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Cu(II)-Macrocylic [H_4]Salen Catalyzed Asymmetric Nitroaldol Reaction and Its Application in the Synthesis of α1-Adrenergic Receptor Agonist (*R*)-Phenylephrine

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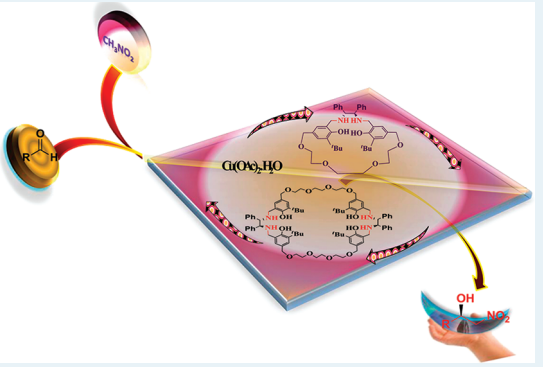
Supporting Information

ABSTRACT: New chiral Cu (II) complexes **1**−**6** were generated in situ by the interaction of different sources of copper(II) salts with chiral monomeric and dimeric macrocyclic [H_4]salen ligands derived from (1*R*,2*R*)-(−)-1,2-diaminocyclohexane and (1*R*,2*R*)-(−)-1,2-diphenyl-1,2-diaminoethane with trigol-bis(aldehyde). A variety of aldehydes were found to be suitable substrates with nitromethane in the presence of chiral macrocyclic [H_4]salen complexes **1**−**6** for asymmetric nitroaldol reaction at RT. Excellent yields (98% with respect to the aldehyde) of β-nitroalcohols with high enantioselectivity (ee, ∼99%) were achieved in the case of 2-fluorobenzaldehyde in ∼20 h with the use of chiral mononuclear and dinuclear macrocyclic Cu(II) salen complexes **2** and **5**. Both chiral mononuclear and dinuclear macrocyclic [H_4]salen catalysts **2**- and **5**-mediated nitroaldol processes are recyclable (up to eight cycles with no significant loss in its performance).



KEYWORDS: enantioselective, chiral Cu(II) macrocyclic complexes, chiral β-nitroalcohols, aldehydes, recyclable

INTRODUCTION

The asymmetric nitroaldol reaction has emerged as a powerful synthetic tool for the stereoselective C−C bond forming reaction.[1,2] The resulting β-hydroxy nitroalkanes are important building blocks to prepare biologically active compounds,[3−5] such as β-amino alcohol derivatives chloroamphenicol, ephedrine, sphingosine, and α-hydroxycarboxylic acid; and β-receptor agonists, namely, (−)-denopamine, (−)-arbutamine, (*S*)-metoprolol, (*S*)-propranolol, (*S*)-pindolol etc. Because of the usefulness of these reaction products in organic synthesis, Shibasaki et al. have reported for the first time a series of heterobimetallic catalysts that have proved to be effective for asymmetric Henry reactions.[6−8] Since then, various metal[9−39,63,68]-based catalysts with chiral ligands (namely, BINOL,[15−21] aminoalcohol,[22,41,42] bis(oxazoline),[43−48] bis(thiazoline),[49−52] bis(imidazoline),[53] sulfonylamine,[54−57] salen,[23,24,58,59] Schiff bases,[27,28,30,35,60] thiols,[61] thiophene,[31] bipiperidine,[10] aminopyridine,[62] oxabispidine,[29] and organocatalyst[39,40]) have been reported for asymmetric Henry reaction under homogeneous systems. Among them, chiral copper complexes with chiral bidentate and polydentate ligands[8,10,27] were found to be most successful in catalyzing the nitroaldol reaction with moderate to high enantioselectivity. In addition, chiral copper complexes are inexpensive and show low toxicity, and the reaction can occur under mild reaction conditions. In addition, in general, the addition of organic/inorganic additives is not required with these catalysts, barring a few reports in which the presence of a base as an additive is essential for achieving good activity and selectivity.

Another important aspect of asymmetric catalysis is the recycling of the expensive chiral catalysts.[67,27,28] In this direction, few examples of effective recovery of chiral metal complexes have been evidenced in the literature under homogeneous and heterogeneous reaction conditions, but they demand major modification in the structure of the catalyst. In addition, chiral Lewis acid catalysts and chiral Brønsted bases, such as guanidine bases and modified cinchona alkaloids, have also been used to promote the asymmetric nitroaldol reaction, but with limited success in terms of choice of the substrates.

