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Chiral Cu(II) Complexes as Recyclable Catalysts for Asymmetric Nitroaldol (Henry) Reaction in Ionic Liquids as Greener Reaction Media

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Abstract Chiral Cu (II) complexes generated in situ from C_2-symmetric chiral secondary bis-amines **1′–4′** based on 1,2-diaminocyclohexane structure having H, *t*-Bu and Cl substituents at 3, 3′, 4, 4′ and 5, 5′ with copper acetate. They were used as catalysts for an environmentally benign protocol for highly enantioselective nitroaldol reaction of various aldehydes with nitromethane in the presence of different ionic liquids as a greener reaction medium at 0 °C. Excellent yields (up to 90% with respect to aldehyde) of *β*-nitroalcohols with high enantioselectivity (*ee*, up to 94%) was achieved when [emim]BF_4 was used as ionic liquid. The present ionic liquid mediated nitroaldol protocol is recyclable (up to five cycles) with no significant loss in its performance.

Keywords Asymmetric nitroaldol reaction · Cu(II) complex · Chiral catalysis · Ionic liquid · Recyclable

1 Introduction

The metal complex catalyzed enantioselective nitroaldol (Henry) reaction is an attractive and quite powerful method in asymmetric synthesis of charily pure nitroalcohols, which are valuable precursors for a wide range of synthetic targets including (*R*)-denopamine and (*R*)-arbutamine. The nitro group in the product can further be conveniently converted into several other functionalities to give synthetically and biologically important bi-functional compounds [1]. In particular, reduction of *β*-hydroxynitroalkanes gives ready access to *β*-amino alcohols, which are now extensively used as chiral ligands in asymmetric catalysis and as important building blocks for the synthesis of natural products pharmaceuticals [2]. In spite of many applications, the catalytic enantioselective version of nitroaldol reaction is relatively less explored as compared to its aldol counterpart due to the non-availability of enantioselective catalysts. Shibasaki has reported the first asymmetric version of nitroaldol reaction in 1992 [3–11]. Since then various metals [3–7, 12–17] and non-metal based catalysts [18, 19] have been investigated for the asymmetric nitroaldol reaction with chiral ligands such as BINOL [5, 10, 20], amino alcohol [21, 22], bis(oxazoline) [23–31], bis(thiazoline) [32], bis(imidazoline) [33–35], sulfonyl diamine [36], salen [37–40], Schiff bases [41–50], thiols [51], thiophene [52], bipiperidine [53–57], aminopyridine [58], oxabispidines [59]. The Cu-catalyzed nitroaldol reaction is however most explored due to its inexpensive and less toxic nature, besides the fact it has demonstrated high catalytic activity under homogeneous reaction conditions [29, 30, 34, 48, 53, 60–65]. Mechanistically, nitroaldol reaction requires both acidic and basic sites for the activation of substrate. For this reason a variety of bases *viz.,* potassium hydroxide [66, 67], cetyltrimethyl ammonium hydroxide [68], sodium carbonate [61], triethyl amine [61], 2,6-lutidine [36], pyridine [36] and aromatic imines [29] have found application as additives to improve the efficiency of typical acidic metal complexes based catalysts in nitroaldol reactions. Although good to

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excellent optical purities were obtained for β-nitroalcohols, most of these methods suffer from limitations, such as relatively high catalyst loading, low reaction temperatures, multistep synthetic procedures for ligand preparation and non-recyclability of the catalysts. As the chiral catalyst are very expensive, their recyclability is an important aspect for economical and scaling-up point of view. There are only few reports [68] available on asymmetric nitroaldol reaction where catalyst can be recycled but demand major modification in the structure of the catalyst.

To overcome this problem, ionic liquids are currently viewed as future reaction media in chemical industry as an eco-friendly alternative to the conventionally used hazardous organic solvents [69, 70]. It has also been observed that switching over to an ionic liquid from traditional organic solvents often results in a significant improvement in reactivity and selectivity of a catalytic system [71–74]. Moreover, ionic liquids also facilitate catalyst recyclability. Among the room temperature ionic liquids (RTILs), 1,3-dialkylimidazolium salts have emerged as leading contenders suitable for multi-phase catalysis for various organic transformations. Herein, we are reporting for the first time the use of ionic liquid as greener media for asymmetric nitroaldol reaction of various aldehyde with nitromethane using in situ generated chiral Cu (II) complexes by the reaction of copper acetate with C_2-symmetric chiral secondary bis-amines based on chiral 1,2-diaminocyclohexane structure having H, *t*-Bu and Cl substituent at 3, 3′, 4, 4′ and 5, 5′ positions of phenyl groups. Excellent yield with high enantiomeric excess (ee, 94%) of chiral β-nitrolcohol was achieved when [emim]BF_4 was used as ionic liquid with added advantage of catalyst recyclability.

