DCM which showed similarity in spectra except to obtain opposite cotton effect for the complexes having opposite chiral arrangement at the diamine collar, confirming that the configuration of the product is solely controlled by the diamine collar.[22]

Table 2. Asymmetric HKR of terminal epoxides using BINOL based polymeric Co(III) salen complex 1.[a]



Substrate	Catalyst loading (mol %)	Time (h)	Unreacted epoxide Yield(%)	ee (%)[b]	1,2-Diol Yield (%)	ee (%)
A	0.01	4	43	99	44	96
B	0.05	5	46	99	45	96
C	0.1	6	45	99	43	95
D	0.1	8	45	99	43	96
E	0.15*	8	42	99	43	96
F	0.005	5	45	99	45	96
G	0.1	12	45	93	42	92
H	0.1	12	45	92	43	90
I	0.05	12	44	99	44	94
J	0.05	6	46	99	42	95
K	0.05	6	42	98	42	95
L	0.05	6	43	99	43	96
M	0.05*	8	41	99	41	94
N	0.05*	8	44	99	42	96
O	0.05	6	45	99	43	96
P	0.1*	10	42	99	42	95



[a]Reaction conditions: racemic epoxide (10 mmol), H_2O (5 mmol), Room temperature. *THF was used as a solvent. [b]Epoxide configuration (*S*)

After having established complex **1** as the best choice for asymmetric hydrolytic kinetic resolution of 1,2-epoxyhexane, we have employed this catalyst with other terminal epoxides. A wide variety of terminal epoxides namely, straight chain aliphatic epoxides (A-E), halogenated epoxide (F), arene epoxides (G, H), aromatic epoxide (I) and aryloxy epoxides (J-P), were used with success in HKR condition using complex **1** and the results are summarized in Table 2.

The reaction was performed under solvent free condition in most of the cases except few where either the substrate epoxide was solid, or the catalyst had poor solubility in the substrate epoxide. When compared our catalytic data with some of the benchmark monomeric/oligomeric/polymeric Co(III) Salen complexes reported so far in the literature, the results are either in parallel or even better particularly in case of long chain aliphatic epoxides at the expense of a lower catalyst loading (0.05 to 0.15 mol %) (See supporting information, Table 4). A series of reactions performed with 4-substituted phenylglycidyl ethers showed no effect of the electronic character or the bulkiness of the substituent on the outcome of the reaction.

Additionally we have isolated the other product i.e. 1,2-diols also in most of the cases with a good isolated yield (up to 45%) and enantioselectivity (up to 96%). However, when employed in asymmetric HKR of terminal arene epoxide the catalyst **1** gives moderate results likened with Jacobsen's oligomeric Co(III) salen complex, reason for which is unknown to us.

Next 1,2-epoxyhexane due to its less volatility was selected as a model substrate for the study of recyclability using complex **1**. A recyclability study carried out for six successive cycles witnessed a diminished catalytic activity, which reflected in an increase of the reaction time without sacrificing the enantioselectivity of the unreacted epoxide. However, a catalyst regeneration step, as per earlier literature reports, after four catalytic cycles shows the similar kinetic behaviour for the HKR of 1,2-epoxyhexane as observed in fresh catalytic reaction (Figure 4).

