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Synthesis of enantiopure β-amino alcohols via AKR/ARO of epoxides using recyclable macrocyclic Cr(III) salen complexes

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ABSTRACT

A series of chiral macrocyclic Cr(III) salen complexes **1**–**8** were synthesized and characterized. These complexes were found to be highly active, regio-, diastereo-, and enantioselective catalysts in aminolytic kinetic resolution (AKR) of racemic *trans*-epoxides as well as asymmetric ring opening (ARO) of prochiral *meso*-epoxides with various anilines as nucleophiles at room temperature in 18–24 h. Excellent yields (>99% with respect to the nucleophile) with high enantioselectivity (ee, >99%) of chiral *anti*-β-amino alcohols was achieved with concomitant recovery of corresponding epoxides in high ee (up to >99%). The complex **1** also catalyzed the ARO of *meso*-epoxides to provide corresponding *syn*-β-amino alcohols in high yield (99%) and ee (up to 91%). Due to built-in basic sites in the catalyst, no external base (as an additive) was required to promote AKR and ARO reactions. The catalyst **1** was conveniently recycled several times with retention of its performance. The AKR of *trans*-stilbene oxide with aniline was successfully demonstrated at relatively higher scale (10 mmol) using the catalyst **1**.

1. Introduction

Chiral β-amino alcohols are valuable intermediates for the preparation of various biologically active compounds[1] and chiral ligands,[2] hence their preparation has attracted attention of many research groups worldover.[3–9] Aminolytic kinetic resolution[8,9] and asymmetric ring opening reactions[4–7] of racemic and *meso*-epoxides are among the smartest strategies to prepare β-amino alcohols in high optical purity because of the ready availability of raw materials at a very economical prices. Jacobsen et al.[10] and Katsuki et al.[11] have demonstrated the amazing ability of chiral salen ligands in preparing various metal complexes to catalyze numerous asymmetric organic transformations. Consequently, Bartoli et al. revealed the use of chiral monomeric Co(III) and Cr(III) salen complexes in catalyzing AKR of terminal and *trans*-aromatic epoxides[8a,b] to produce β-amino alcohols in high ee. The same paper also demonstrated asymmetric aminolysis of *meso*-stilbene oxide to get corresponding *syn*-β-amino alcohol in excellent ee (90%) in the presence of monomeric Cr(III) salen (10 mol %) as a catalyst. However, this reaction needed Et_3N as an additive to promote Cr(III) salen catalyzed AKR of *meso*-stilbene oxide in 40 h. Further, recent several reports have demonstrated a cooperative role of catalytic sites in bimetallic macrocyclic/linear complexes[12,13] in various enantioselective reactions. Taking a clue from these findings, we have designed new recyclable chiral macrocyclic salen complexes **1**–**8** bearing two chiral salen units linked through tertiary nitrogens (basic sites) in hope of harnessing the benefits of multiple catalytic sites (metal centers) and built-in basic sites. This is also in line of our continued interest in developing recyclable enantioselective catalysts for the epoxide ring opening reactions.[5d,6a,8c,d,14] The chiral macrocyclic Cr(III) salen catalysts synthesized for the present study (particularly the complex **1**) have demonstrated excellent performance in asymmetric AKR of racemic *trans*-epoxides with different anilines to give *anti*-β-amino alcohols in quantitative yields with excellent enantioselectivity(ee, >99%) and with concomitant recovery of corresponding epoxides in excellent optical purity (ee up to >99%) in 18 h at room temperature. The complex **1** also displayed its competence in catalyzing ARO of *meso*-epoxides with aniline to produce corresponding *syn*-β-amino alcohols in quantitative yields and high ee (84–91%). Significantly, as visualized, this system does not require an addition of a base additive to promote the reaction. Notwithstanding their excellent performance in AKR and ARO, the complex **1** has also shown very good recyclability.

