Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700788

Link to VoR: http://dx.doi.org/10.1002/adsc.201700788

10.1002/adsc.201700788

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Asymmetric Hydrolytic and Aminolytic Kinetic Resolution of Racemic Epoxides using Recyclable Macrocyclic Chiral Cobalt (III) Salen Complexes

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

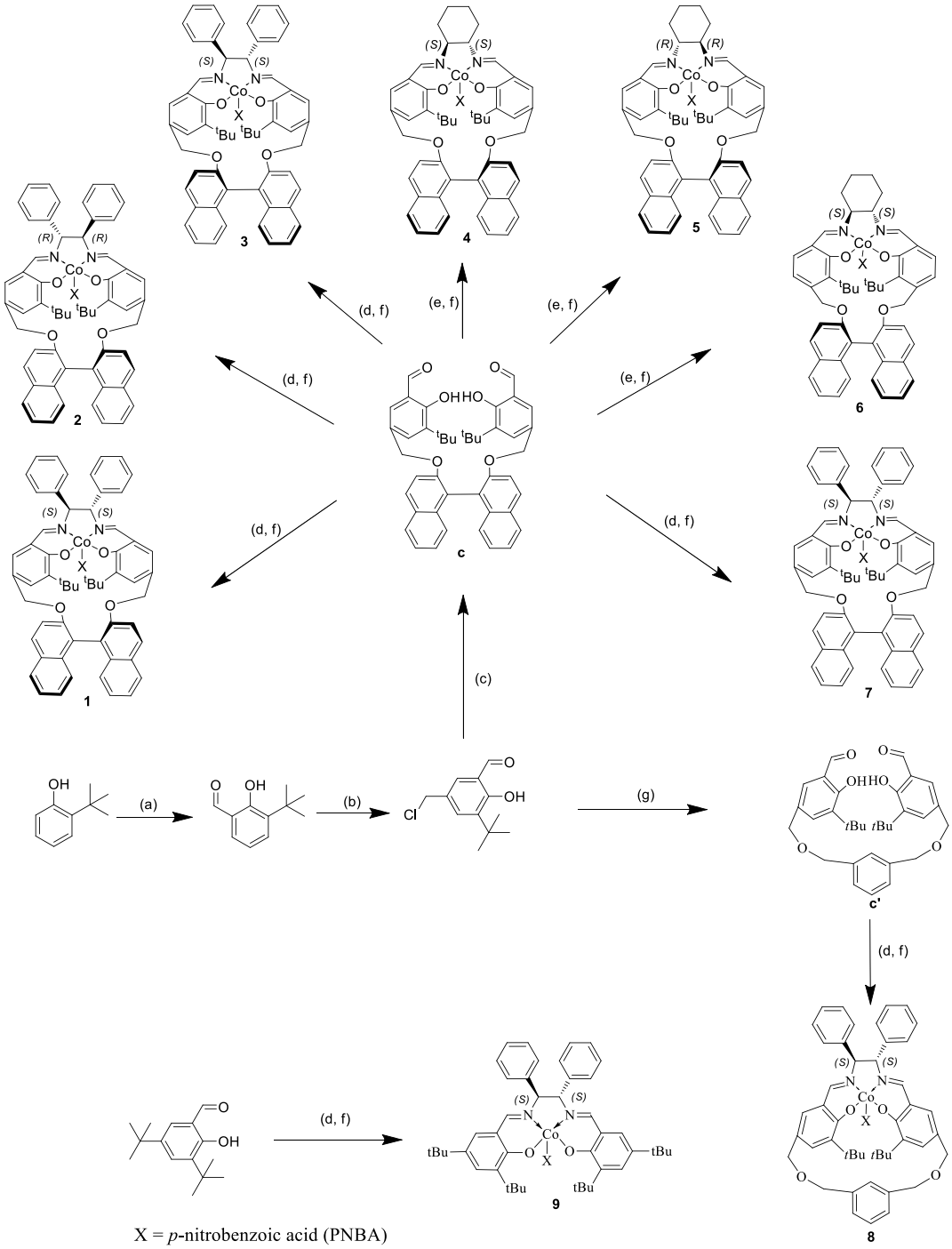
Abstract. New chiral macrocyclic Co(III) salen complexes were synthesized and used as catalyst for asymmetric kinetic resolution of terminal epoxides and glycidyl ethers with aromatic/aliphatic amines and water as nucleophiles. This is the first occasion where a Co(III)-salen complex demonstrated its ability to catalyze AKR as well as HKR reactions. Excellent enantiomeric excess of epoxides, corresponding amino alcohols and diols (upto 99%) with quantitative yield were achieved by using the chiral Co(III) salen complexes in DCM at room temperature. This protocol was further extended for the synthesis of two important drug molecules i.e., (*S*)-Propranolol and (*R*)-Naftopidil. The catalytic system was also explored for the synthesis of chirally pure diol and chiral cyclic carbonate using carbon dioxide as a greener renewable C_1 source. The catalyst was recycled upto 5 catalytic cycles with retention of enantioselectivity.

Keywords: Asymmetric synthesis; Cobalt; Kinetic resolution; macrocyclic ligand; ring opening

Introduction

"High atom economy is one of the prime aspect of green chemistry to be followed by synthetic chemists."[1] Asymmetric kinetic resolution of racemic epoxides is an excellent example in this category where two synthetically important products can be produced in one go with 100% atom efficiency.[2,3] The demands of chiral epoxides,[4] amino alcohols,[5] diols[6] and cyclic carbonates[7] have steadily increased over the years because of their widespread consumption in pharmaceuticals, agrochemicals and fine chemicals. With this backdrop kinetic resolution of inexpensive and readily available racemic epoxides with water and amines to produce valuable diols and *β*-amino alcohols respectively in their high enatio-purity alongwith unreacted enantiomer of respective epoxides is important. Ever since the landmark findings of the kinetic resolution of epoxides by Jacobsen et al.[4d,8] many groups have contributed in this area of research.[9-14] But in most cases different metal ions (may be with the same chiral salen ligands) were required to catalyze hydrolytic kinetic resolution (HKR) [4d,8-14] and aminolytic kinetic resolution (AKR) [15] by using water or an amine as nucleophiles respectively. Here, we are pleased to report that our newly designed and synthesized catalytic systems involving new chiral Co(III) salen complexes of macrocyclic ligands **1a-8a** work very efficiently for AKR as well as HKR of a wide range of inexpensive racemic epoxides like aryl epoxides, terminal epoxides and functionalized epoxides. This was in a way outcome of our continuous efforts towards the asymmetric ring opening reactions.[16] As a result we have achieved excellent enantioselectivity of unreacted epoxides, *β*-amino alcohols and diols (upto 99% ee) with high yields. Further, the chirally pure epoxide i.e., naphthyl glycidyl ether **17a** obtained from the HKR or AKR reaction was used as an intermediate for the synthesis of pharmaceutically important drug (*S*)-Propranolol[17]- a *β*-adrenergic blocking agent and (*R*)-Naftopidil[18] - a α1-adrenoreceptor antagonist. Similarly, the enantiopure diols, obtained from the HKR reaction were