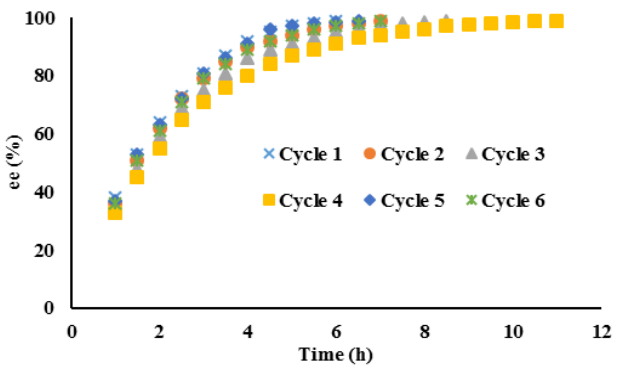


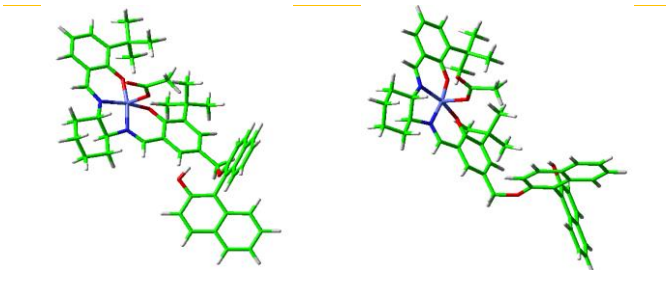
Figure 4. Study of catalyst recyclability using complex **1**. Reaction Condition: 1,2-epoxyhexane (10 mmol), catalyst (0.05 mmol), water (5 mmol), RT.

Chiral β-blockers are important class of bioactive compounds and are potent drug, used in the treatment of several cardiovascular diseases like hypertension, angina, acute myocardial infarction and congestive heart failures. In most of these β-blockers, (*S*)-enantiomer is potentially more active than

its (*R*)-form and hence administered as a single isomer for better activity. Asymmetric HKR of the representative glycidyl ether is one of the simplest routes for the synthesis of the above class of compounds in moderate yield and high enantioselectivity. We have carried out the synthesis of three enantiopure β -blockers namely (*S*)-Metoprolol, (*S*)-Toliprolol and (*S*)-Alprenolol by means of HKR of the corresponding glycidyl ethers using catalyst **1** in moderate yield (up to 44% w.r.t phenols) and high enantioselectivity (>99%) (Scheme 3). An alternative procedure for the synthesis of these β-blockers starting from optically pure epichlorohydrin however, gave the end product with a maximum enantioselectivity of 92%.

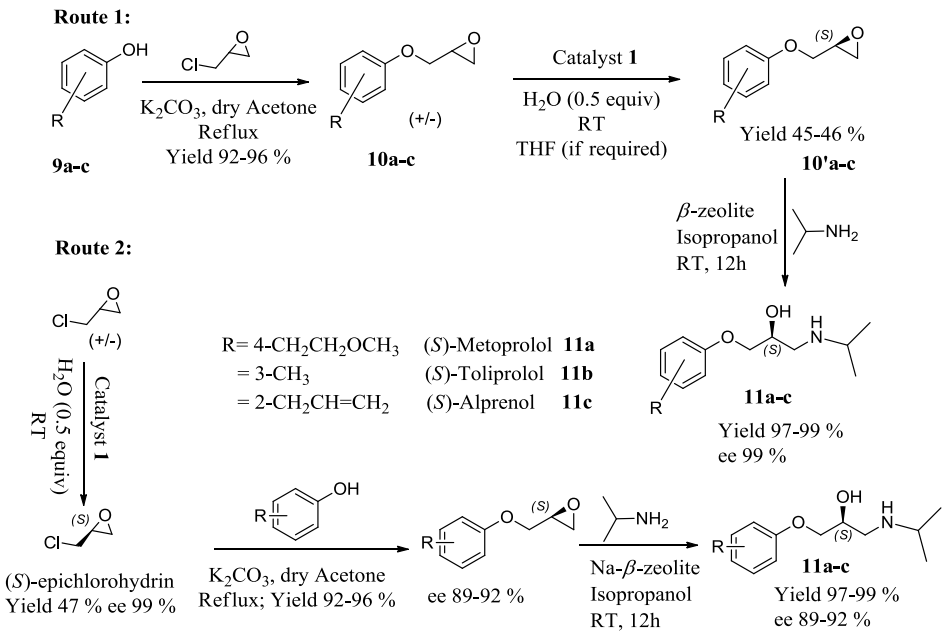
The experimental studies suggested that the enantioselectivity in the HKR of aliphatic terminal 1,2-epoxides is governed by the chiral and stepped conformational nature of Co(III) salen complexes. The importance of chiral BINOL linker in the generation of enantiomeric excess (ee) of aliphatic terminal 1,2-epoxides has been observed (Table 2). We have performed the DFT calculations to unravel the origin of the generation of ee for the studied aliphatic terminal 1,2-epoxide. The salen complexes **1** and **4** are enantiomers and hence they yield similar enantioselectivity as shown in Figure 3. Therefore, we have considered salen complex **1** for our computational study.

