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Reusable Chiral Dicationic Chromium(III) Salen Catalysts for Aminolytic Kinetic Resolution of *trans*-Epoxides

Rukhsana I. Kureshy,[a,*] K. Jeya Prathap,[a] Tamal Roy,[a] Nabin Ch. Maity,[a] Noor-ul H. Khan,[a] Sayed H. R. Abdi,[a] and Hari C. Bajaj[a]

[a] Discipline of Inorganic Materials and Catalysis, Central Salt and Marine Chemicals Research Institute (CSMCRI), Council of Scientific & Industrial Research (CSIR), G. B. Marg, Bhavnagar – 364 021, Gujarat, India
Fax: (+91)-0278-256-6970; e-mail: rukhsana93@yahoo.co.in

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Abstract: A series of new recyclable chiral dicationic chromium(III) salen complexes **1**–**10** bearing different substituents, *viz.*, hydrogen, methyl, *tert*-butyl, triphenylphosphinomethyl, triethylaminomethyl, methylimidazolium, methylpyridinium, methyl-*N,N*-dimethylpyridinium at the 3,3′- and 5,5′- positions of the salen unit with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane, (1*S*,2*S*)-(−)-1,2-diphenyl-1,2-diaminoethane, and (*S*)-(−)-1,1′-binaphthyl-2,2′-diamine collars have been synthesized and characterized by various physico-chemical methods. These complexes were used as catalysts for the highly enantioselective aminolytic kinetic resolution of racemic *trans*-epoxides with different anilines as nucleophiles at room temperature. With the use of catalyst **3**, *anti*-β-amino alcohols were obtained in excellent yields (>99% with respect to the nucleophile) and enantioselectivities (*ee* >99%) with the concomitant recovery of corresponding epoxides in high optical purity (*ee* up to >99%) and quantitative yields in 12 h. The catalyst **3** is recyclable in the aminolytic kinetic resolution process and worked well up to six cycles with retention of enantioselectivity.

Keywords: *anti*-β-amino alcohols; aminolytic kinetic resolution; asymmetric catalysis; chromium(III) salen complexes; dicationic salen; *trans*-epoxides

Introduction

Enantiopure β-amino alcohols are valuable building blocks for biologically active compounds[1] and as chiral auxiliaries in asymmetric synthesis.[2] Among the various efficient catalytic methods developed[3–11] for their synthesis, the chiral metal complexes-catalyzed aminolytic kinetic resolution (AKR) of racemic epoxides with amine is an important strategy. AKR not only affords enantiomerically enriched β-amino alcohols, in a single step, but also this strategy simultaneously produces valuable enantiomerically enriched epoxides from racemic terminal and *trans*-epoxides.[10] Since the landmark discovery of the Mn(III) salen complex as enantioselective epoxidation catalyst by Jacobsen et al., salen-type complexes with different metal ions have also found application in different asymmetric organic transformations.[12] such as hydrolytic kinetic resolution (HKR) of terminal epoxides,[13a,b] asymmetric ring opening (ARO) of *meso*-epoxides.[13c] and C–C bond forming reaction[13d] with different nucleophiles. In spite of high activity and enantioselectivity of these monomeric salen complexes, there is a nagging issue of separation and recycling of the catalyst. As a result, the last decades have witnessed an avid research activity in heterogenizing chiral homogeneous catalysts.[14]

Another strategy for making the chiral catalyst recyclable is to modify the solubility of the catalyst. In this strategy one can still carry out the catalytic reaction under homogenous condition, but at the end of the reaction the catalyst is precipitated out by the addition of a solvent in which the catalyst is insoluble while the reactants and products remain in the solution.[15] The monomeric salen complexes are highly soluble in most of the organic solvents. In order to make them less soluble in some of the non-polar organic solvents, e.g., *n*-hexane, we have earlier reported the dimeric and polymeric version of salen complexes.[7f,g,h,j,l] However, in the present study we have introduced bulky groups as well as charges (akin to ionic liquids) in the monomeric salen complexes in