converted to their corresponding chiral cyclic (CO_2) as a C_1 source.[19] This protocol was carried out at one gram scale for the synthesis of the above described important molecules. The desired configuration (*R* or *S*) of the chiral products i.e., unreacted epoxides, diols and *β*-amino alcohols can carbonates by utilizing the carbon dioxide be produced by just altering the configuration of the catalyst. The chiral Co(III) salen complexes have an added advantage of stability and recyclability. Moreover, we have reused our catalyst several times with the retention of enantioselectivity.



Scheme 1. Synthetic route for the macrocyclic Co(III) salen complexes **1-9**. Conditions: a) 2,6-lutidine, $SnCl_4$, paraformaldehyde, dry toluene, reflux 8 h (yield: 93%); b) HCl, trioxane, 45-50 °C, 48 h (yield: 90%); c) NaH, dry THF, (*R*)/(*S*) Binol, 4-6 h, (yield: 92-95%); d) (1*R*,2*R*)/(1*S*,2*S*)-1,2 diphenylethylene diamine (yield: 84-88%) ; e) (1*R*,2*R*)/(1*S*,2*S*)-1,2 cyclohexane diamine, (yield: 85-87%) dry methanol, 4-5 h; f) toluene, methanol, $Co(OAc)_2 \cdot 4H_2O$, (PNBA) (yield: 83-88%); g) NaH, dry THF, 1,3-dimethanol benzene, 5 h (yield: 90%).

10.1002/adsc.201700788

Results and Discussion

The chiral macrocyclic salen ligands **1a-8a** were synthesized starting from the readily available 2-(*tert*-butyl)phenol for the synthesis of 3-(*tert*-butyl)-2-hydroxybenzaldehyde followed by its conversion to 3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde, which was reacted with (*R*/*S*)-1,1'-bi-2-naphthol (BINOL)/racemic 1,1'-bi-2-naphthol (BINOL)/ 1,3-phenylenedimethanol to prepapre the corresponding dialdehyde.[5e,f,15d,16e] The condensation of thus prepared dialdehydes with (1*R*,2*R*)/(1*S*,2*S*)-1,2-diphenylethylene diamine and (1*R*,2*R*)/(1*S*,2*S*)-1,2 cyclohexane diamine gave macrocyclic chiral salen ligands **1a−8a** [please see the SI]. The newly synthesized and characterized ligands were subjected to metallation with Cobalt(II) acetate as a metal source under nitrogen atmosphere in toluene. Subsequently, *p*-nitrobenzoic acid (PNBA) was added to the reaction mixture while exposing it to air to get macrocyclic Co(III) salen complexes **1-8** [Scheme 3].[4i,7b,7g,15d]
The Jacobsen Co(III) salen complex **9** was prepared by the reported procedure.[4d] All the chiral macrocyclic salen ligands and complexes were characterized by various physicochemical methods viz. NMR, IR, MASS spectrometry, elemental analysis and optical rotation [please see SI]. The attempts to get the single crystal structure of the complexes were failed however, X-ray structure of the ligand **2a** was successfully determined[20] [Figure 1] thereby confirming the macrocyclic nature of ligands **1a-8a**. After successful synthesis and characterization, these complexes were used as catalysts for kinetic resolution of terminal/aryloxy epoxides.

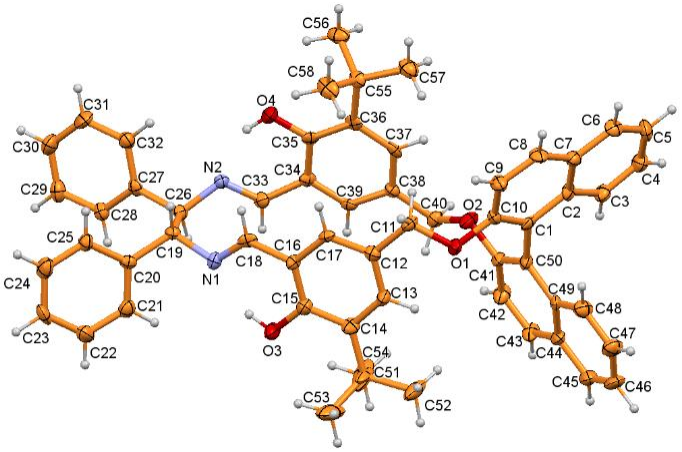
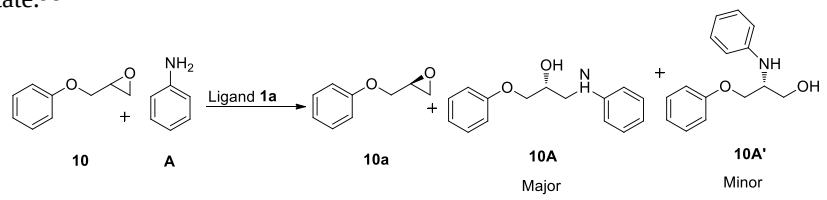


Figure 1. Thermal ellipsoid plot for the ligand **2a** with atom numbering scheme (45% probability factor for the thermal ellipsoids; Lattice DCM is omitted for clarity)[CCDC1556416]