In continuation of our earlier work on the asymmetric nitroaldol reaction using chiral La−Li−BINOL[21] and Cu(II) aminoalcohol[22] supported complexes on mesoporous material and to overcome some of the limitations associated with the existing methodologies, we report the synthesis of new chiral monomeric **1**′,**2**′ and dimeric **4**′, **5**′ macrocyclic [H_4]salen ligands with a flexible trigol linker at the 5,5′ position (Figure 1). The in situ-generated complexes **2** and **5** of these ligands (**2**′ and **5**′) in combination with different copper salts were used as catalysts for asymmetric nitroaldol reaction of various aromatic and aliphatic

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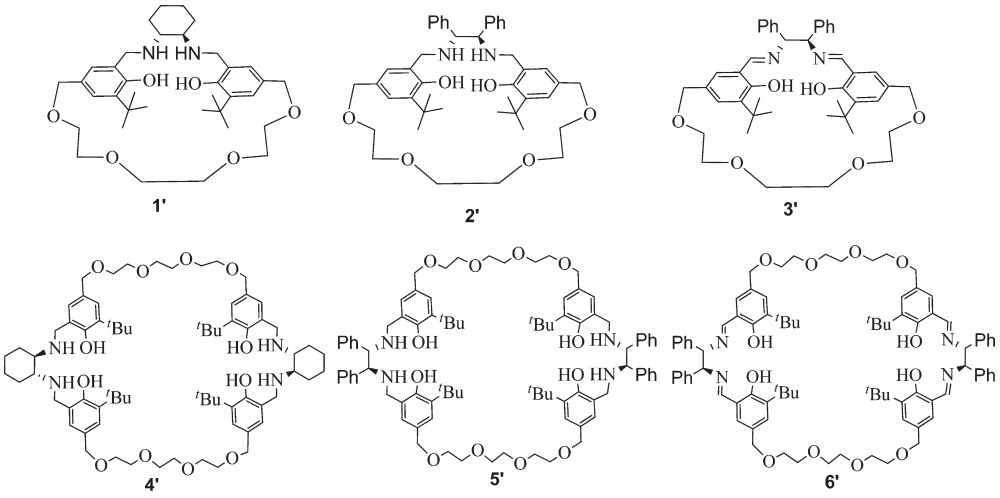
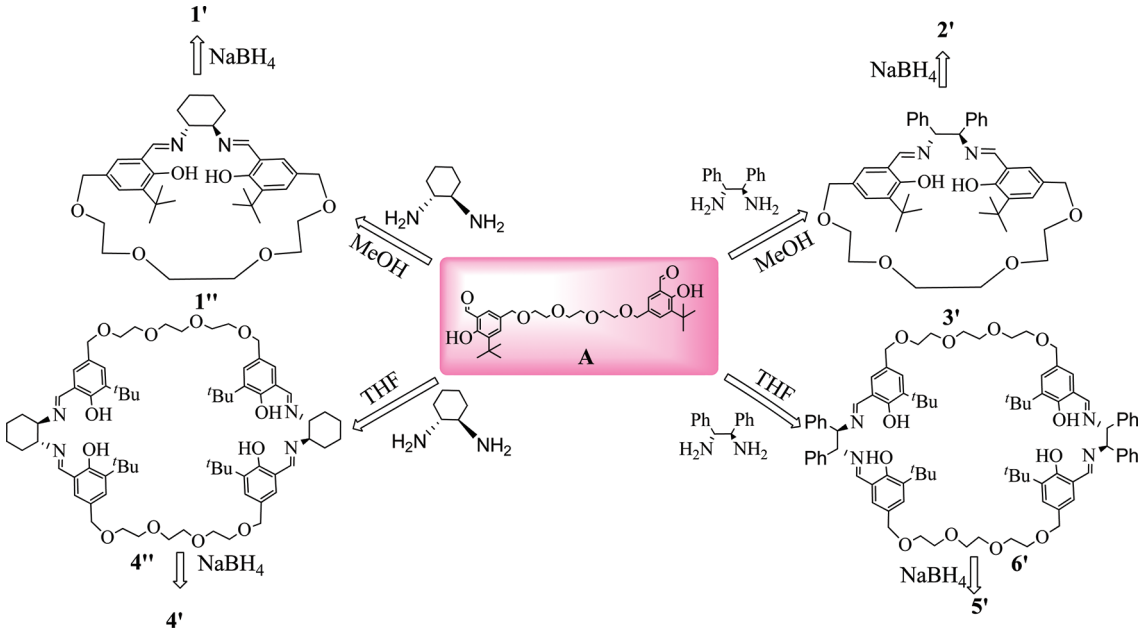


Figure 1. Structure of macrocyclic ligands **1′**−**6′**.