view of harnessing the virtues of homogeneous catalysis at the same time make the catalysts easily recoverable due to their altered solubility in organic solvents. Accordingly we are reporting here the synthesis of new chiral dicationic Cr(III) salen complexes **1**–**10** having different substituents at the 3,3′- and 5,5′-positions of the salen unit. The chiral dicationic Cr(III) salen complexes were used as catalysts for the first time in enantioselective AKR of various *trans*-epoxides, although Co, Mn and Ru complexes of dicationic-salen have also been applied for achiral[16] and chiral organic transformations.[17] Excellent yields (up to >99%) and enantioselectivity (*ee* up to >99%) of chiral *anti*-β-amino alcohols and remaining epoxides in high optical purity (*ee*, up to >99%) were achieved in 12 h at room temperature with the use of the recyclable chiral dicationic Cr(III) salen complexes as catalyst. The most active and enantioselective dicationic Cr(III) salen complex **3** was also subjected to catalyst recycling experiments where the complex **3** retained its catalytic performance over six cycles.

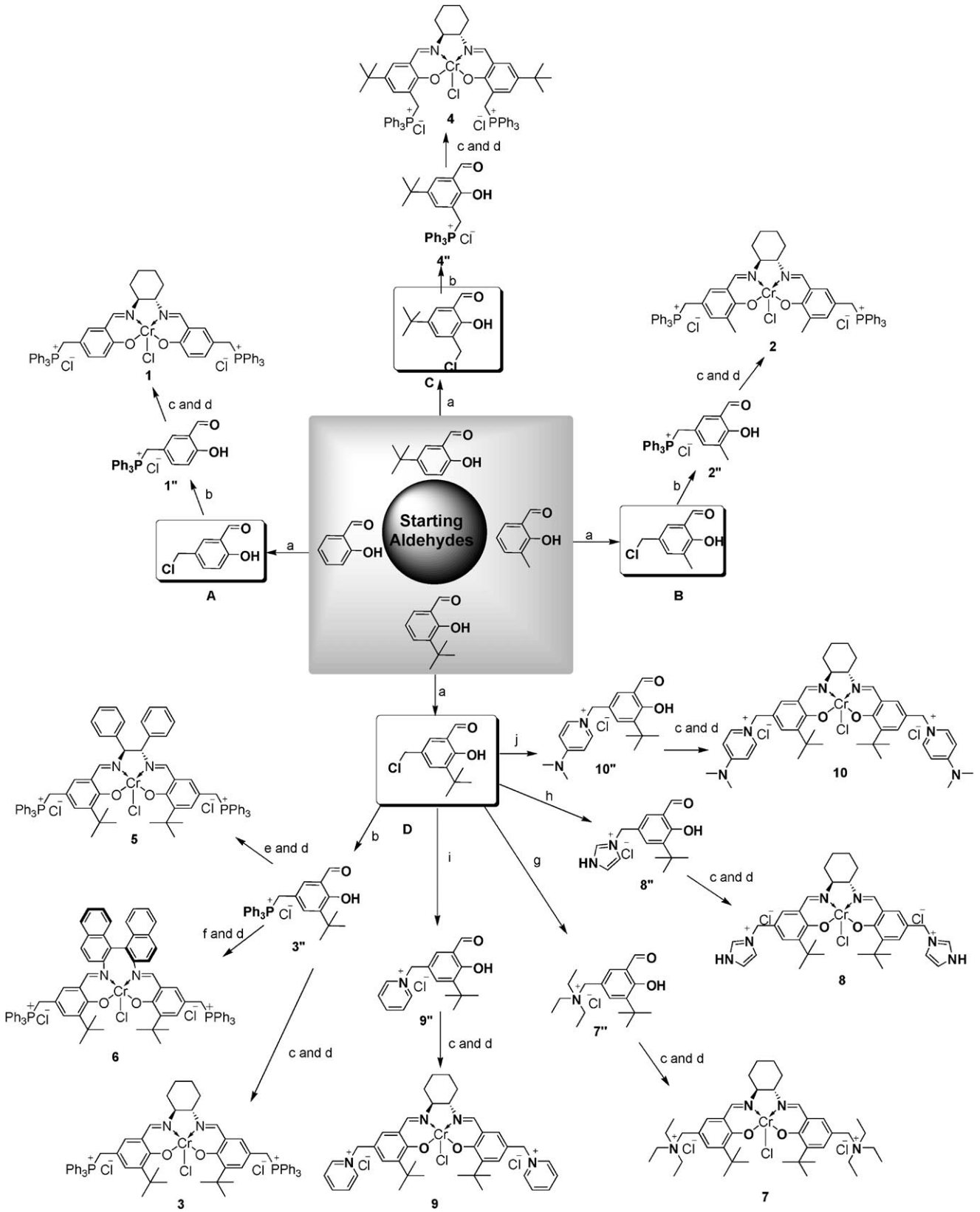
Results and Discussion

Chiral Cr(III) salen complexes **1**–**10** were synthesized by the reaction of respective dicationic chiral salen ligands **1′–10′** with chromium(II) chloride under an inert atmosphere followed by autooxidation (Scheme 1). All chiral dicationic metal complexes were characterized by microanalysis, FT-IR, UV/Vis spectroscopy and optical rotation (see Supporting Information). The substituents on the salen unit of the catalysts **1**–**10** were chosen in such a way that at the end of the present study there emerge some understandings on structure-activity-relationships. Accordingly, the 3,3′- and 5,5′-positions and diamine collar were subjected to change.