To the best of our knowledge, the AKR reaction of aryloxy epoxides with anilines by using chiral Co(III) salen complexes to get the valuable chiral amino alcohols and enantioenriched epoxides in a single step is reported for the first time. In view of the fact that the counter ion, mol% of catalyst, solvent and reaction temperature are the most crucial parameters of any asymmetric transformation, we have closely monitored and optimized the reaction conditions for the present protocol of kinetic resolution of the racemic epoxides. By keeping these facts in mind and based on our past knowledge and experience,[5e,f,15d] here we chose catalyst **1** (1 mol%) with varoius counter ion for the AKR of racemic phenyl glycidyl ether **10** as a model substrate and aniline **A** as representative nucleophile at room temperature (RT) and the data are compiled in [Table 1, entries 1-4]. Among all the four tested counter ion, *p*-nitrobenzoic acid (PNBA) has shown promising results in terms of product yield and enantioselectivity for both the products [Table 1, entries 4]. Our next target was to optimize the amount of the catalyst used varied over mol ratio from 1 mol% to 10 mol% [Table 1, entries 4-8] with respect to the racemic epoxides and found that 5 mol% of the catalyst worked very efficiently and yielded unreacted epoxides in excellent enantioselectivity (ee, 93%) and corresponding amino alcohol in 92% ee (both in quantitative yields). After that we screened several solvents viz., Tol, ACN, THF, DCE and $CHCl_3$ [Table 1, entries 9-13] as reaction media in our model AKR reaction, but among all the above used solvents only DCM showed the best result [Table 1, entry 6]. Likewise, the reaction was subjected to temperature variation [Table 1, entries 14-15], where we observed that, the room temperature (26-28 ^oC) is the optimum temperature [Table 1, entry 6] because on decreasing the reaction temperature below RT, (10 and 0 ^oC) results were adversely affected [Table 1, entries 14-15]. We have extended this protocol to a relatively higher scale (5 mmol) and got similar performance [Table 1, entry 16] for the AKR reaction. After optimization of the reaction parameters, we scrutinized all the above synthesized Co (III) salen complexes **1-9** in our model AKR reaction.
Among these, the performance of catalysts **1-3** bearing chiral 1,2-diphenylethylene diamine as chiral backbone was found to be better than the complexes derived from chiral 1,2-cyclohexane diamine in terms of yield and enantioselectivity of the epoxides as well as of amino alcohols [Figure 2].
During the optimization study we have performed ^1H NMR experiments and observed that the ratio of major **10A** and minor enantiomer **10A'** of amino alcohol was in ratio of 98:2. The major enantiomer formed because of the attack of aniline to phenyl glycidyl ether **10** from its less hindered side. These results supports that our catalytic system was highly regioselective and gave high enantioselectivity in the desired product.

Table 1. Optimization of reaction conditions for AKR reaction of phenyl glycidyl ether **10** with aniline **A** using the ligand **1a** and Co(II) acetate.[a]



Entry	Catalyst [mol%]	Counter ion	Solvent	Temp. [°C]	*t* [h]	Epoxide **10a**		Amino alcohol **10A**	
						Yield[b] %	ee[c] %	Yield[b] %	ee[d] %
1	1.0	Acetic acid	DCM	RT	24	20	68	19	38
2	1.0	Trichloroacetic acid	DCM	RT	24	20	b	21	36
3	1.0	Trifluoroacetic acid	DCM	RT	24	21	78	24	45
4	1.0	PNBA	DCM	RT	24	30	80	28	80
5	2.5	PNBA	DCM	RT	24	37	82	43	89
6	5	PNBA	DCM	RT	20	45	93	46	92
7	7.5	PNBA	DCM	RT	20	46	89	46	92
8	10	PNBA	DCM	RT	18	47	83	47	88
9	5	PNBA	Tol	RT	30	40	80	44	85
10	5	PNBA	ACN	RT	24	35	78	38	79
11	5	PNBA	THF	RT	34	43	75	41	79
12	5	PNBA	DCE	RT	24	44	84	45	82
13	5	PNBA	$CHCl_3$	RT	28	43	85	42	86
14	5	PNBA	DCM	10	40	27	73	30	90
15	5	PNBA	DCM	0	60	21	65	27	89
16[e]	5	PNBA	DCM	RT	24	45	92	46	91

[a]Conditions: Phenyl glycidyl ether **10** (0.2 mmol), aniline **A** (0.1 mmol). [b]Isolated yield of product after flash column chromatography (out of 50% theoretical yield). [c]ee of **10a** determined on Chiralcel OD column. [d]ee of **10A** determined on Chiralcel ADH column. [e]Reaction performed at 5 mmol scale keeping other conditions as per entry 6.

The Jacobsen Co(III) salen complex **9** gave the ring opened product with the ratio of 55:45 of major and minor products of amino alcohol. We have also noticed that both the chiral moieties (diamine and binol) were working synergistically to deliver the products in high enantioselectivity, because when we used racemic 1,1'-bi-2-naphthol and 1,3-phenylenedimethanol (complex **7** & **8**) instead of chiral BINOL then we got inferior results [Figure 2]. Thus, Among all the Co(III) salen complexes, complex **1** was found to be the best and was taken forward for further studies on the AKR reaction as preferred catalyst. Interestingly, the outcome of the AKR reaction showed that the stereochemistry of epoxides and amino alcohols was directly dependent on the configuration of chiral diamine irrespective of the configuration of BINOL. The probable reason of this activity of the chiral Co(III) salen complex was due to the presence of metal centre in close vicinity of diamine molecules. Similar observations were also made by several research groups[7b,21] and us.[5e,f,7g,15d,]

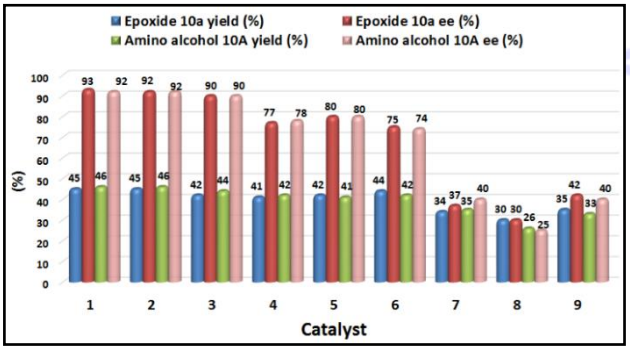


Figure 2. Screening of the catalyst.