Scheme 1. General Scheme for the Synthesis of Ligands 1′−6′



aldehydes with nitromethane in the absence of an external base at RT. The in situ-generated complexes of **2′** and **5′** with $Cu(OAc)_2 \cdot H_2O$ (0.75 equiv for **2′** and 1.4 equiv for **5′**) efficiently catalyzed the nitroaldol reaction to give the product in excellent yield (98%) and enantioselectivity (ee, ∼99%). For the sake of comparison, nonreduced macrocyclic salen ligands **3′** and **6′** were also used as precatalysts for the nitroaldol of 2-*F*-benzaldehyde under the same reaction conditions; however, the results were inferior in terms of both product yield and ee as compared with their hydrogenated ligand counterparts. Incidentally, both complexes **2** and **5** are recoverable and recyclable several times without any apparent loss in their performance. Complex **2** was further used to catalyze asymmetric nitroaldol of 3-MeO-benzaldehyde (1 g scale) to synthesize α1-adrenergic receptor agonist (*R*)-phenylephrine in 85% yield and 94% ee.

RESULTS AND DISCUSSION

Chiral macrocyclic ligands **1′**−**6′** (Scheme 1) were prepared in two easy steps by condensation of trigol-bis(aldehyde) **A** with a chiral diamine, namely, (1*R*,2*R*)-(−)-1,2-diaminocyclohexane and (1*R*,2*R*)-(−)-1,2-diphenyl-1,2-diaminoethane, and hydrogenation of the condensed product (**3′** and **6′**) with sodium borohydride in overall excellent yield.[26] The characterization data of all the ligands are given in the Supporting Information.

Ligands **1′**−**6′** (15 mol %) in combination with $Cu(OAc)_2 \cdot H_2O$ (10 mol %) were first evaluated for their efficacy as catalysts in the enantioselective nitroaldol reaction of 2-*F*-benzaldehyde (as a representative substrate) with nitromethane at RT in EtOH + CH_2Cl_2 in a 1:1 solvent mixture (due to solubility reasons) (Table 1). The results are indicative of the superiority of the catalysts derived from ligands having a diphenyldiamine collar (**2′** and **5′**), which yielded the product β-nitroalcohols in excellent yield

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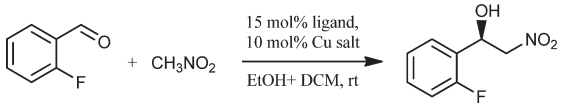
Table 1. Screening of in Situ-Generated Chiral Macrocyclic Salen Complexes with Ligands 1′−6′ and $Cu(OAc)_2 \cdot H_2O$ As the Source of Metal at RT[a]

entry	ligands	time (h)	yield[b] (%)	ee[c] (%)
1	1′	20	85	81
2	2′	20	90	97
3	3′	20	89	50
4	4′	15	64	56
5	5′	15	94	96
6	6′	15	75	45

[a] All reactions were carried out with 0.2 mmol of 2-*F*-benzaldehyde and 10 equiv of nitromethane in 0.3 mL of EtOH + 0.3 mL of DCM with 15 mol % of ligand, 10 mol % $Cu(OAc)_2 \cdot H_2O$ at RT for 20 h. [b] Isolated yield. [c] Determined by HPLC (Chiralcel AD).

Table 2. Variation of Metal Ion Sources in Asymmetric Nitroaldol Reaction[a]



entry	ligand	metal source	time (h)	yield[b] (%)	ee[c] (%)
1 (2)	2′ (5′)	$Cu(OAc)_2 \cdot H_2O$	20 (15)	90 (96)	97 (96)
3 (4)	2′ (5′)	$Cu(OTf)_2 \cdot H_2O$	20 (15)	20 (30)	35 (27)
5 (6)	2′ (5′)	$CuCl_2$	20 (15)	45 (55)	3 (5)
7 (8)	2′ (5′)	CuI_2	20 (15)	40 (45)	31 (35)

[a] All reaction were performed with 0.2 mmol of 2-*F*-benzaldehyde and 10 eqv of nitromethane with 15 mol % of ligand, 10 mol % $Cu(OAc)_2 \cdot H_2O$ in 0.3 mL EtOH+ 0.3 mL of DCM at RT. [b] Isolated yield. [c] Determined by HPLC (Chiralcel AD).