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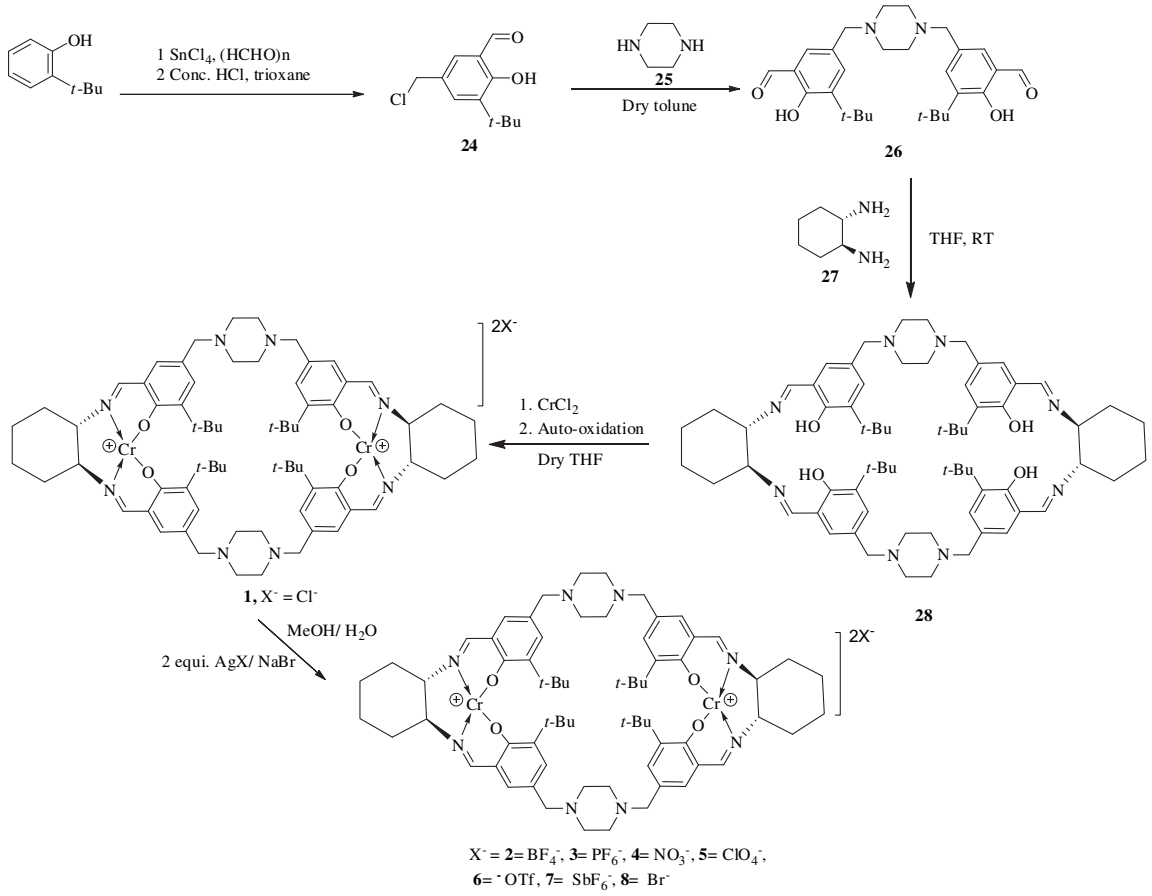
2. Results and discussion

The synthesis of chiral macrocyclic salen complexes is presented in Scheme 1. The dialdehyde **26** was prepared in high yield by the reaction of 3-*t*-Bu-5-chloromethyl-2-hydroxy benzaldehyde[15] **24** with piperazine **25** in dry toluene. The macrocyclic chiral salen ligand **28** was synthesized by reacting stoichiometric amount of the dialdehyde **26** with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane **27** in THF under stirring at room temperature for 3 h. Remarkably, the product constituted mostly dimeric macrocyclic salen ligand **28** (~97%) with a small amount of its monomeric version (~3%) as determined by ^{1}H NMR, LCMS, and MALDI-TOF data. A further purification of the dimeric ligand was hampered as it strongly binds on silica gel and various grades of alumina. Recrystallization with various solvents was also of little consequence. The absence of residual aldehyde group in ^{1}H NMR and IR spectra in the dimeric macrocyclic salen ligand **28** suggested its cyclic nature. A molecular peak at 1088.488 in MALDI-TOF (scanned up to 5000 *m*/*z* value to look for higher molecular weight structures) for ligands **28** further established its proposed cyclic structure (data are given in Supplementary data). The ligand **28** on reaction with anhydrous Cr(II) chloride followed by its auto-oxidation gave chiral macrocyclic Cr(III) salen complex **1**. The ICP data confirmed the complete metalation of the ligand **28** to give the complex **1**. The complex **1**, when allowed to react with NH_4BF_4, NH_4PF_6, or silver salts of NO_3^-, ClO_4^-, OTf^-, SbF_6^-, or with KBr resulted in the formation of the complexes **2**–**8**, respectively.

a representative nucleophile at room temperature (27±2 °C) in various solvents.

The reaction failed in dichloromethane (DCM) possibly due to the poor solubility of the catalyst (Table 1, entry 1). The catalyst was completely soluble in methanol and the AKR conducted in this solvent provided β-amino alcohol in excellent yield and fairly good ee (entry 2). Interestingly, a mixture of DCM/MeOH (1:1 v/v) improved ee of the product (entry 3). A further increase in DCMMeOH ratios 7:1 and 9:1 gave steadily better performance (entries 4 and 5). These results encouraged us to explore other solvents viz., $CHCl_3$, dichloroethane (DCE), THF, acetonitrile (ACN), and toluene in combination with MeOH, ethanol (EtOH), and isopropanol (IPA) in 9:1 v/v ratio (entries 6–12). Overall chloroalkane in combination with an alcoholic solvent worked better in terms of activity and enantioselectivity of *anti*-β-amino alcohol (entries 5–7, 11, and 12), best being DCM/MeOH (9:1 v/v) (entry 5). Therefore, taking this mixed solvent system as suitable medium, the catalyst loading was varied for the AKR of racemic *trans*-stilbene oxide **9** by keeping other reaction parameters constant. On increasing the catalyst loading from 1 mol % to 5 mol %, there was an increase in the reactivity of the complex but a decrease in ee of the product and unreacted epoxide was observed (entries 13 and 14). On the other hand, 0.5 mol % catalyst loading gave improved performance in 18 h (entry 15). A further decrease in the catalyst loading slowed down the reaction with a slight decrease in the ee of the products (entry 16). Therefore, we took parameters in entry 15 as optimum as far as the catalyst loading and solvent system is concerned. This reaction



Scheme 1. Synthetic route for chiral macrocyclic Cr(III) salen complexes **1**–**8**.