The catalytic activity and selectivity of catalysts **1**–**10** (2 mol%) were explored for the AKR of *trans*-stilbene oxide **11** (2.0 mmol) as a model test substrate with aniline **12a** (1.0 mmol) as nucleophile at room temperature and the data are summarized in Table 1. In the first set of screening of complexes **1**–**3**, we altered the substituents (H, Me and *t*-Bu) at 3,3′-positions of the salen unit by fixing the substituent (triphenylphosphinomethyl) at the 5,5′-positions and the diamine collar originating from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane. The results (entries 1–3) clearly show that as we increase the size of the substituent (H< Me<*t*-Bu) there is a steady increase in the *ee* of the desired *anti*-β-amino alcohol **13a** (*ee*, 58<70<99%, respectively).

However, the yield of the product was quantitative (~99%) in all the cases. The *ee* of the unreacted epoxide **11′** followed same pattern of H<Me<*t*-Bu=56<65<99%. On exchanging the positions of the *t*-Bu and triphenylphosphinomethyl groups as in the case of complex **4**, the *ee*s of the *anti*-β-amino alcohol and unreacted epoxide declined sharply (entry 4). Moreover, this catalyst also took 35 h for completion of the AKR reaction. As best results in terms of yield and *ee* were achieved with catalyst **3**, for our next AKR experiments we fixed the *t*-Bu group at the 3,3′-positions and triphenylphosphinomethyl groups at the 5,5′-positions and changed to the 1,2-diamino collars originating from (1*S*,2*S*)-(−)-1,2-diphenyl-1,2-diaminoethane and (*S*)-(−)-1,1′-binaphthyl-2,2′-diamine (catalysts **5** and **6**). In both the case we achieved excellent conversion of the *anti*-β-amino alcohol in 12–15 h but, the *ee*s were low (entries 5 and 6). Having established that the enantioselectivity is higher for the complexes derived from (*1S,2S*)-(+)-1,2-diaminocyclohexane and salicylaldehyde having *t*-Bu groups at the 3,3′-positions, we kept these positions fixed and changed the groups at the 5,5′-positions (complexes **7**–**10**). These complexes **7**–**10** having different aminoalkyl groups, *viz.*, triethylaminomethyl, methylimidazolium, methylpyridinium, methyl-*N*-*N*-dimethylpyridinium at the 5,5′-positions of salen ligands gave the *anti*-β-amino alcohol in excellent yield in 24 h with 58–80% *ee* (entries 7–10) but none could match the performance of catalyst **3** (entry 3) (Figure 1).