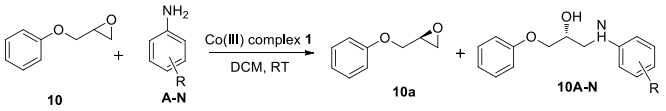
Consequently, it is possible to get the desired configuration of the product by selecting the suitable configuration of the catalyst. In the present case, the macrocyclic Co(III) salen complex **1** provided (*R*)-configuration of amino alcohol and (*S*)-configuration of chiral epoxides and on altering the macrocyclic Co(III) salen complex **1** to complex **2** we got (*S*)-configuration of amino alcohol and (*R*)-configuration of chiral epoxides. Therefore, Co(III) salen complex **1** was used for the further studies of kinetic resolution of aryloxy/terminal epoxides with anilines. During the course of reaction we found that if AKR reaction runs beyond the specified time, the NH group of chirally pure aminoalcohol ((*R*)-1-phenoxy-3-(phenylamino)propan-2-ol) **10A** can act as nucleophile and react with the enantiopure phenyl glycidyl ether **10a** to form 2-((2-hydroxy-3-phenoxypropyl)(phenyl)amino)-3-phenoxypropan-1-ol **10AB** (isolated by flash column chromatography and characterized by ^{1}H NMR and HRMS- please see SI).

After successful optimization of the catalyst and the reaction conditions, we extended the scope of Co(III) salen complex **1** for AKR of phenyl glycidyl ether **10** with a variety of amines **A-N** like 4-substituted anilines viz., 4-Me, 4-OMe, 4-Cl, 4-Br, 4-CF_3, 4-NO_2 aniline [Table 2, entries 2-7] and also with 2-substituted anilines such as 2-Me, 2-OMe, 2-Cl aniline [Table 2, entries 8-10]. In all these anilines we got excellent enantioselectivity of the corresponding amino alcohols (89-94%) and of phenyl glycidyl ether (87-93%) with very good recovery of both products by flash column chromatography. We have also checked activity of the Co(III) salen complex **1** with some bulkier amines, like 1-naphthylamine **K**, and achieved the product in a very high yield (47%) with moderate enantioselectivity (ee, 78%) (Table **2**, entry 11).

AKR reaction with aliphatic amines are always a challenging task for scientist around the world due to their more basic nature, they generally deactivate the metal catalyst,[5f-5h,16e] but we are very much pleased that our catalytic system worked very efficiently with aliphatic amines also. We have scrutinized some of such amines namely, piperidine **L**, morpholine **M** and thiomorpholine **N** as a nucleophile in the AKR reaction with our model substrate i.e. phenyl glycidyl ether **10** and found that they gave high yield (upto 46%) of the corresponding amino alcohols with very good enantioselectivity (ee, 77-80%) [Table 2, entries 12-14]. In all these cases we were able to recover unreacted enantioenriched epoxide **10a** with good ee (upto 80-95%) in quantitative yields.

After getting very exciting and encouraging results we extended our study and explored the AKR activity of our catalyst with other Ph-protected glycidols such as glycidyl-2-methyl phenyl ether **11**, 4-chloro phenyl glycidyl ether **12**, 4-methoxy phenyl glycidyl ether **13**, 4-*tert*-butyl phenyl glycidyl ether **14**, styrene oxide **15**, 2-((benzyloxy)methyl)oxirane **16** and naphthylglycidyl ether **17** with aniline **A** [Scheme 2]. In all these cases we achieved high yield (upto 45% out of 50% theoretical yield) and excellent enantioselectivity (ee upto 92%) for the corresponding amino alcohols.

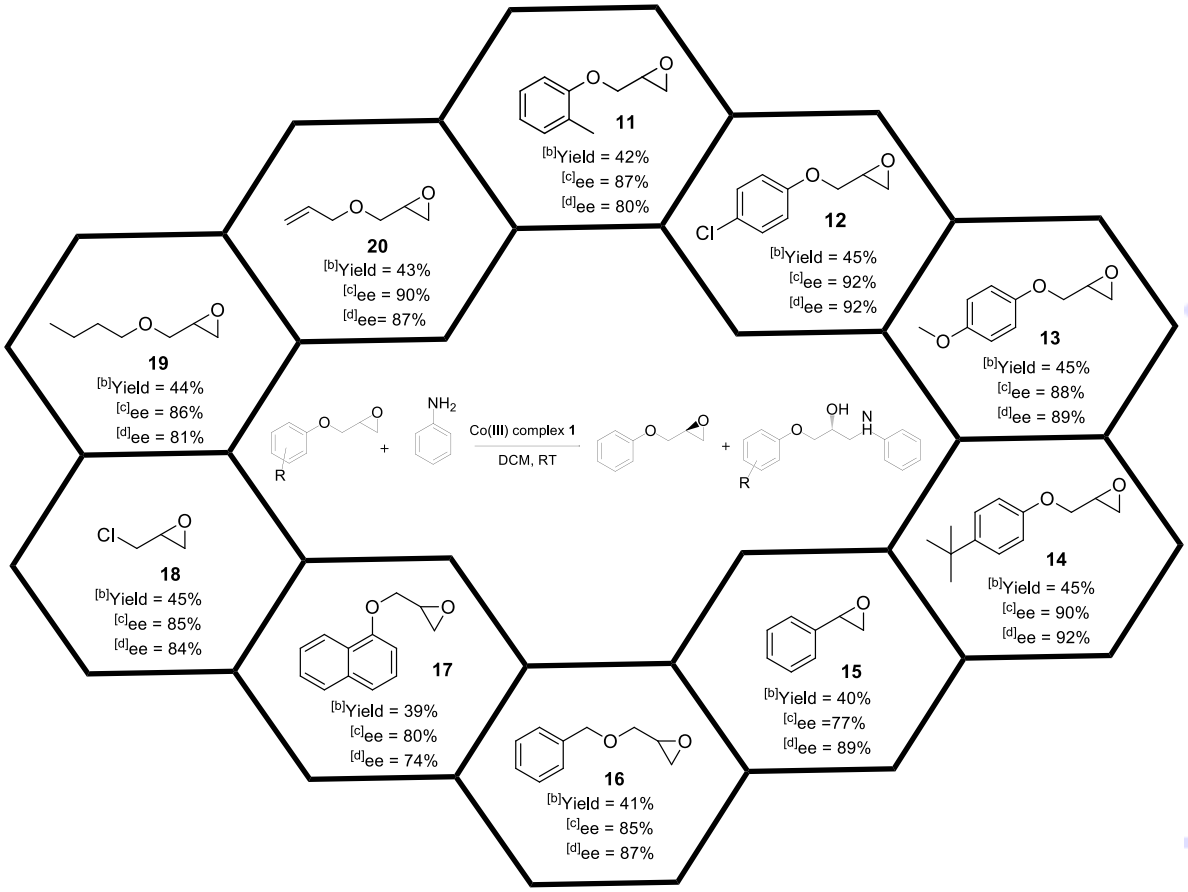
Table 2. Product yield and ee values of AKR reaction of phenyl glycidyl ether **10** with different amines **A-N** as nucleophile catalyzed by macrocyclic Co(III) salen complex **1**.[a]