The complex **1** (1 mol % with respect to racemic epoxide) was first screened as a catalyst in the AKR of racemic *trans*-stilbene oxide **9** (2 equiv) as a model substrate with aniline **10a** (1 equiv) as was found to be sensitive toward temperature as well. It was observed that an increase in temperature (35 °C) caused decrease in enantioselectivity (entry 17) while a decrease in temperature

(10 °C) slowed down the reaction (entry 18). Hence, 0.5 mol % catalyst loading and solvent mixture of CH_2Cl_2/MeOH 9:1 v/v ratio at room temperature was taken as optimum reaction parameters to explore the effect of an external additives viz., triphenylphosphine, triethylamine, (*S*)-2-MeO-imine,[6a] (−)-cinchonine, triphenylphosphine oxide, and pyridine *N*-oxide on the performance of the AKR of racemic *trans*-stilbene oxide **9** with aniline **10a**. It is evident from the entries 19–24, that the presence of these additives in the AKR reaction was counterproductive. A possible reason for this behavior can be attributed to the built-in *tertiary* amine sites in the catalyst **1**, which are sufficient to promote the AKR reaction in the absence of an external base.

Table 1
Optimization of reaction conditions for the AKR of *trans*-stilbene oxide **9** with aniline **10a**[a]

Entry	Catalyst (mol %)	Temp (°C)	Solvent	Time (h)	Unreacted epoxide ee (%)[b]	β-Amino alcohol	
						Yield(%)[c]	ee(%)[d]
1	1	rt	DCM	24	00	00	00
2	1	rt	MeOH	24	63	99	65
3[e]	1	rt	DCM+MeOH	20	92	91	92
4[f]	1	rt	DCM+MeOH	20	93	95	94
5[g]	1	rt	DCM+MeOH	18	94	99	96
6	1	rt	$CHCl_3$+MeOH	20	92	99	94
7	1	rt	DCE+MeOH	19	93	99	94
8	1	rt	THF+MeOH	18	85	99	88
9	1	rt	ACN+MeOH	20	70	99	72
10	1	rt	Toluene+MeOH	24	83	99	85
11	1	rt	DCM+EtOH	20	90	99	92
12	1	rt	DCM+IPA	22	87	99	90
13	2.5	rt	DCM+MeOH	16	90	99	92
14	5	rt	DCM+MeOH	15	85	99	80
15	0.5	rt	DCM+MeOH	18	>99	99	>99
16	0.25	rt	DCM+MeOH	24	97	99	98
17	0.5	35	DCM+MeOH	15	83	99	85
18	0.5	10	DCM+MeOH	22	>99	99	>99
19[h]	0.5	rt	DCM+MeOH	18	90	98	92
20[h]	0.5	rt	DCM+MeOH	17	93	98	95
21[h]	0.5	rt	DCM+MeOH	24	83	98	85
22[h]	0.5	rt	DCM+MeOH	24	90	98	90
23[h]	0.5	rt	DCM+MeOH	16	92	98	93
24[h]	0.5	rt	DCM+MeOH	15	90	98	92
25[i]	0.5	rt	DCM+MeOH	19	>99	99	>99

[a] Conditions: epoxide **9** (0.2 mmol), RNH_2 **10a** (0.1 mmol), **1**(0.25–5 mol %) in DCM+MeOH.
[b] Unreacted epoxide was recovered in quantitative yields after the AKR reaction.
[c] Isolated yield with respect to the nucleophile.
[d] Based on HPLC Chiral pack OD column.
[e] Reaction was conducted in the presence of 1:1 DCM+MeOH.
[f] Reaction was conducted in the presence of 7:1 DCM+MeOH.
[g] Reaction was conducted in the presence of 9:1 DCM+MeOH.
[h] Reaction was conducted in the presence of 10 mol % additives viz., triphenylphosphine, triethylamine, (*S*)-2-MeO-imine,[6a] (−)- cinchonine, triphenylphosphine oxide, pyridine *N*-oxide, respectively.
[i] Reaction was conducted at a 10 mmol scale of **9** and 5 mmol of **10a** by keeping other reaction conditions as per entry 15.

The catalyst **1** has Cl^- as counter ion in macrocyclic Cr(III) salen complex and counter ions are known to influence the activity and enantioselectivity in the AKR reaction due to difference in their basicity.[8c] Therefore, we have varied the counter anions viz., BF_4^-, PF_6^-, NO_3^-, ClO_4^-, OTf^-, SbF6$^-$, Br^- and carried out AKR of racemic *trans*-stilbene oxide **9** with aniline **10a** under the above optimized reaction conditions (Table 2, entry 1). The reactivity of the catalysts **1**–**8** was nearly same (∼99%) but there was some variation in the enantioselectivity (ee, 80–99%), highest being with catalyst **1** having Cl^- as counter ion (entry 1). Among others, catalyst **3**, **4**, and **5** having PF_6^-, NO_3^-, and ClO_4^- ions, respectively, gave similar enantioselectivities (ee 93±1%) (entries 3–5), which are closely behind the catalyst **1**. The lowest enantioselectivity (ee, 80%) amid these was however, obtained with catalyst **2** having BF_4^- as counter ion (entry 2). Since the difference in enantioselectivities is not remarkably large, it is difficult to assign a single reason for these results.