Having revealed that the complex **3** is most active and enantioselective catalyst at 2 mol% loading, next we used this catalyst to optimize the reaction parameters such as catalyst loading, temperature and solvent variations for the AKR reaction of *trans*-stilbene oxide **11** as model substrate and aniline **12a** as nucleophile. A catalyst loading ranging over 1–5 mol% was explored and the data are given in Table 2 (entries 1–3). A catalyst loading of 1 mol% gives the product *anti*-β-amino alcohol **13a** with an *ee* of 95% in 20 h (entry 2), whereas 5 mol% of the catalyst was able to produce the desired product with *ee* >99% in 8 h (entry 3). Looking at the *ee* (>99%) of the product obtained with 2 mol% catalyst loading and the time taken for the completion of the reaction (12 h) *vis-à-vis* 5 mol% catalyst loading, it was decided to take 2 mol% catalyst loading as the optimum (entry 1). Next, we varied the reaction temperature from 0 to 40 °C (entries 4–6) and found that room temperature (28 °C) is just right for the AKR reaction (entry 1). This protocol worked well in terms of yield of *anti*-β-amino alcohol even at a relatively higher scale (10 mmol) in 13 h (Table 2, entry 7). The nature of the solvents is known to influence the reactivity and enantioselectivity of the AKR of racemic epoxide.[7g] Hence, we conducted the AKR in different solvents, *viz.*, THF, CH_3CN, $CHCl_3$, toluene and MeOH (entries 8–12) keeping other optimized parameters constant (CH_2Cl_2, entry 1). However, best results were obtained with the use CH_2Cl_2 as solvent which was used as solvent of choice in our subsequent studies.



Scheme 1. Synthetic route for chiral dicationic Cr(III) salen complexes. *Conditions:* a) concentrated HCl, trioxane, 45–50 °C, 72 h (yield: 90%); b) TPP, dry benzene, 4–6 h, 60 °C (yield: 90–91%); c) (1*S*,2*S*)-(+)-1,2-diaminocyclohexane, dry methanol, reflux, 4-5 h (yield: 90–98%); d) dry THF, anhydrous $CrCl_2$/autooxidation (yield: 90–95%); e) (1*S*,2*S*)-(−)-1,2-diphenyl-1,2-diaminoethane, dry methanol, reflux, 4–5 h (yield: 95%); f) (*S*)-(−)-1,1′-binaphthyl-2,2′-diamine, dry methanol, reflux, 4–5 h (yield: 85%); g) TEA, dry benzene, 4-6 h, 60 °C (yield: 90%); h) imidazole, dry benzene, 4–6 h, 60 °C (yield: 92%); i) pyridine, dry benzene, 4–6 h, 60 °C (yield: 93%); j) *N*,*N*-dimethylamine, dry benzene, 4–6 h, 60 °C (yield: 95%).

Table 1. Screening of the catalysts **1–10** for enantioselective AKR of *trans*-stilbene oxide **11** with aniline **12a** at room temperature.[a]

Entry	Complex	Time [h]	Unreacted epoxide *ee* [%][b]	β-Amino alcohol Yield [%][d]	*ee* [%][c]
1	**1**	24	56	99	58
2	**2**	24	65	99	70
3	**3**	12	>99	>99	>99
4	**4**	35	28	99	28
5	**5**	12	30	99	35
6	**6**	15	43	98	12
7	**7**	24	78	98	80
8	**8**	24	56	98	58
9	**9**	24	72	98	70
10	**10**	24	69	98	65

[a] *Conditions:* epoxide **11** (0.2 mmol), RNH_2 **12a** (0.1 mmol), **1–10** (2 mol%) in CH_2Cl_2.
[b] Unreacted epoxide recovered in quantitative yield after AKR reaction.
[c] Based on an HPLC Chiral pack OD column.
[d] Isolated yield with respect to nucleophile.