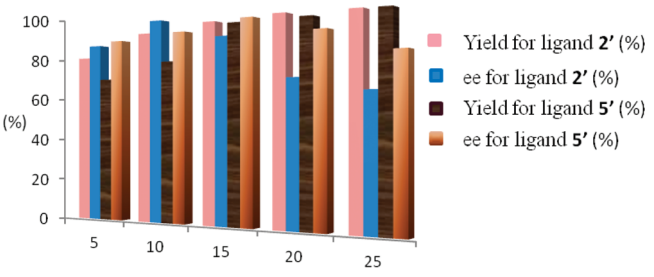


Figure 2

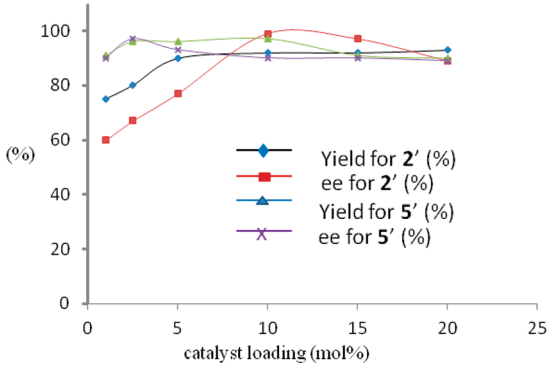
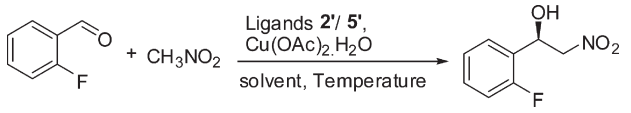


Figure 3

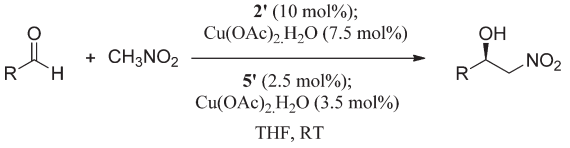
Table 3. Optimization of Reaction Conditions of Asymmetric Nitroaldol Reaction of 2-*F*-Benzaldehyde[a]



entry	ligands	solvents	temp °C	yield[b] (%)	ee[c] (%)
1 (2)	2′ (5′)	THF	0	35 (40)	90 (88)
3 (4)	2′ (5′)	THF	10	52 (60)	91 (89)
5 (6)	2′ (5′)	THF	RT (27)	92 (98)	> 99 (98)
7 (8)	2′ (5′)	THF	40	95 (97)	83 (80)
9 (10)	2′ (5′)	toluene	RT	85 (80)	92 (88)
11 (12)	2′ (5′)	acetonitrile	RT	87 (67)	90 (84)
13 (14)	2′ (5′)	EtOH + DCM	RT	92 (96)	98 (98)

[a] All reactions were carried out with 0.2 mmol of 2-*F*-benzaldehyde and 10 equiv of nitromethane in 0.6 mL of solvent for 20 and 15 h. [b] Isolated yield. [c] Determined by HPLC (Chiralcel AD).

Table 4. Variation of Different Aldehydes in Asymmetric Nitroaldol Reaction[a]



entry	R	yield[b] (%)	ee[c] (%)
1 (2)	Ph	84 (90)	93 (95)
3 (4)	4-NO_2−Ph	95 (90)	93 (89)
5 (6)	2-*F*-Ph	92 (98)	> 99 (98)
7 (8)	4-*F*-Ph	85 (90)	92 (90)
9 (10)	4-*Br*-Ph	85 (85)	95 (92)
11 (12)	3-*Cl*-Ph	78 (81)	95 (89)
13 (14)	4-*Cl*-Ph	84 (85)	94 (88)
15 (16)	2-MeO-Ph	85 (87)	94 (90)
17 (18)	3-MeO-Ph	90 (85)	94 (92)
19 (20)	2-Me-Ph	45 (47)	97 (90)
21 (22)	1-naphthyl	91 (92)	93 (88)
23 (24)	2-naphthyl	90 (91)	96 (89)
25 (26)	*n*-hexyl	90 (90)	93 (93)
27 (28)	cyclohexyl	80 (85)	90 (95)
29 (30)	thiophene-2-carboxyl	81 (83)	92 (78)
31 (32)	pyridine-2-carboxyl	95 (96)	15 (3)
33 (34)	α-methyl-*trans*-cinnamyl	75 (80)	97 (91)

[a] All reactions were performed with 0.2 mmol of aldehydes and 10 equiv of nitromethane at RT for about 20 h for catalyst **2** and for 15 h for catalyst **5**. [b] Isolated yield. [c] Determined by HPLC (Chiralcel AD, AD−H,OD,OD−H).

(90−94%) and ee (96−97%) (entries 2, 5) over their 1,2-diaminocyclohexyl counterparts 1′ and 4′, which gave product yields of 85−64% and ee's of 81−56% (entries 1, 4). A reason for this difference in enantioselectivity in the product can be visualized by comparing the energy-minimized structures of the copper complexes derived from ligands 1′, 2′, 4′, and 5′ (structures are given in the Supporting Information) which