Table 2
Screening of the chiral macrocyclic Cr(III) salen complexes **1**–**8** in the presence of different counter ions in the AKR of *tran*-stilbene oxide **9** with aniline **10a** at room temperature[a]

Entry	Catalyst	Time (h)	Unreacted epoxide ee (%)[b]	β-Amino alcohol	
				Yield (%)[c]	ee (%)[d]
1	**1**	18	>99	99	>99
2	**2**	22	82	98	80
3	**3**	24	90	98	92
4	**4**	19	94	98	94
5	**5**	18	90	98	92
6	**6**	20	86	98	88
7	**7**	22	82	98	84
8	**8**	20	85	98	86

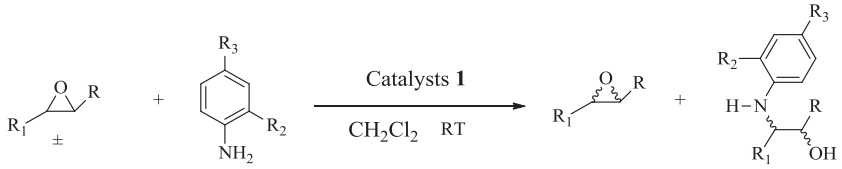
[a] Conditions: epoxide **9** (0.2 mmol), RNH_2 **10a** (0.1 mmol), **1**–**8** (0.5 mol %) in DCM+MeOH at rt.
[b] Unreacted epoxide recovered in quantitative yield after the AKR reaction.
[c] Isolated yield with respect to nucleophile.
[d] Based on HPLC Chiral pack OD column.

In view of the highest enantioselectivity obtained with the complex **1**, it was taken as a preferred catalyst to expand the scope of this AKR protocol of *trans*-stilbene oxide **9** with a variety of anilines as nucleophiles viz., aniline **10a**, 2-MeO-**10b**, 4-MeO-**10c**, 4-Me-**10d**, 2-Cl-**10e**, 4-Cl-**10f**, and 4-NO_2-aniline **10g** under the optimized reaction conditions (Table 3). Although β-amino alcohols were obtained in high ee with all the nucleophiles used in the present study, the best results in terms of yield and enantioselectivity was achieved with aniline **10a** and 4-MeO aniline **10c** (entries 1 and 3). The AKR of *trans*-stilbene oxide **9** failed with strongly electron deficient nucleophile, 4-NO_2-aniline **10g** (entry 7). In order to check general applicability of the present protocol we conducted the AKR reaction of *trans*-β-methyl styrene oxide **12** and *trans*-butene oxide **13** with aniline and substituted anilines (**10a**–**g**). Agreeably, *trans*-β-methyl styrene oxide **12** and *trans*-butene oxide **13** gave excellent yield (96–99%) of respective chiral *anti*-β-amino alcohols. However, excellent chiral induction (ee >99%; entry 8) and regioselectivity was obtained in the case of AKR of *trans*-β-methyl styrene oxide **12** with aniline **10a**. The nucleophile aniline also worked well with *trans*-butene oxide **13** by giving high ee (89%; entry 15) in the product.

Other nucleophiles also fared well with both epoxides (entries 9–13 and 16–20) except for strongly electron withdrawing nitroaniline **10g**, which failed to open the epoxide ring (entries 14 and 21). In all the catalytic runs, the (*S*)-form of chiral recyclable macrocyclic Cr(III) salen complexes converted the epoxides **9** and **12** into predominantly (*S*)-*anti*-β-amino alcohols as determined by comparing the HPLC profiles reported in the literature for these products.[8a,c,14a] However, *trans*-butene oxide **13** favored the formation of (*R*)-*anti*-β-amino alcohol as dominant enantiomer. The reasons behind the inversion of the configuration in the case of the products from epoxide **13** is not known but this kind of behavior has been observed earlier.[9c,14c,14d]

The catalyst **1** was also explored for its use in the ARO of different *meso*-epoxides viz., *meso*-stilbene oxide **16**, *cis*-butene oxide **17**, cyclohexene oxide **18**, and cyclopentene oxide **19** with aniline **10a**. Different catalyst loadings (0.25–0.75 mol %) were screened for the ARO of *meso*-stilbene oxide **16** taken as a model substrate and aniline **10a** as a nucleophile at room temperature. The reaction proceeded well and gave excellent yield (99%) of β-amino alcohol **20a** (Table 4, entry 1) with 84% ee in 24 h with 0.5 mol % catalyst loading. The catalyst **1** (loading of 0.5 mol %) was further explored in the ARO of *cis*-butene oxide **17**, cyclohexene oxide **18**, and cyclopentene oxide **19** with aniline **10a** as nucleophile at room temperature (entries 6–8). Although all the *meso*-epoxides gave

Table 3
Enantioselective AKR of racemic *trans*-epoxides with different anilines[a]

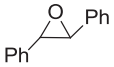
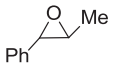
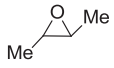


9 R = R_1=Ph
12 R = Ph, R_1=CH_3
13 R = R_1=CH_3

10a, R_2 = H, R_3 = H
10b, R_2 = OMe, R_3 = H
10c, R_2 = H, R_3 = OMe
10d, R_2 = H, R_3 = Me
10e, R_2 = Cl, R_3 = H
10f, R_2 = H, R_3 = Cl
10g, R_2 = H, R_3 = NO_2