The a bove optimal AKR conditions (Table 2 entry 1) were then applied for the synthesis of a series of *anti*-β-amino alcohols with catalyst **3** using other anilines as nucleophile, *viz.*, aniline (**12a**), 2-MeO- (**12b**), 4-MeO- (**12c**), 4-Me- (**12d**), 2-Cl- (**12e**), 4-Cl (**12f**) and 4-NO_2-aniline (**12g**) with *trans*-stilbene oxide **11** (Scheme 2). A good to excellent yield (82–99%) for *anti*-β-amino alcohol was achieved for all anilines while high enantioselectivity (*ee* >99%) was

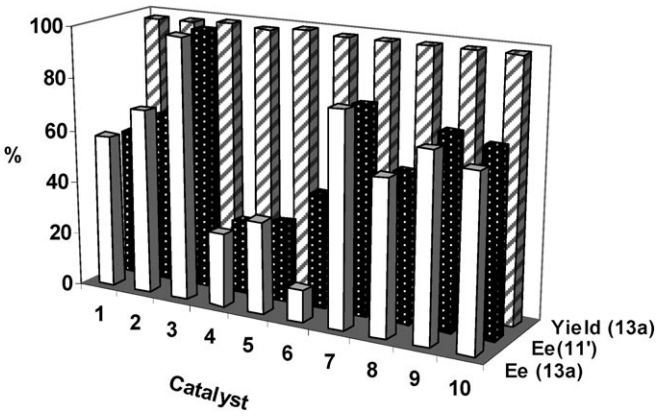


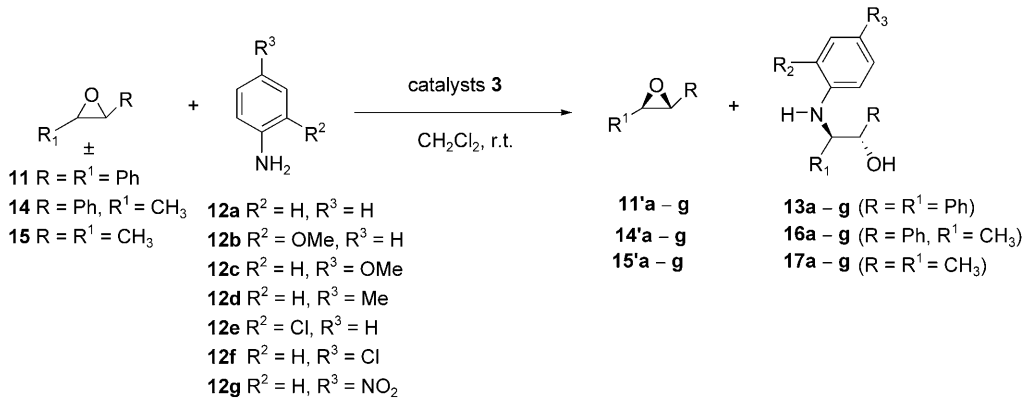
Figure 1. Yield [%] and *ee* [%] of chiral *anti*-β-amino alcohols with the catalysts **1–10.**

observed in the case of the respective products **13a, 13b** and **13e** obtained from the ring opening of *trans*-stilbene oxide with **12a, 12b** and **12e** in 10–18 h (Table 3, entries 1, 2 and 5) (Figure 2). However, the ring opening reaction of **11** with 4-chloroaniline **12f** gave a low enantioselectivity (entry 6) while 4-nitroaniline **12g** as nucleophile failed to undergo the AKR reaction (entry 7) possibly due to its poor nucleophilicity. Agreeably, the unreacted epoxides **11′a, 11′b** and **11′e** were recovered in quantitative yield with excellent optical purity (>99%) (Table 3, entries 1 and 2). We further explored the AKR reaction of *trans*-β-methylstyrene **14** and *trans*-butene oxide **15** with aniline and substituted anilines (**12a–g**). Ironically, *trans*-β-methylstyrene oxide and *trans*-butene oxide gave good to excellent yields (84–98%) of the respective chiral *anti*-β-amino alcohols, but high chiral induction

Table 2. Optimization of reaction condition for enantioselective AKR of *trans*-stilbene oxide **11** with aniline **12a** in the presence of complex **3**.[a]