2 Experimental

2.1 Materials and Methods

Solvents were dried according to the standard procedures and distilled prior to their use. Most reagents and ionic liquids were purchased from Aldrich or Across Chemicals and were used as received. ^{1}H NMR spectra were recorded at 200 MHz (Varian) in $CDCl_3$ as solvent and tetramethylsilane was used as an internal standard. The enantiomeric excess was determined by HPLC (Agilent 1200 Series) on Chiralcel OD-H column.

2.2 Synthesis of Chiral Ligands **1′–4′**

The chiral ligands **1′–4′** (Fig. 1) were synthesized by the modified reported procedure [46, 48, 75]. In a 100 mL round bottom flask aldehyde/substituted aldehydes (1 mmol) was taken in ethanol (20 mL), to which (*1S*, *2S*)-(+)-1,2-diaminocyclohexane (0.5 mmol) was added at 0 °C. The reaction mixture was then stirred at this temperature for 1 h then refluxed for 10–12 h. After completion of the reaction (checked on TLC), it was cooled to room temperature and 4 mmol of sodium borohydride was slowly added with stirring. The resulting solution thus obtained was refluxed for 10 h. Subsequently, the solvent was removed on rotaevaporator and the resulting mass was washed with distilled water and extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulphate and evaporated to get the desired product as viscous solid. The characterization of the ligands was accomplished by different physicochemical methods, which matched well with the earlier reports [46, 48, 75].

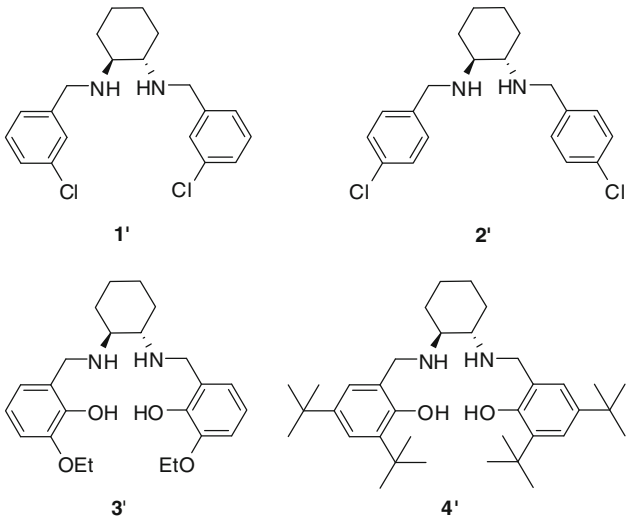


Fig. 1 Structure of the chiral ligands (**1′–4′**)

2.2.1 *(1S,2S)-N,N-Bis(3-Chlorobenzyl)Cyclohexane-1, 2-Diamine (**1′**)*

Pale yellow solid, m.p. = 60–64 °C. ^{1}HNMR (200 MHz, $CDCl_3$): δ = 0.89–1.76 (m, 8H), 1.88 (brs, 2H), 2.14–2.26 (m, 2H), 3.57 (d, J = 13 Hz, 4H), 7.14–7.40 (m, 8H). $[\alpha]_D^{25}$ = +75 (c = 1, CH_2Cl_2). IR: 3300, 3045, 2919, 2840, 1590, 1560, 1450, 1220, 1110, 860, 770 cm^{-1}.

2.2.2 *(1S,2S)-N,N-Bis(4-Chlorobenzyl)Cyclohexane-1, 2-Diamine (**2′**)*

Colourless oil. ^{1}HNMR (200 MHz, $CDCl_3$): δ = 0.90–1.70 (m, 8H), 1.80 (brs, 2H), 2.15–2.25 (m, 2H), 3.57(d, J = 13 Hz, 4H) 7.10–7.35 (m, 8H). $[\alpha]_D^{25}$ = +60 (c = 1, CH_2Cl_2). IR: 3280, 3010, 2900, 2815, 1575, 1460, 1410, 1200, 1135, 810, 765 cm^{-1}.

2.2.3 6,6′-(1S,2S)-Cyclohexane-1,2-Diylbis(Azanediyl) Bis(Methylene)Bis(2-Ethoxyphenol) (3′)

Light yellow oil. ^{1}HNMR (200 MHz, $CDCl_3$): $\delta = 1.20$ (m, 4H), 1.41 (t, $J = 7$, 6H), 1.63 (m, 4H), 2.07 (m, 2H), 2.35 (brs, 2H), 3.80 (d, $J = 13$, 4H), 3.94 (q, $J = 7$ Hz, 4H), 6.67–7.56 (m, 6H), 11.2 (brs, 2H). $[\alpha]_D^{25} = +45$ (c = 1, CH_2Cl_2) IR: 3200, 2910, 1560, 1530, 1480, 1410, 1260, 1220, 1135, 1077 s, 945, 900, 834 cm^{-1}.