Entry	R	*t* [h]	Yield%[b]	ee% 10a[c]	ee% 10A-N[d]
1	H, **A**	24	46	93	92
2	4-Me, **B**	24	47	90	92
3	4-OMe, **C**	24	47	92	93
4	4-Cl, **D**	24	45	87	91
5	4-Br, **E**	24	46	92	92
6	4-CF_3, **F**	24	47	92	92
7	4-NO_2, **G**	38	trace	nd	nd
8	2-Me, **H**	24	45	89	94
9	2-OMe, **I**	24	47	92	89
10	2-Cl, **J**	24	45	90	91
11	1-Napthyl amine, **K**	24	47	80	78
12	Piperidine, **L**	34	45	72	77
13	Morpholine, **M**	34	45	79	80
14	Thiomorpho-line, **N**	30	46	77	78

[a]Conditions: Phenyl glycidyl ether **10** (0.2 mmol), amines **A-N** (0.1 mmol), chiral Co(III) salen complex **1** (0.01 mmol). [b]Isolated yield of amino-alcohol **10A-N** after flash column chromatography (out of 50% theoretical yield). [c]ee of epoxide **10a** determined on Chiralcel OD column. [d]ee of amino alcohols determined on Chiralcel ADH column.

Besides, Ph-protected glycidols, we have also examined the catalytic efficiency of Co(III) salen complex **1** with aliphatic epoxides like epichlorohydrin **18**, butyl glycidyl ether **19** and allyl glycidyl ether **20** with aniline **A** as a nucleophile which gave amino alcohols in good yield (upto 43-45%) and excellent enantioselectivity (ee upto 81-87%). In all these AKR reactions the corresponding unreacted chirally pure epoxides were isolated with good yield and with excellent enantioselectivity (ee upto 90%).



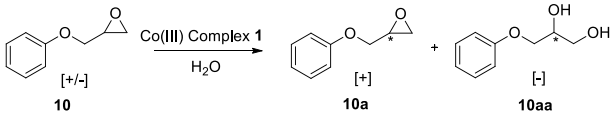
Scheme 2. Variation of the substrate.[a]

[a]Conditions: Terminal epoxides **11-20** (0.2 mmol), aniline **A** (0.1 mmol), chiral Co(III) salen complex **1** (0.01 mmol). [b]Isolated yield of amino alcohol after flash column chromatography (out of 50% theoretical yield). [c] ee of enantioenriched epoxide. [d]ee of amino alcohol.

After successfully implementing our catalytic system in the AKR reaction, we have explored its application in hydrolytic kinetic resolution (HKR) of epoxides by keeping all the other parameters same [as per Table 1, entry 6]. The literature says that the most important parameters for HKR reactions are catalyst loading and solvent of the reaction, so we have initiated our study with phenyl glycidyl ether **10** as model substrate by using Co(III) salen complex **1**. First we varied catalyst loading from 0.1 mol% to 0.01 mol% [Table 3, entries 1-5] and found that 0.025 mol% of catalyst loading was optimum to catalyze the reaction efficiently and gave the unreacted epoxides in 46% yield (out of 50% theoretical yield) with 86% ee and 45% yield and 86% ee for corresponding diol. The nature of solvent is known to influence reactivity and enantioselectivity of HKR of racemic epoxides. Therefore, 0.025 mol % of complex **1** (Table 3, entry 4) at RT was used to screen various solvents viz., CH_3CN, $CHCl_3$, THF, DCE, Tol, Et_2O [Table 3, entries 6-11]. However, among all these solvents screened, only DCM was found to be the solvent of choice [Table 3, entry 4]. Unfortunately with the above optimized conditions we were unable to produce highly optically pure epoxides and diols. Therefore, we decided to screen all the above synthesised Co(III) salen complexes **1-6** in HKR reaction of phenyl glycidyl ether **10** [Table 4]. It has been established by many research group [4d,8b,22] that chiral 1,2-cyclohexane diamine (in salen complexes) works better in comparsion to 1,2-diphenylethylene diamine as a chiral backbone especially in HKR

reactions. Similarly, in the present system our Co(III) salen complex **4** worked well to yield epoxides as well as diols in high enantioselectivity.
Like AKR reaction, here also the configuration of the product is dependent on the diamine part of the salen irrespective of the configuration of BINOL in chiral macrocyclic Cobalt (III) salen complex 4 (0.025 mol%) [Table 4]. The Co(III) salen complex 4 derived from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane gave the (*R*) form of diol and (*S*) form of the epoxides, moreover, Co(III) salen complex **5** originating from (1*R*,2*R*)-1,2-(-) diamine cyclohexane favored the formation of (*S*) form of the diol and (*R*) form of the epoxides.[4d,4i,7g,8a]

Table 3. Optimization of reaction conditions for the hydrolytic kinetic resolution of phenyl glycidyl ether **10** using the macrocyclic Co(III) salen complex **1**.[a]



Entry	Cat [mol%]	Sol	*t* [h]	10a Yield%[b]	10a ee%[c]	10aa Yield%[b]	10aa ee%[c]
1	0.1	DCM	8	47	68	46	65
2	0.075	DCM	8	46	64	46	62
3	0.050	DCM	8	46	78	45	81
4	0.025	DCM	8	45	86	46	86
5	0.010	DCM	8	42	66	43	67
6	0.025	THF	6	45	82	46	80
7	0.025	ACN	15	46	67	41	62
8	0.025	$CHCl_3$	12	46	78	43	75
9	0.025	Tol	16	46	79	40	69
10	0.025	DCE	12	46	78	42	74
11	0.025	Et_2O	12	46	81	44	79

[a]Conditions: Phenyl glycidyl ether **10** (5 mmol), H_2O (2.5 mmol), chiral Co(III) salen complex **1**. [b]Isolated yield after flash column chromatography (out of 50% theoretical yield). [c]ee of **10a** determined on Chiralcel OD column. [d]ee of **10aa** determined on Chiralcel ADH column.