Entry	Catalyst [mol%]	Temp. [°C]	Solvent	Time [h]	Unreacted epoxide *ee* [%][b]	β-Amino alcohol Yield [%][d]	*ee* [%][c]
1	2	r.t.	CH_2Cl_2	12	>99	>99	>99
2	1	r.t.	CH_2Cl_2	20	99	99	95
3	5	r.t.	CH_2Cl_2	8	>99	>99	>99
4	2	0	CH_2Cl_2	30	99	99	99
5	2	10	CH_2Cl_2	24	99	99	99
6	2	40	CH_2Cl_2	8	82	99	80
7[e]	2	r.t.	CH_2Cl_2	13	99	99	99
8	2	r.t.	THF	28	50	99	40
9	2	r.t.	CH_3CN	30	42	99	36
10	2	r.t.	$CHCl_3$	20	78	99	80
11	2	r.t.	Toluene	24	00	00	00
12	2	r.t.	MeOH	24	00	00	00

[a] *Conditions:* epoxide **11** (0.2 mmol), RNH_2 **12a** (0.1 mmol), **3** (2 mol%) in different solvents
[b] Unreacted epoxide recovered in quantitative yield after AKR reaction.
[c] Based on an HPLC Chiral pack OD column.
[d] Isolated yield with respect to nucleophile.
[e] Reaction conducted at 10-mmol scale of **11** and 5 mmol of **12a** in CH_2Cl_2 keeping other conditions as per entry 1.

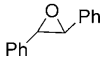
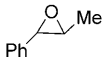
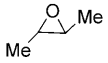


Scheme 2. AKR of racemic *trans*-epoxides with different anilines.

(*ee* >99%, 95%) was obtained only in the case of ring opening of butene oxide **15** with 2-MeO-aniline **12b** and 2-Cl-aniline **12e** (Table 3, entries 16 and 19). In fact *trans*-β-methyl styrene oxide **14** as substrate has undergone the AKR reaction well in terms of reactivity with several anilines (entries 8–13) albeit with moderate enantioselectivity. It is to be noted that results obtained in the present study are significantly superior in term of yields (99%, 12 h) and enantioselectivity of the products chiral *anti*-β-amino alcohols (>99%) and unreacted epoxides (*ee* >99%) as compared to the earlier reported non-recyclable monomeric Cr(III) salen complexes[10] for similar *trans*-epoxides under homogeneous system. In all catalytic runs, the (*S*)-form of chiral recyclable dicationic Cr-(III) salen complexes converted all epoxides into predominantly (*R*)-*anti*-β-amino alcohols as determined by comparing the HPLC profiles reported in the literature for these products.[7g,k,10]

In addition to high reactivity and enantioselectivity in the AKR reaction, the catalyst **3** is recyclable as evidenced by the recycling experiments (Table 4). The recyclability experiments were carried out by using *trans*-stilbene oxide **11** (2.0 mmol) as a model sub-

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

Entry	*trans*-Epoxide	Amine	Time [h]	Unreacted epoxide[b]	*ee* [%]	β-Amino alcohol	Yield [%][d]	*ee* [%][c]
1		**12a**	12	**11′a**	>99	**13a**	>99	>99
2		**12b**	18	**11'b**	>99	**13b**	98	99
3		**12c**	12	**11'c**	92	**13c**	96	88
4		**12d**	15	**11'd**	89	**13d**	96	86
5		**12e**	10	**11'e**	97	**13e**	82	99
6		**12f**	10	**11'f**	46	**13f**	96	50
7		**12g**	24	**11'g**	racemic	**13g**	–	–
8		**12a**	20	**14′a**	60	**16a**	97	62
9		**12b**	20	**14'b**	67	**16b**	96	71
10		**12c**	20	**14'c**	58	**16c**	98	62
11		**12d**	20	**14'd**	65	**16d**	96	68
12		**12e**	24	**14'e**	40	**16e**	96	45
13		**12f**	24	**14'f**	46	**16f**	98	49
14		**12g**	24	**14'g**	racemic	**16g**	–	–
15		**12a**	20	**15′a**	48	**17a**	95	50
16		**12b**	20	**15'b**	98	**17b**	98	>99
17		**12c**	20	**15'c**	50	**17c**	94	52
18		**12d**	24	**15'd**	51	**17d**	95	54
19		**12e**	24	**15'e**	92	**17e**	98	95
20		**12f**	24	**15'f**	48	**17f**	84	50
21		**12g**	24	**15'g**	racemic	**17g**	–	–