(2*R*,3*R*)-**9**
(2*R*,3*R*)-**12**
(2*S*,3*S*)-**13**

11a-g (R = R_1=Ph)
14a-g (R = Ph, R_1=CH_3)
15a-g (R = R_1=CH_3)

Entry	*Trans* epoxide	Amine	Time (h)	Unreacted epoxide ee (%)[b]	β-Amino alcohol	
					Yield (%)[c]	ee (%)[d]
1		**10a**	18	>99	>99	>99[e]
2		**10b**	18	80	99	81[e]
3		**10c**	18	85	98	87[e]
4		**10d**	18	82	98	84[e]
5	**9**	**10e**	20	70	92	71[e]
6		**10f**	24	73	96	78[e]
7		**10g**	24	Racemic	—	—
8		**10a**	18	>99	>99	>99[f]
9		**10b**	18	80	99	81[f]
10		**10c**	24	69	98	69[f]
11		**10d**	30	62	96	64[f]
12	**12**	**10e**	24	67	96	68[f]
13		**10f**	20	52	98	53[f]
14		**10g**	18	Racemic	—	—
15		**10a**	20	85	96	86[g]
16		**10b**	18	70	98	70[g]
17		**10c**	19	74	96	76[g]
18		**10d**	19	42	95	45[g]
19	**13**	**10e**	24	56	98	58[g]
20		**10f**	24	53	98	50[g]
21		**10g**	24	Racemic	—	—

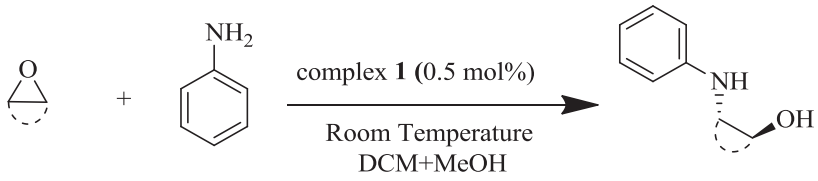
[a] Conditions: epoxide **9**, **12**, **13** (0.2 mmol), RNH_2 **10a** (0.1 mmol), **1** (0.5 mol %) in DCM+MeOH at rt.
[b] Unreacted epoxide was recovered in quantitative yield after the AKR reaction.
[c] Isolated yield is with respect to nucleophile.
[d] Based on HPLC using Chiral pack OD column.
[e] Confign. of the product (1*S*,2*R*).
[f] Confign. of the product (1*S*,2*R*).
[g] Confign. of the product (2*R*,3*S*).

corresponding β-amino alcohols **20a**–**23a** in quantitative yields (99–95%), the best result in terms of enantioselectivity was achieved with *cis*-butene oxide **17** (ee, 91%, entry 6).

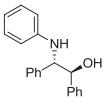
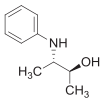
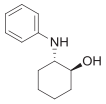
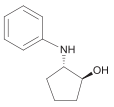
For the sake of comparison, the ARO reaction was also conducted with monomeric Cr(III) salen complex[8a] (0.5 mol %) in the presence and absence of triethylamine (as an additive) using *meso*-stilbene oxide **16** as a representative substrate with aniline **10a** under the optimized reaction conditions (Table 4, entries 4 and 5). The product chiral *syn*-β-amino alcohol was obtained in quantitative yield with 60% ee in the absence of triethylamine in 32 h. The addition of triethylamine to the above reaction resulted in an increase in the ee (73%) in 48 h for similar conversion. Significantly, results obtained under the identical reaction conditions with the chiral dimeric macrocyclic complex **1** (no triethylamine added) gave chiral *syn*-β-amino alcohol in 99% yield with 84% ee in 24 h. These results are even better than the results obtained with polymeric Cr(III) salen complexes reported by us,[8c] possibly due the built-in basic sites and better cooperation between the two salen sub-units in the case of dimeric complex **1**.

Recyclability of the catalyst **1** in the AKR reaction of *trans*-stilbene oxide **9** with aniline **10a** under the optimized reaction conditions was carried out and the results are given in Table 5. After the first catalytic run, the products were extracted with *n*-hexane/diethyl ether (70:30). The products *anti*-β-amino alcohol **11a** and enantioenriched epoxide **9a** were recovered from the organic layer and separated by column chromatography. The recovered catalyst was then dried overnight in a vacuum desiccator and used directly in the next catalytic run. It is evident from the results that the performance

Table 4
Product yield and ee of enantioselective ring opening reaction of different *meso*-epoxides with aniline as nucleophile catalyzed by complex **1** under optimized reaction condition[a]



Meso-epoxide **16-19** | **10a** | Amino alcohols **20a - 23a**

Entry	*Meso*-epoxides	Nucleophile	Product	Catalyst loading (mol %)	Time (h)	Yield (%)[c]	ee (%)[b]
1	 **16**		 **20a**	0.50	24	99	84[f]
2				0.25	40	95	82[f]
3				0.75	20	99	78[f]
4[d]				0.50	32	99	60[f]
5[e]				0.50	48	99	73[f]
6	 **17**		 **21a**	0.50	28	99	91[f]
7	 **18**		 **22a**	0.50	24	98	75[f]
8	 **19**		 **23a**	0.50	28	98	30[f]

[a] Catalyst **1** (0.5 mol %), *meso*-epoxide (1 mmol), anilines (1 m mol) in DCM+MeOH at rt.
[b] Based on HPLC using Chiral pack OD column.
[c] Isolated yield with respect to the nucleophile.
[d] Reaction was conducted in the absence of triethylamine with monomeric Cr(III) salen complex (0.5 mol %).
[e] Reaction conducted in the presence of triethylamine with monomeric Cr(III) salen complex (0.5 mol %).
[f] Confign. of the product (1R,2*R*).

of the catalyst does not change over four reuse catalytic runs. Similarly ARO of *meso*-stilbene oxide **16** with aniline **10a** by using complex **1** showed excellent recyclability over four recycle catalytic runs (Table 6). The isolation of the complex from the reaction mixture and reuse protocol remained the same as given above.