The earlier reports suggest that both the enantiomers (*S,S*)-Co(III) salen with *R*-BINOL and (*R,R*)-Co(III) salen with *S*-BINOL shows the high enantio-selectivity compared to the corresponding (*S,S*)-Co(III) salen with *S*-BINOL and (*R,R*)-Co(III) salen with *R*- BINOL, respectively.[23] Therefore, we have also examined the stability of the (*S,S*)-Co(III) salen complex with chiral *R*- and *S*- BINOL, respectively. The binding energy calculated for (*S,S*)-Co(III) salen with *R*-BINOL using B3LYP/ 6-31G* level of theory suggests that it is energetically 1.0 kcal/mole more stable than the corresponding *S*-BINOL linker (Figure 5).



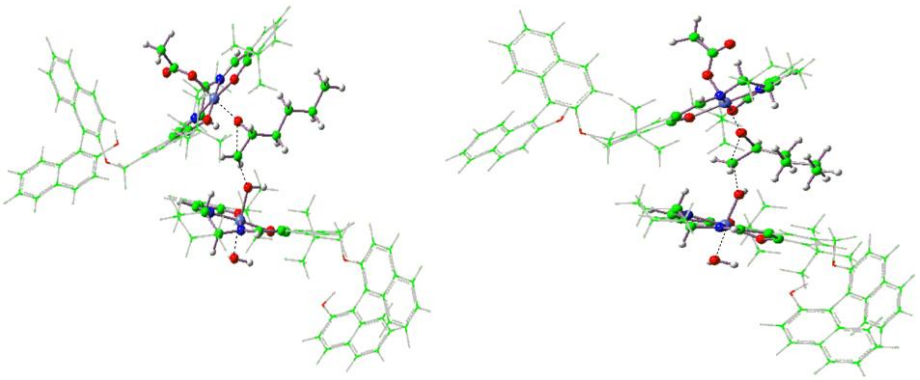
	R-BINOL with (*S,S*)-Co(III) salen	*S*-BINOL with (S,S)-Co(III) salen
*B3LYP/6-31G**		
ΔE(kcal/mol)	[0.0]	[1.0]

Figure 5. The optimized structures of *R*-BINOL with (*S,S*)-Co(III) salen and *S*- BINOL with (*S,S*)-Co(III) salen with B3LYP/6-31G* level of theory.



Scheme 3. Synthesis of chiral β-blockers using complex **1**.

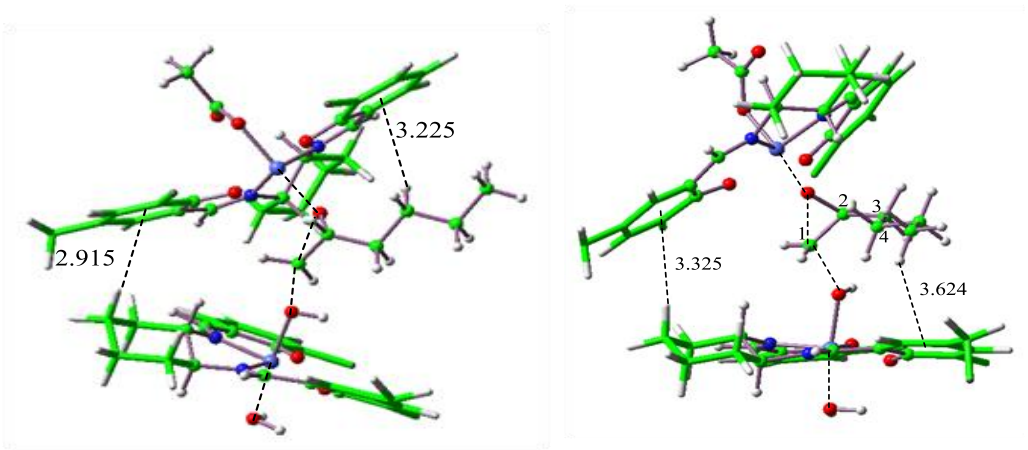
The (*S*,*S*)-Co(III) salen complex with chiral *R*-BINOL linker has been used to examine the formation of ee for 1,2-epoxyhexane. We have determined the two possible transition states of bimetallic (*S*,*S*)-Co(III) salen complex with *R*- and *S*-1,2-epoxyhexane. Due to the bigger size of the two salen complexes, ONIOM (B3LYP/6-31G*:STO3G) method was employed. Recent studies have shown that two salen complexes are necessary to induce the ee in substituted 1,2-epoxides.[24] The transition state (TS-1) for *R*-1,2-epoxyhexane and the transition state (TS-2) for *S*-1,2-epoxyhexane is shown in Figure 6. The activation energy barriers calculated for the TS-1 and TS-2 suggest that the TS-1 is energetically favoured as compared to the TS-2 (Figure 6). Single-point energy calculations performed with M06-L/6-31+G** level of theory using the ONIOM-optimized geometries also corroborate the experimental observations.