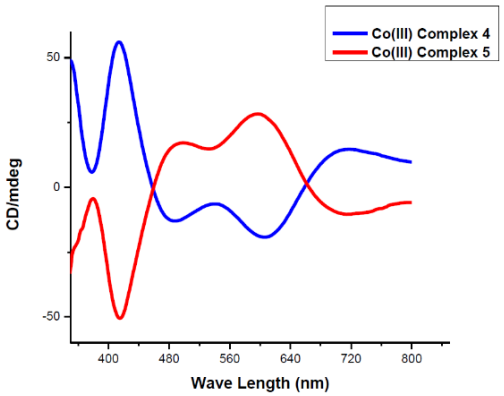
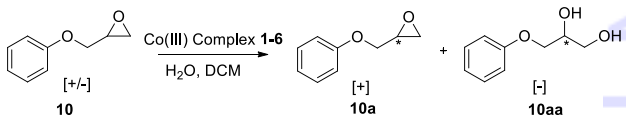


Figure 3. CD spectra of macrocyclic Co(III) salen complexes **4** and **5** in DCM ($1x10^{-3}$M).

To strengthen the observed phenomenon we recorded circular dichroism (CD) spectra of the Co(III) salen complexes **4** and **5** in DCM and found two equally opposites humps at 420 nm and 610 nm [Figure 3]. Complex **4** (Figure 3, blue color) favors (*R*) form of diol and (*S*) form of the epoxides while complex **5** (Figure 3, red color) favors (*S*) form of diol and (*R*) form of the epoxides.[23]

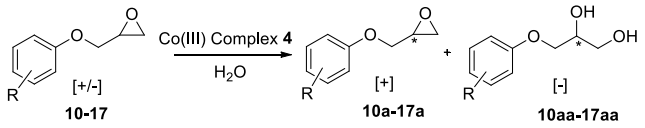
Table 4. Screening of chiral macrocyclic Co(III) salen complexes **1**−**6** for the hydrolytic kinetic resolution of Phenyl glycidyl ether **10**.[a]

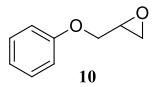
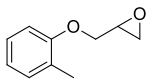
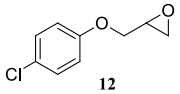
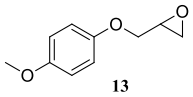
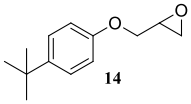
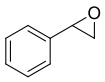
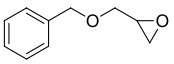
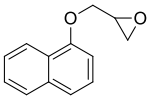


Entry	Cat.	*t* [h]	10a Yield%[b]	10a ee%[c]	10aa Yield%[b]	10aa ee%[c]
1	**1**	8	45	86[e]	46	86
2	**2**	8	44	85[f]	44	85
3	**3**	8	41	82[e]	42	86
4	**4**	8	49	99[e]	48	99
5	**5**	8	48	98[f]	47	95
6	**6**	8	47	95[e]	43	94

[a]Conditions: Phenyl glycidyl ether **10** (5 mmol), H_2O (2.5 mmol). [b]Isolated yield after flash column chromatography (out of 50% theoretical yield). [c]ee of **10a** determined on Chiralcel OD column. [d]ee of **10aa** determined on Chiralcel ADH column. [e]Epoxide configuration (*S*). [f]Epoxide configuration (*R*).

Table 5. Enantioselective hydrolytic kinetic resolution of Ph-protected glycidols catalyzed by macrocyclic Co(III) salen complex **4**.[a]



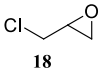
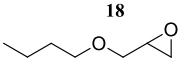
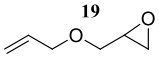
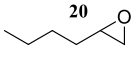
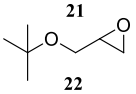
Entry	Epoxide	catalyst [mol%]	*t* [h]	Epoxide Yield%[b]	Epoxide ee%[c]	Diol Yield%[b]	Diol ee%[c]
1	 **10**	0.025	6	49	99	48	99
2	 **11**	0.025	6	49	99	48	97
3	 **12**	0.025	6	49	99	48	97
4	 **13**	0.05	6	49	99	48	95
5	 **14**	0.05	6	49	99	48	94
6	 **15**	0.01	6	49	99	48	96
7	 **16**	0.01	8	49	97	48	96
8	 **17**	0.05	6	49	99	48	96

[a]Conditions: Epoxides **10-17** (5 mmol), H_2O (2.5 mmol), chiral Co(III) salen complex **4** at RT in DCM. [b]Isolated yield after flash column chromatography (out of 50% theoretical yield). [c]ee determined on Chiralcel OD, ADH, ASH, ODH, IC HPLC column.

Having established the reaction parameters for use of Co(III) salen complex **4,** it was further explored in HKR of variety of Ph-protected glycidols viz., glycidyl-2-methyl phenyl ether **11**, 4-chloro phenyl glycidyl ether **12**, 4-methoxy phenyl glycidyl ether **13**, 4-*tert*-butyl phenyl glycidyl ether **14**. High yield as well as excellent enantiomeric excess of epoxides and diols (upto 99 %) [Table 5, entries 1-5] was obtained. Next, the Co(III) salen complex **4** was screened for styrene oxide **15** and 2-((benzyloxy)methyl)oxirane **16** where less amount of catalyst loading (0.01 mol%) was sufficient for getting optimal results [Table 5 entries 6,7]. Furthermore, we have also checked the activity of catalyst **4** for naphthylglycidyl ether **17**, which gave the best result with catalyst loading of 0.05 mol%.