Table 5
Enantioselective AKR of **9** with **10a** using recovered complex **1** in DCM+MeOH[a]

Run	1	2	3	4	5
Time (h)	18	18	18	18	18
Yield(%)[b]	99	99	99	98	97
ee (%)[c]	99	99	99	99	99

[a] Conditions: epoxide **9** (0.2 mmol), RNH_2 **10a** (0.1 mmol), **1** (0.5 mol %) in DCM+MeOH at rt.
[b] Isolated yield of *trans*-β-amino alcohol with respect to nucleophile.
[c] ee of *trans*-β-amino alcohol based on HPLC Chiral pack OD column.

Table 6
Enantioselective ARO of **16** with **10a** using recovered complex **1** in DCM+MeOH[a]

Run	1	2	3	4	5
Time (h)	24	24	24	24	24
Yield (%)[b]	99	99	98	98	97
ee (%)[c]	84	84	84	84	84

[a] Catalyst **1** (0.5 mol %), *meso*-epoxide **16**(1 mmol), anilines **10a**(1 mmol) in DCM+MeOH at rt.
[b] Isolated yield of *syn*-β-amino alcohol with respect to nucleophile.
[c] ee of *syn*-β-amino alcohol based on HPLC Chiral pack OD column.

3. Conclusions

In conclusion, an efficient synthetic strategy for the preparation of new chiral macrocyclic Cr(III) salen complexes with piperazine linker has been demonstrated. Among all the complexes prepared complex **1** showed excellent activity and enantioselectivity in the

AKR of racemic *trans*-epoxides and ARO of *meso*-epoxides with anilines as nucleophile in the absence of an external base as an additive at room temperature. Overall the results are found to be superior than the chiral monomeric and polymeric Cr(III) salen complexes reported earlier for these reactions. Additionally, the macrocyclic Cr(III) salen complex **1** was efficiently recovered and reused several times and scaled up to 10 mmol batch size.

4. Experimental section

4.1. General

Anhydrous chromium chloride, racemic *trans*-epoxides viz., *trans*-stilbene oxide **9**, *trans*-butene oxide **12**, aniline **10a**, 2-MeO-**10b**, 4-MeO-**10c**, 4-Me-**10d**, 2-Cl-**10e**, 4-Cl-**10f** 4-NO_2-aniline **10g**, and TBME were purchased from Aldrich. 3-*t*-Bu-5-chloromethyl-2-hydroxy benzaldehyde **24** was synthesized by the reported method.[15b] Racemic epoxide of *trans*-β-methyl styrene was prepared by its oxidation with *m*-CPBA.[8c] The solvents were dried by standard procedures, distilled, and stored under nitrogen. HPLC traces were compared with racemic samples prepared with the use of racemic [Cr(salen)Cl] catalyst.[8a]

4.2. Preparation of ligand precursors

*4.2.1. Synthesis of 5,5′-(piperazine-1,4-diylbis(methylene))-bis-(3-t-Bu-2-hydroxybenzaldehyde) (**26**).* A solution of chloromethylsalicylaldehyde[15b] **24** in dry toluene (40 mmol, 20 mL) was added drop-wise to a stirring solution of piperazine **25** in dry toluene (20 mmol, 20 mL) at room temperature. The resulting yellow solution was allowed to heat at 80 °C with vigorous stirring for 6 h to give dialdehyde dichloride as a white precipitate, which was washed with solvent ether (3×10 mL) and toluene (3×10 mL) to remove unreacted starting materials. The resulting solid was treated with saturated sodium bicarbonate solution (20 mL) and the desired dialdehyde **26** was extracted with CH_2Cl_2 (4×10 mL). The organic layer was washed with water (2×10 mL) and brine (2×10 mL), and dried over anhydrous Na_2SO_4. The removal of the organic solvent gave dialdehyde **26** in high yield, which was used as such without further purification for the preparation of macrocyclic salen ligand **28**.

4.3. Characterization data of dialdehyde (26)

White solid; Yield: 90%. Mp 140–143 °C; [Found: C, 72.10; H, 8.23; N, 6.04. $C_{28}H_{38}N_2O_4$ requires C, 72.07; H, 8.21; N, 6.00%]; ν_{max} (KBr): 3138, 2953, 2812, 2312, 1930, 1805, 1782, 1652, 1596, 1434, 1380, 1320, 1291, 1260, 1233, 1203, 1154, 1008, 965, 926, 888, 800, 753, 708, 619, 550, 529 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 11.70 (s, 2H), 9.85 (s, 2H), 7.44 (s, 2H), 7.35 (s, 2H), 3.48 (s, 4H), 2.48 (s, 8H), 1.41 (s, 18H); δ_C 199.0, 162.2, 139.9, 137.1, 133.9, 130.2, 122.2, 64.1, 54.9, 36.7, 31.2; ESI mass spectra (M+1) 467, (M+Na) 489.