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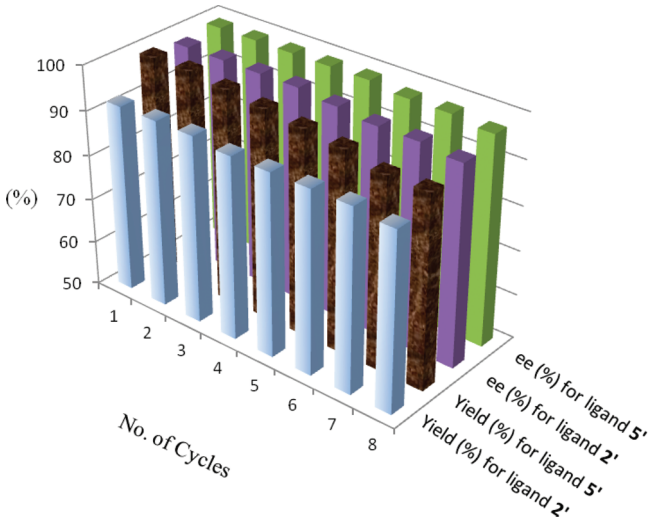
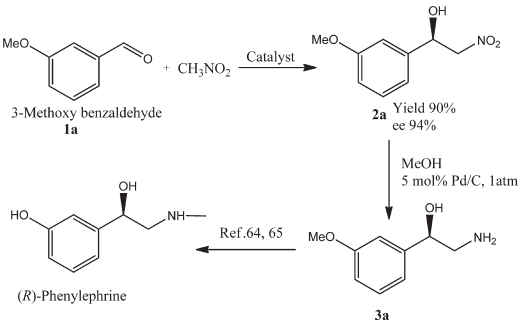
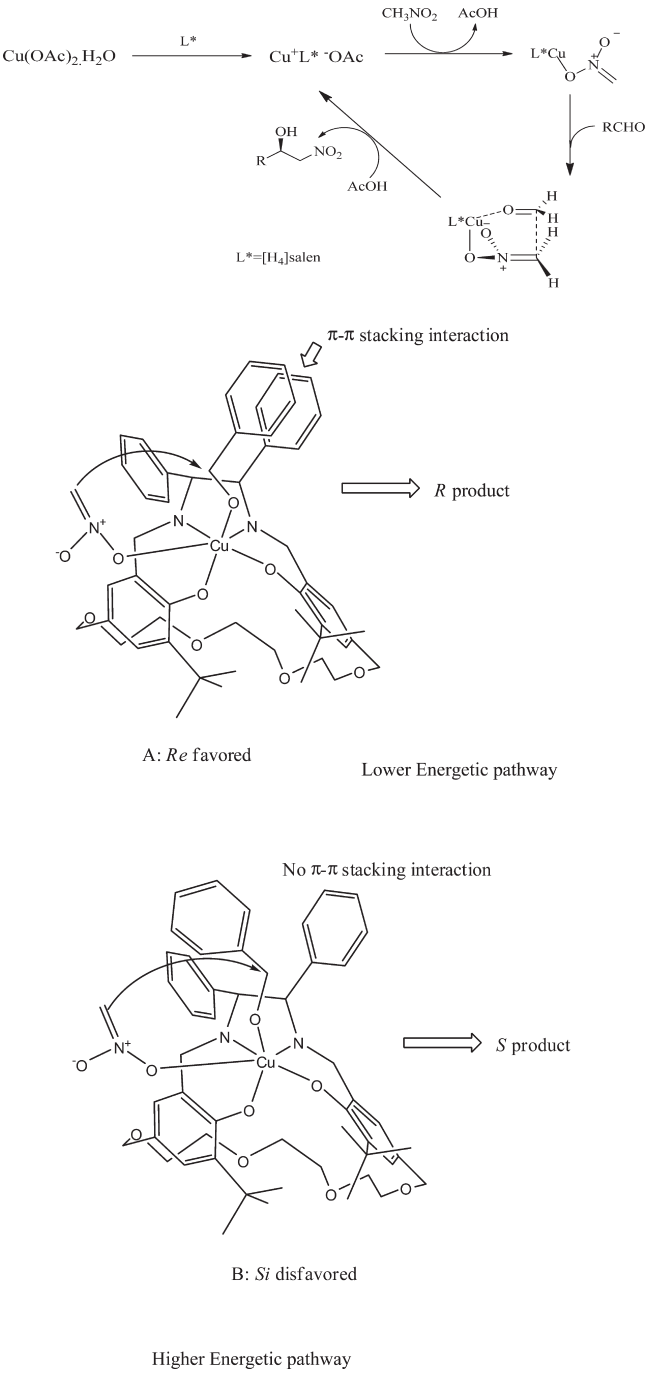


Figure 4

Scheme 2



Scheme 3



display steric crowding around the catalytic copper center by the phenyl groups in the complexes **2** and **5**.