[a] *Conditions:* epoxides **11**, **14**, **15** (0.2 mmol), RNH_2 **12a–g** (0.1 mmol), **3** (2 mol%) in CH_2Cl_2.
[b] Unreacted epoxide recovered in quantitative yield after AKR reaction.
[c] Based on an HPLC Chiral pack OD column.
[d] Isolated yield with respect to nucleophile.

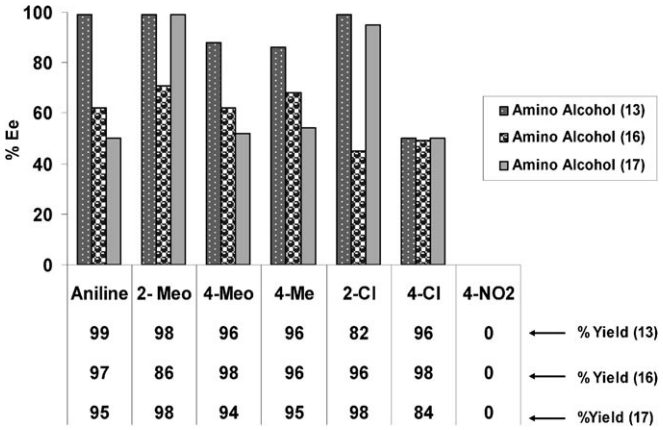


Figure 2. Yield [%] and *ee* [%] of chiral *anti*-β-amino alcohols with different anilines using the catalyst **3**.

Table 4. Enantioselective AKR of **11** with **12a** using recovered complex **3** in dichloromethane.[a]

Run	1	2	3	4	5	6
Time [h]	12	12	12.5	12.5	12.5	13
Yield [%][b]	99	99	99	98	98	97
ee [%][c]	>99	>99	>99	>99	>99	>99

[a] *Conditions:* epoxides **11** (0.2 mmol), RNH_2 **12a** (0.1 mmol), **3** (2 mol%) in CH_2Cl_2. Unreacted epoxide recovered in quantitative yield after AKR reaction.
[b] Isolated yield with respect to nucleophile.
[c] Based on HPLC Chiral pack column.

strate with aniline **12a** (1.0 mmol) as nucleophile in dichloromethane at room temperature using the complex **3** (2 mol%) as catalyst. After completion of the catalytic reaction, the products were extracted with *n*-hexane. The products *anti*-β-amino alcohol and enantioenriched epoxide were recovered from the organic layer and separated by column chromatography. The recovered complex was dried under vacuum and was used as such for the subsequent catalytic runs, which worked well up to 6 catalytic runs with retention of the reactivity and enantioselectivity. From the recycling experiments it is evident that the dicationic Cr(III) salen complexes are fairly stable and do not deteriorate during the course of the AKR reaction.

Conclusions

In summary, chiral dicationic Cr(III) salen complexes **1–10** having different substituents at the 3,3′- and 5,5′-positions of salen unit were prepared and used for the AKR of racemic *trans*-epoxides with anilines at room temperature. Among all the complexes used in the present study the complex **3** having triphenylphosphinomethyl groups at the 5,5′-positions and *t*-Bu groups at the 3,3′-positions worked efficiently in term of reactivity and enantioselectivity. The products from the AKR of *trans*-stilbene oxide, *viz.*, *anti*-β-amino alcohols (*ee* >99%) and epoxides (*ee* >99%) were efficiently separated from the precipitated catalyst in *n*-hexane by simple filtration. To the best of our knowledge, there are no other reports on the AKR reaction of *trans*-epoxide using a recyclable monomeric dicationic Cr(III) salen complex under homogeneous conditions which circumvent the need of a multi-step process of anchoring the homogeneous catalyst on various solid supports for recycling purposes.