The reactivity and selectivity of the Co(III) salen complex **4** was further investigated with other aliphatic terminal epoxides, viz., epichlorohydrin **18**, butyl glycidylether **19**, allyl glycidylether **20**, 1,2-epoxyhexane **21**, *tert*-butylglycidylether **22** with catalyst loading (0.01 mol%). In all these reactions we got excellent enantioselectivity (>99%) of the epoxides with very good yield [Table 6].

Table 6. Enantioselective hydrolytic kinetic resolution of aliphatic terminal epoxides catalyzed by macrocyclic Co(III) salen complex **4**.[a]

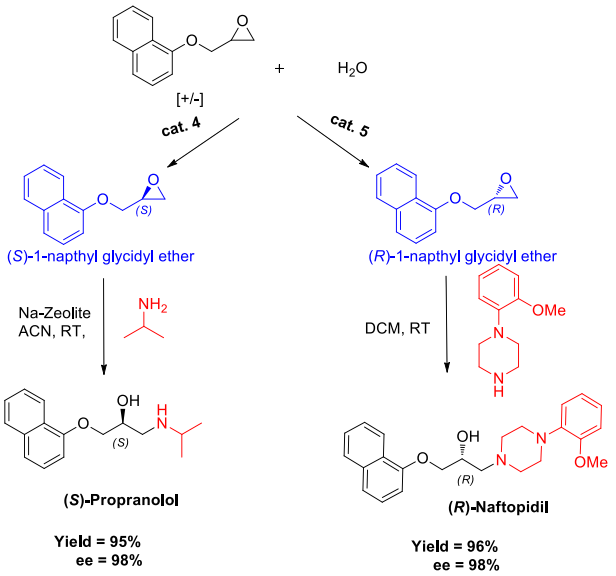
Entry	Epoxide	catalyst [mol%]	*t* [h]	Epoxide Yield%[b]	Epoxide ee%[c]
1	 **18**	0.01	12	46	>99
2	 **19**	0.01	12	44	>99
3	 **20**	0.01	12	42	>99
4	 **21**	0.01	12	48	>99
5	 **22**	0.01	12	44	>99

[a]Conditions: Epoxides **18-22** (5 mmol), H_2O (2.5 mmol), chiral Co(III) salen complex **4** (0.01 mol%), Time 12 h at RT. [b]Isolated yield of enantioenriched epoxide (out of 50% theoretical yield). [c]ee of epoxide determined on Chiraldex GTA column.

Encouraged by the overall results of AKR and HKR reaction in terms of yield and enantioselectivity of amino alcohols, diols and chiral epoxides, we have evaluated the synthetic potential of this protocol for the preparation of chiral drugs, viz., (*S*)-Propranolol and (*R*)-Naftopidil by using chirally pure epoxides obtained with our HKR protocol [Scheme 3].

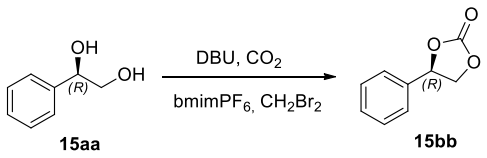
In order to make a comparison of present catalytic system using the catalyst **4** with our earlier reported polymeric Co(III) salen complex[15d] we would like to state that in polymeic system, one additional step was needed to get the desired drug molecules, however in this study the well-known *β*-adrenergic blocker, (*S*)-propranolol,[17] was obtained directly in good yield (95%) with excellent enantioselectivity (98%) by the ring-opening reaction of chirally pure (*S*)-1-naphthyl glycidyl ether with isopropylamine by using Na-zeolite as a catalyst [Scheme 3]. Similarly when we used catalyst **5** then from the same reaction we got the enantiomerically pure (*R*)-1-napthyl glycidyl ether.

The ring opening of this epoxide with 1-(2-methoxyphenyl)piperazine gave (*R*)-Naftopidil[18] in very good yield (96%) with exceptional enantioselectivity (98%) in DCM [Scheme 3].



Scheme 3. Synthesis of chiral drugs (*S*)-Propranolol and (*R*)-Naftopidil.

In a present scenario utilization of green-house gases are one of the important part of research across the globe, so keeping this in mind we used CO_2 as renewable C_1 source for the synthesis of chirally pure cyclic carbonate with recovered diols from the HKR reaction. The coupling reaction of carbon dioxide (CO_2) and (*R*)-1-phenylethane-1,2-diol **15aa** [Scheme 4] by using DBU, bmimPF_6, and CH_2Br_2 under the pressure of 10 bar of CO_2 gave chirally pure cyclic carbonate **15bb** with very good enantiomeric excess (ee, 96%) in quantitative yield.[19]



Scheme 4. Synthesis of cyclic carbonate.

Catalyst recycling:

The chiral macrocyclic Cobalt (III) salen catalyst **4** was recovered quantitatively from the reaction mixture by adding non-polar solvent like hexane after the first catalytic run in HKR reaction. The precipitated catalyst was dried in oven at 60 ºC for 4 h and then it was directly used for next catalytic run without further purification.

The products diol **10aa** and chirally enriched epoxide **10a** were recovered from organic layer by column chromatography. The catalyst was successfully reused five times with retention of enantioselectivity but in slightly decreased yield of the diols possibly due to the physical loss of the catalyst during the recovering process [Figure 4]. Further, we have also checked leaching experiment of the Co metal from complex **4** by ICP–AES (inductively coupled plasma atomic emission spectroscopy) analysis and did not find any trace of the metal in organic layer during the recovery process.

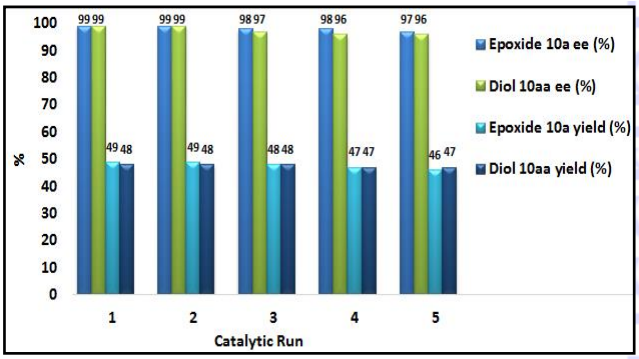


Figure 4. Study of catalyst recyclability using Co(III) salen complex **4**. Reaction condition: Phenyl glycidyl ether **10** (10 mmol), catalyst (0.025 mol%), water (5 mmol), RT.