Mechanistically speaking, the nitroaldol reaction requires both acidic center (to activate aldehyde) and a basic center (to abstract proton from nitroalkane). In our complexes, although the role of a Lewis acid is played by copper, the counteranions may facilitate the abstraction of a proton from the nitroalkane to generate a nitronate ion, which acts as a nucleophile in the nitroaldol reaction. Hence, we picked better performing ligands **2′** and **5′** as catalyst precursors with different metal salts in the nitroaldol of 2-*F*-benzaldehyde under the above-mentioned reaction conditions. The results in Table 2 show that $Cu(OAc)_2 \cdot H_2O$ performed best among the different copper salts used (entries 1, 2). The performance of the other catalysts clearly follow the order of increasing basicity of the counterion ($I^- < Cl^- < TfO^- < AcO^-$) (Table 2).

Conventionally, whenever a catalytically active metal complex is generated in situ by the addition of an organic ligand and a metal salt, their molar ratio markedly affects the activity and enantioselectivity of the target reaction. This is possibly due to the varying degree of complexation occurring in the solution during catalysis, as against the use of a preformed catalyst. For this reason, it is important to vary the ligand and metal salt ratio. For the present study, we used fixed amounts of ligand **2′** (15 mol %) or **5′** (10 mol %) with varying amounts of $Cu(OAc)_2 \cdot H_2O$ (5−25 mol %) (Figure 2) to catalyze nitroaldol of 2-*F*-benzaldehyde with nitromethane at RT. It is understood from the Figure that in the case of monomeric ligand **2′** (15 mol %), the activity (92%) and enantioselectivity (98%) are highest when $Cu(OAc)_2 \cdot H_2O$ is 10 mol %, indicating that a slightly higher concentration of ligand is essential for its complete metalation in solution. An increase in the metal content caused a reduction in the ee of the product, but with some increase in the product yield. Possibly the excess free metal is also working as a catalyst that has produced the racemic product, and thus, there is a drop in the overall enantioselectivity. A similar trend was observed with dimeric ligand **5′** (10 mol %), in which 15 mol % of $Cu(OAc)_2 \cdot H_2O$ was found to give the best results in terms of product yield (96%) and ee (96%).

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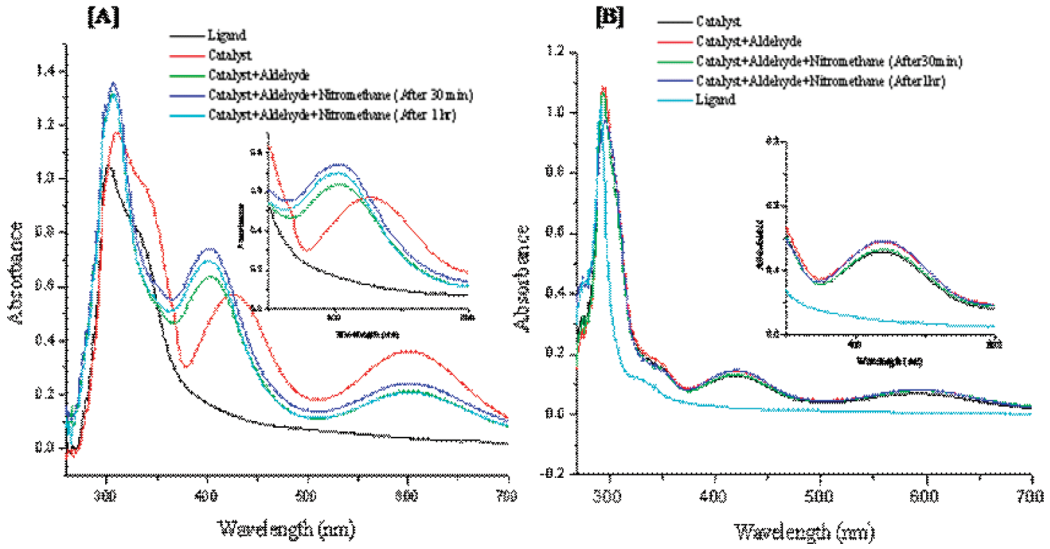

Figure 5. Stepwise UV−visible spectra obtained with a 1 mM solution of THF in the presence of Cu $(OAc)_2 \cdot H_2O$, aldehyde, and nitromethane: (A) ligand **2′** and (B) ligand **1′**.

Having achieved the right ligand-to-metal ratio, we next varied the ligand loading for the nitroaldol of the 2-*F*-benzaldehyde under the same reaction conditions. Accordingly, the loading of ligand **2′** was studied over 2.5−20 mol % while maintaining the optimized ratio of $Cu(OAc)_2 \cdot H_2O$ (Figure 3), in which 10 mol % was found to be optimal in terms of the product yield (92%) and ee (99%). Similarly, the loading of ligand **5′** (having two $[H_4]$salen units) was studied over 1−10 mol % for the same reaction and under similar reaction conditions. The results suggested that 2.5 mol % loading of **5′** with the corresponding loading of $Cu(OAc)_2 \cdot H_2O$ 3.5 mol % gave the best yield (96%) of β-nitroalcohols with an ee of (98%).