TS-1 **TS-2**

ONIOM(B3LYP/6-31G:STO3G)*		
ΔE(kcal/mol)	[0.0]	[2.30]
ΔG(kcal/mol)	[0.0]	[3.21]
*M06-L/6-31+G**//ONIOM (B3LYP/6-31G*:STO3G)*		
ΔE(kcal/mol)	[0.0]	[7.83]

Figure 6. Transition state structures of (S,S)-(salen)Co(III) with chiral R- BINOL towards the ring opening of (R)-1,2-epoxyhexane and (S)-1,2-epoxyhexane calculated with ONIOM(B3LYP/6-31G*:STO-3G) level of theory. Single point energy calculations are also given at M06-L/6-31+G** level of theory.



TS-1 **TS-2**

Figure 7. ONIOM(B3LYP/6-31G*:STO3G) optimized geometries of the two transition states TS-1 and TS-2 and the C-H… π distances are given in (Å)

The transition state structures show that the C-H….π interactions are present in both the TS-1 and TS-2, respectively (Figure 7). It appears that the TS-1 is more stabilized via non-covalent C-H… π interactions as the distances in this case is much shorter compared to the TS-2 structure. Further, the geometrical analysis reveal that the alkyl chain of 1,2-epoxyhexane in the TS-1 orients in the trans-fashion, however, the alkyl chain in TS-2 adopts a gauche conformation and hence there is energy penalty in the later conformation.[25]

Experimental

Materials and Methods

(1*R*,2*R*)-(-)-1,2-diaminocyclohexane, counter ion sources, epoxides (1,2-epoxypropane, 1,2-epoxybutane, 1,2-epoxyhexane, 1,2-epoxyoctane, 1,2-epoxydecane, 1,2-epoxydodecane, epichlorohydrin, 1,2-epoxy-5-hexene, 1,2-epoxy-8-nonene, styrene oxide, phenylglycidyl ether, 2-methyl phenylglycidyl ether, 4-chloro phenylglycidyl ether, 4-*tert*-butyl phenylglycidyl ether, 4-methoxy phenylglycidyl ether, benzylglycidyl ether) and isopropyl amine were purchased from Sigma-Aldrich, Across and Alfa-Aesar and were used without any further purification. Cobalt acetate was purchased from SD Fine Chemicals India and was used as received. Naphthylglycidyl ether was prepared as per the procedure depicted in the literature.[26] The solvents used for present study were dried prior to use. Microanalysis of the intermediates, ligand and catalysts was carried out on a Perkin Elmer 2400 CHNS analyzer. All the melting points reported here were determined on a Mettler Toledo-FB62 and were uncorrected. ^{1}H &^{13}C NMR spectra were recorded on Bruker 200 MHz or 500 MHz spectrometer at ambient temperature and referenced against TMS as an internal standard. FTIR spectra were recorded as KBr pellet on a Perkin Elmer Spectrum GX spectrophotometer. Optical rotation of the chiral polymeric salen ligands were recorded on an automatic polarimeter (Digipol 78, Rudolph) instrument. High-resolution mass spectra were obtained with a LC-MS (Q-TOFF) LC (Waters), MS (Micromass), MALDI-TOF, Model make Ultra flex TOF/TOF, Burker Daltonics, Germany instruments. All the products were purified either by distillation or *via* flash chromatography using silica gel 60-200 mesh purchased from SD Fine-Chemicals Limited, Mumbai (India). The purity of the solvents, epoxides and the analysis of the products were carried out by gas chromatography (GC) on Shimadzu GC 14B instrument with a stainless-steel column (2 m long, 3 mm inner diameter, 4 mm outer diameter) packed with 5% SE30 (mesh size 60–80) and equipped with an FID detector. Ultrapure nitrogen was used as carrier gas (rate 30 mL/min). Injection port and detector temperature was kept at 200 °C. The ee of aliphatic epoxides and their corresponding diols were determined on GC using a chiral capillary column (Chiraldex ATA, Chiraldex BTA or Chiraldex GTA). For ee determination of aromatic epoxides and their derivatives chiral HPLC was performed on Shimadzu SCL-10AVP by using a Chiralcel OD column.