Experimental Section

Preparation of Chiral Ligand Precursors (1″-4″and 7″–10″)

An appropriate chloromethylsalicylaldehyde **A–D** (see Supporting Information) (2 mmol) in 20 mL benzene was added dropwise to a stirring solution of triphenylphosphine, triethylamine, imidazole, pyridine and *N,N*-dimethylaminopyridine, (2 mmol) in 20 mL of dry benzene. The resulting cloudy solution was allowed to reflux with vigorous stirring for 6 h to give the products (3-formyl-4-hydroxybenzyl)triphenylphosphonium chloride **1″**, (3-formyl-4-hydroxy-5-methylbenzyl)triphenylphosphonium chloride **2″**, (3-*tert*-butyl-5-formyl-4-hydroxybenzyl)triphenylphosphonium chloride **3″**, (5-*tert*-butyl-3-formyl-2-hydroxybenzyl)triphenylphosphonium chloride **4″**, *N*-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl)-*N,N,N*-triethylammonium chloride **7″**, 3-(3-*tert-butyl*-5-formyl-4-hydroxybenzyl)-1*H*-imidazol-3-ium chloride **8″**, 1-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl) pyridinium chloride **9″**, 1-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl-)-4-(dimethylamino)pyridinium chloride **10″**; yields: 92–95% (see Supporting Information).

Preparation of Dicationic Chiral Salen Ligands 1′–10′

To an ethanolic solution of an appropriate aldehyde **1″–10″** (2 mmol) was added the chiral diamine, *viz.*, (1*S*,2*S*)-(+)-1,2-diaminocyclohexane, (1*S*,2*S*)-(−)-1,2-diphenyl-1,2-diaminoethane, or (*S*)-(−)-1,1′-binaphthyl-2,2′-diamine (1 mmol) and the resulting mass was allowed to reflux for 7–8 h. The solvent was partially removed under reduced pressure on a rotary evaporator, and the yellow product of **1′–10′** was precipitated by *n*-hexane. The chiral ligands **1′–10′** were filtered and dried under vacuum (see Supporting Information).

Preparation of Dicationic Chiral Cr(III) Salen Complexes 1–10

A 100-mL, 2-necked, round-bottom flask with a nitrogen inlet and outlet was charged with a solution of **1′–10′** in dry degassed THF (26 mL). To the yellow solution, anhydrous chromium(II) chloride was added and the solution turned into dark brown which was stirred for 4 h under a blanket of nitrogen and then exposed to air for a further 3 h. The dark brown solution was diluted with TBME (*t*-butyl methyl ether) resulting in the precipitation of the complexes **1–10**. The complexes were filtered and washed with saturated

NH_4Cl solution and brine to remove the excess of chromium chloride, the complexes were dried over night under vacuum (see Supporting Information).

Asymmetric Aminolytic Kinetic Resolution (AKR) of Racemic *trans*-Epoxides

In a small vial equipped with a magnetic stirring bar, the dicationic Cr(III) salen complexes **1**–**10** (2 mol%) were taken in dichloromethane (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 nucleophile (0.1 mmol). 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). The product *trans*-β-amino alcohols **13a–g, 16a–g, 17a–g** and the unreacted epoxides **11′a–g, 14′a–g, 15′a–g** were recovered by column chromatography. The recovered catalyst was dried under vacuum and stored in desiccator for its use in subsequent catalytic runs.

Recycling of the Catalyst 3

At the end of the catalytic run (checked on TLC) the solvent was completely removed under reduced pressure. The residue was extracted with hexane, and the remaining solid was further washed with *n*-hexane/diethyl ether (70:30) (10 mL). The recovered solid was dried under reduced pressure for 1–2 h and was used as catalyst for recycle experiments of the AKR reaction of *trans*-stilbene oxide **11** as representative substrate with aniline **12a** as nucleophile.

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