The above optimized catalyst loadings were then tested for their efficacy in different solvents: acetonitrile, toluene, and THF (Table 3). Among these, THF turned out to be the most suitable solvent for this reaction, with both ligands **2′** and **5′** (entries 5, 6). The reaction was further subjected to temperature variation (entries 1−8). The data suggest that RT (27 °C) is the optimum temperature to carry out nitroaldol reaction (entries 5, 6) because a positive or negative deviation from this temperature had an adverse effect on the results, particularly on enantioselectivity.

The above optimized reaction conditions (Table 3; entries 5, 6) was further used to carry out nitroaldol reaction of a variety of aldehydes, including aromatic, heteroaromatic, aliphatic, and $\alpha-\beta$-unsaturated aldehydes; namely, benzaldehyde, 4-nitrobenzaldehyde, 2-fluorobenzaldehyde, 4-fluorobenzaldehyde, 4-bromobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2-MeO-benzaldehyde, 3-MeO-benzaldehyde, 2-Me-benzaldehyde, 1-naphthaldehyde, 2-naphthaldehyde, *n*-hexanal, cyclohexanal, thiophene-2-carboxaldehyde, pyridine-2-carboxaldehyde, and α-methyl-*trans*-cinnamaldehyde. In all the cases, the present protocol gave the desired nitoaldol products in high to excellent yield (78−98%), except for the substrate 2-Me-benzaldehyde (Table 4; entries 19, 20), with which only a moderate yield (∼47%) of the product was achieved. However, excellent enantioselectivity was achieved in most cases, irrespective of the aromatic or aliphatic nature of the aldehyde, with the exception of the substrate pyridine-2-carboxaldehyde, for which the ee of the product was 15 and 3% with ligand systems **2′** and **5′**, respectively (Table 4; entries 31, 32). Possibly the presence of the coordinating nitrogen of pyridine-2-carboxaldehyde significantly altered the transition state responsible for product formation.

Overall, the in situ-generated copper catalyst from monomeric ligand **2′** (10 mol %) gave slightly better performance, particularly in terms of enantioselectivity, than with dimeric ligand **5′** (2.5 mol %), but the catalyst generated in situ with dimeric ligand **5′** was found to be nearly 2 times more active than its monomeric version; thus, some amount of cooperation between the two $[H_4]$salen units cannot be ruled out.

Incidentally, both monomeric and dimeric ligand systems were found to generate active catalysts, which were recovered and recycled eight times without any noticeable loss in their activity and enantioselectivity (Figure 4).

A gram scale nitroaldol reaction of 3-MeO-benzaldehyde with nitromethane gave the corresponding nitroalcohol in high ee (94%) and yield (90%) with ligand system **2′** under the optimized reaction conditions. The nitroaldol product gave (*R*)-phenylephrine in three steps in overall 85% yield with 94% ee (Scheme 2).

On the basis of the experimental results, a working model can be proposed for the possible transition state (Scheme 3). The asymmetric induction mechanism is proposed on lines similar to those reported by Feng et al.[26] In the catalytic cycle, nitromethane is activated through coordination of its nitro group to soft metal. The acetate ion acted as a base to abstract a proton from the thus activated nitromethane to generate an active nucleophile, which attacks the activated benzaldehyde (by the copper center) to give the nitroaldol product. On the basis of the observed absolute configuration of the product, a possible transition state with hexacoordinated copper metal center was generated by energy minimization. Transition A is indicative of $\pi-\pi$ stacking interaction between the substrate and catalyst phenyl groups making the Re face attack of the nucleophile to the carbonyl of the benzaldehyde more favorable energetically than the Si face attack, which will lack $\pi-\pi$ stacking interactions, as shown in transition state B. To get an experimental clue for the validation of transition state B, the nitroaldol reaction of benzaldehyde was monitored by UV−vis spectroscopy using in situ-generated catalysts from ligands **1′**

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(having no phenyl group on the diamine collar) and **2′** (having two phenyl groups on the diamine collar) under the same reaction conditions (Figure 5). A significant blue shift of 24.14 nm (LMCT) from complex **2** (Figure 5A) was observed on the addition of substrate benzaldehyde, but no such shift was observed with complex **1** (Figure 5B), indicating the probable $\pi-\pi$ stacking interaction between the phenyl groups of catalyst **2** and benzaldehyde.

Catalyst recycling studies were carried out by precipitating catalysts **2** and **5** (with 5 mmol of 2-*F*-benzaldehyde) by the addition of hexane to the postcatalytic reaction mixture. To the recovered catalyst, fresh substrates and reactants were supplied in a manner similar that in the case of fresh catalyst. The data for eight-time use of the same catalyst is given in Figure 4. The activity of the recycled catalysts slightly decreased upon successive use, possibly due to some physical loss of the catalyst but enantioselectivity remained nearly the same until the last run, suggesting that these catalysts are fairly stable under the reaction conditions. The recyclability of this catalytic system, particularly with dinuclear catalyst **5**, shows a fairly high cumulative turnover number (~305) reported so far for this reaction.