Preparation of polymeric salen ligands 1'-8'

Di-aldehydes **A**-**E** *viz.*, (*R*)-5,5'-(1,1'-binaphthyl-2,2'-diylbis(oxy))-bis(methylene)-bis(3-*tert*-butyl-2-hydroxybenzaldehyde)[19] **A** / (*S*)-5,5'-(1,1'-binaph-thyl-2,2'-diyl-bis(oxy))-bis(methylene)-bis(3-*tert*-butyl-2-hydroxybenzaldehyde)[19] **B**, (2S,3S)-diethyl-2,3-bis(3-*tert*-butyl-5-formyl-4-hydroxybenzyloxy) succinate[20] **C**, 5,5'-(piperazine-1,4-diylbis-(methylene))-bis(3-*tert*-butyl-2-hydroxy benzaldehyde)[18b] **D** and 5,5'-(2,5,8,11-tetraoxadodecane-1,12-diyl)-bis(3-*tert*-butyl-2-hydroxylbenzalde-hyde)[21] **E** (1 mmol) were dissolved in dry THF: EtOH mixture (2:1) at 65 °C to which (1*R*,2*R*)/(1*S*,2*S*)-diaminocyclohexane (0.136 g, 1.2 mmol) in EtOH were added slowly under nitrogen atmosphere. The resulting solutions were stirred for 4 h under refluxing condition (TLC checked) and the solvent was partially removed from the each reaction mixture on a rotary evaporator that gave yellow precipitate. The solid obtained after filtration were washed with hexane:DCM (50:1) to get the yellow coloured desired polymeric ligands **1'-8'** (Scheme 1).

Preparation of polymeric salen catalysts 1-8

In 50 mL three neck RBF (equipped with a magnetic bar) under nitrogen atmosphere, the polymeric salen ligands **1'-8'** (1 mmol) were dissolved in deoxygenated toluene (10 mL). In another 25 mL vial $Co(OAc)_2.4H_2O$ (1.5 mmnol) was dissolved in deoxygenated methanol (10 mL) under nitrogen for 10 min to ensure complete deoxygenation. The solution of $Co(OAc)_2.4H_2O$ in MeOH (purple) was transferred under nitrogen via cannula to the solution of polymeric salen ligand (yellow), affording a dark red precipitate. The mixture was stirred for 2 h at RT and then the solvent was removed under vacuum, dissolved the residue in DCM (50 mL) and passed through celite-545 pad to remove the excess of metal ions. The filtrate was evaporated by vacuum afforded a dark red powder. To get the desired active catalysts, Co(II) chiral polymeric salen complexes were dissolved in DCM (2 mL) under dry oxygen atmosphere and an appropriate counter ion source (1.2 mmol) was added to them and the resulting solutions were stirred for 5 h to convert Co(II) chiral polymeric salen complexes to Co(III) chiral polymeric salen complexes **1**-**8** (Scheme 1).

Typical Procedure for asymmetric HKR of terminal epoxides

An appropriate amount of pre-catalyst **1-8** (0.005-0.15 mol % w.r.t. substrate) was taken in DCM in a vial and treated with 2 equivalent of suitable counter ion source and the resulting solution was stirred for 1 h. After 1 h the solvent was evaporated and the epoxide (10 mmol) was introduced into the reaction *via*l either in neat condition or in presence of THF as a solvent. Water (5 mmol) was added drop wise to this solution placing the vial at 0 °C. Subsequently, the reaction mixture was allowed to warm gradually to RT and stirred at this temperature for required amount of time. After completion of the reaction the catalyst was precipitated out from the reaction medium with

the addition of hexanes washed several times with hexane:ethyl acetate (90:10), dried overnight in a desiccator under vacuum and subsequently reused in next cycle. The epoxide was separated from the mixture either by distillation or by column chromatography and checked on GC or HPLC for enantioselectivity. Enantio-purity of the remaining diol was determined as trifluoroacetate derivative on GC or HPLC.