4.4. Synthesis of chiral macrocyclic ligand (28)

A solution of dialdehyde **26** (2 mmol, 2 equiv) in THF (1.2 mL) was added to a solution of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane**27** (2 mmol, 2 equiv) in THF (0.8 mL) and the resulting mass was stirred for 3 h at room temperature (checked on TLC). After the completion of the reaction, the solvent was completely removed under reduced pressure on a rotary evaporator to give chiral macrocyclic salen ligand **28** in high yield, which was used as such for the preparation of the complex **1** without further purification.

4.5. Characterization data of macrocyclic salen ligand (28)

Yellow solid; Yield: 90%. Mp 236–238 °C; [Found: C, 74.86; H, 8.79; N, 10.20. $C_{68}H_{96}N_8O_4$ requires C, 74.96; H, 8.88; N, 10.28%]; $[\alpha]_D^{27}$ +760 (*c* 0.083, $CHCl_3$); ν_{max} (KBr): 2937, 2863, 2806, 2364, 1629, 1441, 1385, 1319, 1265, 1206, 1159, 1095, 1009, 926, 878, 821, 772, 707 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 13.79 (s, 4H), 8.26 (s, 4H), 7.11 (br s, 4H,), 6.96 (s, 4H), 3.34–3.22 (br s, 12H), 2.41 (s, 16H), 1.96–1.64 (m, 16H), 1.37 (s, 36); δ_C (200 MHz) 167.3, 161.2, 138.6, 132.3, 131.8, 128.7, 120.1, 74.3, 64.4, 54.7, 36.6, 35.0, 31.3, 26.2; ESI mass spectra (M+H) 1089(55), 831(10), 319(100); MALDI-TOF found *m*/*z* 1088.488 $C_{68}H_{96}N_8O_4$ required 1088.

4.6. Synthesis of chiral macrocyclic Cr(III) salen complex (1)

To a solution of **28** (1.0 mmol) in dry degassed THF (25 mL) was added solid anhydrous Cr(II) chloride (1.1 mmol) in a glove box and the resulting solution (dark brown in color) was stirred for 4 h under an inert atmosphere at room temperature. Subsequently, the resulting reaction mixture was exposed to air with stirring for 3 h for auto-oxidation. The dark brown solution was diluted with TBME (30 mL) to give chiral macrocyclic Cr(III) salen complex **1** as a brown precipitate. The precipitate thus obtained was washed with TBME (3×20 mL) and dried overnight under vacuum. (For characterization please see the Supplementary data).

4.7. Synthesis of chiral macrocyclic Cr(III) salen complexes 2–8

*4.7.1. Synthesis of chiral macrocyclic Cr(III) salen complex (**2**).* Complex **2** was prepared by the reaction of methanolic solution of dimeric complex **1** (0.500 mg, 0.397 mmol, 20 mL) with an aqueous solution of NH_4BF_4 (0.83 mg, 0.8 mmol, 0.4 mL). The resulting suspension was stirred for 12 h. After that the reaction mixture was centrifuged at 4500 rpm for 30 min. The solvent from the supernatant was removed to dryness to yield the complexes **2**. (Data is given in Supplementary data).

*4.7.2. Synthesis of chiral macrocyclic Cr(III) salen complex (**3**).* Complex **3** was prepared by the reaction of methanolic solution of dimeric complex **1** (0.500 mg, 0.397 mmol, 20 mL) with an aqueous solution (0.130 mg, 0.8 mmol, 0.4 mL) of NH_4PF_6. The resulting suspension was processed similarly as for the preparation of complex **2** given above to get the complexes **3**. (Data is given in Supplementary data).

*4.7.3. Synthesis of chiral macrocyclic Cr(III) salen complex (**4**).* Complex **4** was prepared by the reaction of methanolic solution of dimeric complex **1** (0.500 mg, 0.397 mmol, 20 mL) with an aqueous solution of $AgNO_3$ (0.136 mg, 0.8 mmol, 0.4 mL). The resulting suspension was stirred for 6 h and the white precipitate of AgCl was removed by centrifugation as described above. The removal of the solvent from supernatant gave the complexes **4** in quantitative yield. (Data is given in Supplementary data).

*4.7.4. Synthesis of chiral macrocyclic Cr(III) salen complex (**5**).* Complex **5** was prepared by the reaction of methanolic solution of dimeric complex **1** (0.500 mg, 0.397 mmol, 20 mL) with an aqueous solution of $AgClO_4$ (0.165 mg, 0.8 mmol, 0.4 mL). The resulting suspension was stirred for 6 h and the reaction mixture was processed as described above to yield the complexes **5**. (Data is given in Supplementary data).

*4.7.5. Synthesis of chiral macrocyclic Cr(III) salen complex (**6**).* Complex **6** was prepared by the reaction of methanolic solution of dimeric complex **1** (0.500 mg, 0.397 mmol, 20 mL) with an aqueous solution (0.206 mg, 0.8 mmol, 0.4 mL) of AgOTf. The

resulting suspension was stirred for 6 h and the reaction mixture was processed as mentioned above to yield the complexes **6**. (Data is given in Supplementary data).