CONCLUSION

We have designed new chiral monomeric and dimeric macrocyclic [H_4] salen ligands for copper-catalyzed asymmetric nitroaldol reaction. This catalyst system gave synthetically valuable β-nitroalcohols with excellent enantioselectivities and high yield for a range of aldehydes, including aromatic, aliphatic, heteroaromatic, and α, β-unsaturated aldehydes. The chiral mononuclear and dinuclear [H_4]salen Cu(II) complexes also are the most efficient recyclable system reported so far in the literature. Both the catalysts were recovered after their first use and recycled eight times effectively. (*R*)-Phenylephrine, an α1-adrenergic receptor agonist receptor was prepared in very good yield and excellent optical purity by the nitroaldol of the commercially available 3-methoxybenzaldehyde in three steps.

EXPERIMENTAL SECTION

General. Copper acetate monohydrate, copper triflet, copper chloride, copper iodide, benzaldehyde, 2-methoxybenzaldehyde, 3-methoxybenzaldehyde, 4-fluorobenzaldehyde, 2-fluorobenzaldehyde, 4-nitrobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 1-naphthaldehyde, 2-naphthaldehyde, hexanal, cyclohexanal, α-methyl-*trans*-cinnamaldehyde, trigol, sodium borohydride, nitromethane, (*1R,2R*)-(−)-1,2-diaminocyclohexane, and (1*R*,2*R*)-(−)-1,2-diphenyl-1,2-diaminoethane were purchased from Aldrich Chemicals and used as received. 2-Methylbenzaldehyde was purchased from Merck. All the solvents were dried by standard procedures,[32] distilled, and stored under nitrogen. ^{1}H NMR spectra were obtained with a Bruker F113 V spectrometer (200 MHz) and are referenced internally with TMS. FT-IR spectra were recorded on Perkin-Elmer Spectrum GX spectrophotometer in KBr window. High-resolution mass spectra were obtained with a LC−MS (Q-TOFF) LC (Waters), MS (Micromass) instruments. For the product purification, column chromatography was performed using silica gel 60−200 mesh purchased from s. d. Fine-Chem Limited Mumbai (India). Enantiomeric excesses (ee) of the products were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD, OD, AD-H, OD-H columns with 2-propanol/hexane as eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter (Rudolph Instruments). Synthesis of chiral macrocyclic salen Rligands **1″**, **3′**, **4″** and **6′** was carried out by our reported procedure.[66]

Procedure for Reduction of Schiff Base by $NaBH_4$. Chiral monomeric and dimeric macrocyclic salen ligands **1″**, **3″**, **4″**, and **6′** (1 mmol) were dissolved in 45 mL of dry methanol and 5 mL of dichloromethane. $NaBH_4$ (4 mmol) was added portion-wise in four steps. Reaction was monitored by TLC. After completion of the reaction, the solvents were completely evaporated under reduced pressure. Then the reaction mass was washed by water and extracted with dichloromethane and dried by anhydrous Na_2SO_4. Further purification was done by flash column chromatography (EtOAc/hexane = 1:4) on a neutral alumina column.

Typical Experimental Procedure for Nitroaldol Reaction. Chiral monomeric macrocyclic [H_4]salen ligand **2′** (0.02 mmol) and dimeric macrocyclic [H_4]salen ligand **5′** (0.005 mmol) and $Cu(OAc)_2.H_2O$ (0.015 mmol) for monomeric macrocyclic and 0.007 mmol for dimeric macrocyclic ligands were added to a screw-capped vial containing a stir bar. Anhydrous THF (0.6 mL) was then added, and a clear green solution formed under stirring. The resulting solution was stirred for 45 min at RT. To the resulting solution nitromethane (1.26 mL, 2.0 mmol, 10 equiv) and various aldehydes (0.2 mmol, 1 equiv) were added. After stirring for the specified time as given in Table 4, the volatile components were removed under reduced pressure, and the crude product was purified by flash column chromatography.

Recycling of the Catalyst 2, 5. At the end of the catalytic run (checked on TLC), the solvent was completely removed from the reaction medium of mononuclear and dinuclear macrocyclic [H_4]salen complexes **2** and **5** under reduced pressure. The residue was extracted with hexane to remove the reactants. The remaining solid was further washed with hexane (10 mL), dried under reduced pressure for 1−2 h, and used as recovered catalysts for recycling experiments of an asymmetric nitroaldol reaction of 2-fluorobenzaldehyde as a representative substrate with nitromethane as the nucleophile.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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