For kinetics study of the reaction an aliquot was withdrawn from the reaction mixture at certain interval, quenched and after separation of the catalyst by precipitation checked on GC for conversion and enantioselectivity of the remaining 1,2-epoxyhexane.

General procedure for the synthesis of chiral β-blockers

To a stirred solution of an apt phenol **9a-c** (20 mmol) and K_2CO_3 (30 mmol, 4.14 g) in dry acetone (100 mL), epichlorohydrin (30 mmol, 2.4 mL) was added and the reaction mixture was allowed to reflux until all of the phenol had been consumed (checked on TLC). Subsequently the reaction mixture was filtered and the residue was purified by column chromatography using ethyl acetate and hexane as eluent to obtain the glycidyl ethers (**10a-c**) in pure form.

Next the above synthesized glycidyl ether (10 mmol) was subjected to HKR using catalyst **1** to get the (*S*)-glycidyl ethers (**10' a-c**) in an enantiopure form. The enantiopure epoxides obtained thus were purified by column chromatography and consequently reacted with isopropyl amine (2 equivalents) in presence of Na-β-zeolite as a catalyst and isopropanol as a solvent to obtain optically pure (*S*)-Metoprolol (**11a**), (*S*)-Toliprolol (**11b**) and (*S*)-Aleprenolol (**11c**).

Computational Methods

The ground state and transition state geometries were fully optimized using ONIOM (B3LYP/6-31G*:STO-3G) method.[27] Single-point energy calculations were performed at M06-L/6-31+G** level of theory using the optimized structures of ground and transition states with ONIOM method.[28] To reduce the computational cost, the wire-frame moieties in the optimized structures were treated with lower level B3LYP /STO-3G level in ONIOM calculations. The pseudo-potential combined with valence double zeta basis set, LANL2DZ has been used for effective core potential of cobalt[29] and 6-31G* basis set[30] for the other atoms (C, H, O, N) in the high level these ONIOM calculations. The stationary points were characterized by frequency calculation in order to verify that the transition structures had one, and only one, imaginary frequency and ground state geometries were characterized with no imaginary frequency. All calculations were performed with the Gaussian 09 suite of program.[31]

Conclusions

A series of chiral polymeric Co(III) salen complexes with several chiral and achiral linkers were synthesized so as to achieve higher catalytic activity and enantioselectivity in hydrolytic kinetic resolution of terminal epoxides. In case of chiral linker all possible permutation and combinations of linker configuration vis-à-vis salen configuration were screen in order to understand the role of additional element of chirality in influencing the configuration of the product. The experimental results clearly indicate that, while the configuration of the salen unit decides the configuration of the product, the configuration of linker does effect enantioselectivity. Out of several catalysts used in the present study, catalyst **1** with opposite absolute configuration of BINOL linker and the diamine collar of the salen moiety gives best results in terms of activity and enantioselectivity as compared to the catalysts based on other chiral or achiral linker. Moreover, catalyst **1** can be effectively reused in the present reaction condition for six successive runs at the expense of only one catalyst regeneration step. Furthermore, a gram scale synthesis of β-blockers (*S*)-Metoprolol, (*S*)-Toliprolol and (*S*)-Alprenol in their desired enantiomeric forms suggests practical applicability of the catalyst. The DFT calculations suggest that the *R*-BINOL linker preferably bind with (*S,S*)-Co(III) salen complex compared to the *S*-BINOL linker. The computational analysis suggests that the enantioselective ring opening of terminal 1,2-epoxyhexane is governed by the non-covalent C-H… π interaction and steric effects induced in the transition state geometries.

Acknowledgements

CSIR-CSMCRI Communication No. 072/2014.The authors are thankful to DST and CSIR network project CSC-0135 for financial assistance. Tamal Roy and Sunirmal Barik are thankful to CSIR and UGC respectively for their SRF and JRF. The authors are also thankful to analytical science discipline for providing instrumental facilities.

Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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