*4.7.6. Synthesis of chiral macrocyclic Cr(III) salen complex (**7**).* Complex **7** was prepared by the reaction of methanolic solution of dimeric complex **1** (0.500 mg, 0.397 mmol, 20 mL) with an aqueous solution (0.275 mg, 0.8 mmol, 0.4 mL) of $AgSbF_6$. The resulting suspension was stirred for 6 h and centrifuged. The solvent removal from the supernatant yielded the complex **7**. (Data is given in Supplementary data).

*4.7.7. Synthesis of chiral macrocyclic Cr(III) salen complex (**8**).* To prepare complex **8**, a solution of complex **1** (0.500 mg, 0.397 mmol) in methanol containing 5% water (20 mL), which was passed slowly over a bed (1 cm×10 cm) of KBrover 3 h. The solvent was then removed completely and the residue was dried in a desiccator to get the complex **8** in quantitative yield (Data is given in Supplementary data).

4.8. Typical procedure for the AKR of racemic *trans*-epoxides

In a small vial equipped with a magnetic stirring bar, the chiral macrocyclic Cr(III) salen complexes **1**–**8** (1 mol % based on monomeric unit) were taken in DCM+MeOH (9:1, 0.4 mL) and the resulting solution was stirred for 5 min followed by the addition of an appropriate epoxide (0.2 mmol). The resulting mass was stirred for 10 min followed by the addition of desired aniline as a nucleophile (0.1 mmol) at room temperature. The progress of the catalytic reaction was monitored on TLC. At the end of the reaction the reaction mixture was repeatedly extracted with *n*-hexane/diethyl ether (70:30, 2×5 mL). The product *trans*-β-amino alcohols **11a**–**g**, **14a**–**g**, **15a**–**g** and the unreacted epoxides (2*R*,3*R*)-**9**, (2*R*,3*R*)-**12**, (2*S*,3*S*)-**13** were recovered by column chromatography. The recovered catalyst was dried under vacuum and stored in a desiccator for its use in the subsequent catalytic runs.

4.9. Typical experimental procedure for ring opening of *meso*-epoxides

To a 5 mL round bottom flask equipped with rubber septum and a magnetic stirring bar, the chiral macrocyclic Cr(III) salen complex **1** (0.5 mol %) was taken in DCM+MeOH (9:1, 0.4 mL) and the resulting solution was stirred for 5 min followed by the addition of an appropriate *meso*-epoxide (0.2 mmol). Subsequently, after 20 min, aniline (0.2 mmol) was added and the reaction mixture was further allowed to stir for the specified time at room temperature. The progress of the reaction was checked on TLC using hexane/ethyl acetate (8/2) as mobile phase. After the completion of the reaction, solvent was removed under vacuum and the product was purified by column chromatography using silica gel 100–200 mesh as stationary phase and hexane/ethyl acetate (8:2) as mobile phase. All the products were characterized by appropriate spectroscopic techniques, microanalysis, LCMS, and optical rotation, which were found to be in consonance with the reported values.[5c,5d,6a,6b]

4.10. Typical experimental procedure for 10 mmol scale of *trans*-stilbene oxide with aniline

In a 25 mL vial equipped with a magnetic stirring bar, the chiral macrocyclic Cr(III) salen complex **1** (0.063 g, 1 mol % based on monomeric unit) was taken in DCM+MeOH (9:1, 4 mL) and the resulting solution was stirred for 5 min followed by the addition of *trans*-stilbene oxide (1.962 g, 10 mmol). The resulting mass was stirred for 10 min to which aniline (0.455 mL, 5 mmol) was added at room temperature. The progress of the catalytic reaction was monitored on TLC. At the end of the reaction the solvent was completely removed and the residue was repeatedly extracted with *n*-hexane/diethyl ether (70:30, 5×6=30 mL). The residue left was the catalyst and the organic layer contained the products *trans*-β-amino alcohol (1*S*,2*R*)-**11a** and the unreacted epoxides (2*R*,3*R*)-**9**, recovery of which was done by column chromatography in quantitative yields using hexane+ethyl acetate (9:1) as an eluent.

4.11. Recycling of the catalyst 1

Catalyst recycle experiments were carried out at the 5 mmol scale of the substrates *trans*-stilbene oxide **9** (0.981 g) and aniline **10a** (0.227 mL) with 1 mol % of the catalyst **1** (0.031 g) under the above optimized reaction conditions. At the end of the catalytic run (checked on TLC) the solvent was completely removed under reduced pressure. The residue was extracted with *n*-hexane/diethyl ether (70:30) (3×5 mL) and the remaining solid (catalyst) was further washed with hexane (2×5 mL). The recovered solid was dried under the reduced pressure for 1–2 h and was used as recovered catalyst for recycle experiments of AKR reaction of *trans*-stilbene oxide. The products aminoalcohol and enantioenriched epoxide were obtained in the manner described in preceding paragraph. Similar scale and procedure was followed for the catalyst **1** recycle experiment conducted for the ARO of *meso*-stilbene oxide **16** with aniline **10a**.

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Supplementary data

Characterization data of chiral macrocyclic ligand, its precursor and chiral Cr(III) salen complexes including ^{1}H, ^{13}C NMR, FT-IR, CHN, ICP, mp, Optical rotation, ESI-MS, MALDI-TOF, and HPLC profile. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.077.

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