Conclusion:

In summary, we have designed and synthesized a series of novel and very efficient macrocyclic Co(III) salen complexes as AKR and HKR catalysts for the ring opening reaction of a variety of terminal/aryloxy epoxide. Enantiopure epoxides, diols and amino alcohols with moderate to excellent yields (upto 96%) with excellent enantioselectivities (upto 99%) were obtained by using a variety of amines including aromatic, aliphatic amines and water as nucleophile. The reaction conditions were mild and having high atom efficiency in both types of kinetic resolution reactions. The enantiopure products obtained from kinetic resolution of racemic epoxides with amines or with water were efficiently converted into pharmaceutically important *β*-adrenergic blocker chiral drugs, viz., (*S*)-Propranolol and (*R*)-Naftopidil. We have also transformed the chiral diol obtained from HKR reaction into cyclic carbonate by using CO_2 as a C_1 source. The representative Co(III) salen complex **4** was successfully demonstrated for its re-use (five times) in HKR with the retention of enantioselectivity.

Experimental section:

Synthesis of macrocyclic salen ligands:

The chiral macrocyclic salen ligands **1a-8a** were synthesized in stepwise manner starting from 3-(*tert*-butyl)-2-hydroxybenzaldehyde followed by its conversion to 3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde, which was reacted with (*R*/*S*)-1,1'-bi-2-naphthol (BINOL)/racemic 1,1'-bi-2-naphthol (BINOL)/ 1,3-phenylenedimethanol to prepare the corresponding dialdehyde.[5e,f,15d,16e] The condensation of thus prepared dialdehydes with (1*R*,2*R*)/(1*S*,2*S*)-1,2-diphenylethylene diamine and (1*R*,2*R*)/(1*S*,2*S*)-1,2 cyclohexane diamine gave macrocyclic chiral salen ligands **1a**−**8a** (details of the synthesis is given SI).

Synthesis of macrocyclic Co(III) salen complexes:

In a 50 mL three necked round bottom flask (equipped with a magnetic stirring bar), chiral macrocyclic salen ligands **1a-8a** (1 mmol) were dissolved in deoxygenated toluene (10 mL) under nitrogen atmosphere. The metal salt $Co(OAc)_2{\cdot}4H_2O$ (0.37 g, 1.5 mmol) was dissolved in methanol (10 mL) and deoxygenated by N_2 for 10 min. and was transferred in to the solution of macrocyclic salen ligands under N_2 atmosphere via cannula. A dark red precipitate appeared and the mixture was stirred for 2 h at room temperature. Excess solvent was removed under vacuum and the residue was dissolved in DCM (50 mL) and passed through the Celite-545 pad to remove excess of $Co(OAc)_2{\cdot}4H_2O$. The filtrate was evaporated under vacuum affording a dark red powder and stored in desiccator. The desired active catalysts were prepared by dissolving chiral macrocyclic Co(II) salen complexes (1.0 mmol) in DCM (2 mL) and PNBA (1.2 mmol) was added to them, stirred the solution for 5 h to get the desired chiral macrocyclic Co(III) salen complexes **1-9**.

Typical experimental procedure for aminolytic kinetic resolution:

To a 5 mL round bottom flask fitted with a rubber septum and equipped with a magnetic stirring bar, Co(III) salen complexes **1-9** (0.01 mmol) were taken in dichloromethane (0.8 mL) and the resulting solution was stirred for 5 min followed by the addition of an appropriate epoxide (0.2 mmol). The resulting reaction mixture was stirred for 10 min followed by the addition of the desired aniline as a nucleophile (0.1 mmol) at room temperature (27-28 ^oC). The reaction mixture was allowed to stir at the specified time. The progress of the reaction was checked by TLC using *n*- hexane/ethyl acetate (8:2) as the mobile phase. After the completion of the reaction, the solvent was removed under vacuum and the product was purified by column chromatography using silica gel 100–200 mesh as a stationary phase and *n*-hexane/ethyl acetate (8:2) as a mobile phase.

Typical experimental procedure for hydrolytic kinetic resolution:

A 5 mL round bottom flask equipped with a magnetic stirring bar was charged with Co(III) salen complex **4** (0.05-0.01 mol% with respect to the epoxide) in DCM and then epoxides (5 mmol) were added in to it, stirred for 15 minutes at RT. After that reaction flask was put in an ice bath and water (2.5 mmol) was added dropwise to this solution. Subsequently, the reaction mixture was allowed to reach at RT and stirred it over specified time. After completion of the reaction the catalyst was recovered from the reaction mixture by addition of hexane, dried and subsequently reused in next cycle. The epoxides were separated from the reaction mixture either by distillation or by column chromatography and checked their enantioselectivity on GC or HPLC depend upon the nature of the epoxides.

Acknowledgements:

(CSMCRI Communication No.087/2017)Rajkumar tak and RIK are thankful to UGC and MLP 0028 for financial assistance. Rajkumar Tak is thankful to AcSIR for Ph. D. Registration. Authors are also thankful to Analytical Science and centralized instrument facilities for providing instrumental facilities.

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FULL PAPER

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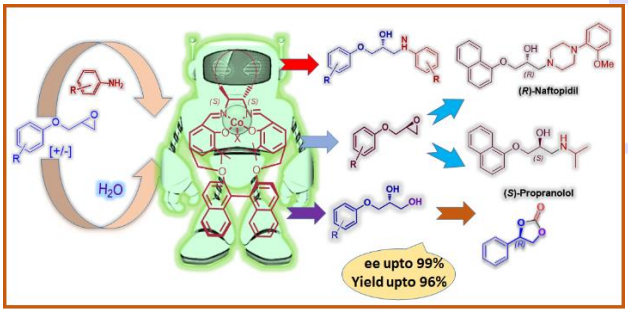

10.1002/adsc.201700788