2.2.4 6,6′-(1S,2S)-Cyclohexane-1,2-Diylbis(Azanediyl) Bis(Methylene)Bis(2,4-Di-Tert-Butylphenol) (4′)

White solid mp = 142–145 °C. ^{1}HNMR (200 MHz, $CDCl_3$): $\delta = 1.68$–1.02 (m, 44H), 2.14 (m, 2H), 2.42 (m, 2H), 3.94 (d, $J = 13$, 4H), 6.90–7.20 (m, 4H), 10.70 (brs, 2H). $[\alpha]_D^{25} = +34$ (c = 0.5, CH_2Cl_2). IR: 3270, 2990, 1570, 1540, 1455, 1430, 1240, 1210, 1145, 1090 s, 930, 890, 800 cm^{-1}.

2.3 General Procedure for Asymmetric Nitroaldol Reaction

Chiral ligands (**1′**–**4′**) (0.06 mmol, 12 mol.%) and $Cu(OAc)_2{\cdot}H_2O$ (10.0 mg, 0.05 mmol, 10 mol.%) were mixed together in 0.125 mL absolute ethanol and the resulting blue colour solution was stirred for 30–45 min. at room temperature. To this solution 250 mg ionic liquid was added and the resulting mixture was transferred into a double wall jacketed glass reactor. To this solution aldehyde (1 mmol) was added and allowed the mixture to be stirred further for 15–20 min. The resulting solution was brought to 0 °C and nitromethane (5.0 mmol) was slowly added in an interval of 1 h by using a syringe. The progress of the reaction was checked on TLC. After 30 h the product was separated using repetitive washing of the reaction mixture (five times) with hexane ethyl acetate 4:1 mixture. After complete washing, the ionic liquid containing a copper complex was dried under vacuum and stored in desiccator for its use in subsequent catalytic runs. The blue solution was directly used for catalytic reaction, however the solvent from the blue solution was evaporated and the residue was washed several times with solvent ether and dried under vacuum. The blue complex thus obtained was used as catalyst under the identical reaction conditions in order to compare the catalytic reactions carried out with in situ generated catalysts. The enantiomeric excess (ee) of the product was determined by HPLC using OD-H column with 2-PrOH/hexane (90:10) as eluent. HPLC traces of products were compared with the respective racemic samples. Analytical data of a few chiral β-hydroxy nitroalkanes from various aldehydes are as follows and all the values well matched with the reported literature.

2.3.1 (R)-2-Nitro-1-Phenylethanol

Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.89$ (br s, 1H), 4.39–4.43 (m, 2H), 5.34 (m, 1H), 7.13–7.33 (m, 5H; ArH) ppm; ^{13}CNMR (50 MHz, $CDCl_3$): $\delta = 69.00$, 79.19, 125.10, 128.94, 129.01, 138.11 ppm. $[\alpha]_D^{25} = -41.5$ ($c = 1.0$, CH_2Cl_2). HPLC analysis (Chiracel OD-H column, 0.8 mL/min, n-hexane/i-PrOH 90:10, $\lambda = 210$ nm). Retention times: 21.03 min [major (*R*)-enantiomer] and 25.99 min [minor (*S*)-enantiomer].

2.3.2 (R)-2-Nitro-1-(3-Nitrophenyl)Ethanol

Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.89$ (br s, 1H), 4.60–4.57 (m, 2H), 5.62–5.60 (m, 1H), 8.30–7.29 (m, 4H) ppm. $[\alpha]_D^{25} = -32.5$ ($c = 1.01, CH_2Cl_2$), HPLC analysis (Chiracel OD-H column, 0.5 mL/min, n-hexane/i-PrOH 85:15, $\lambda = 210$ nm). Retention times: 41.97 min [major (*R*)-enantiomer] and 49.10 min [minor (*S*)-enantiomer].

2.3.3 (R)-2-Nitro-1-(3-Chlorophenyl)Ethanol

Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.44$ (brs, 1H), 4.60–4.47 (m, 2H), 5.45–5.40 (m, 1H), 7.47–7.28 (m, 4H) ppm. ^{13}C NMR (50 Hz, $CDCl_3$) $\delta = 69.2$, 83.0, 123.0, 124.1, 126.9, 129.2, 134.8, 142.0 ppm. $[\alpha]_D^{25} = -32.0$ ($c = 0.85$, CH_2Cl_2) HPLC analysis (Chiracel OD-H column, 0.8 mL/min, n-hexane/i-PrOH 90:10, $\lambda = 210$ nm). Retention times: 20.26 min [major (*R*)-enantiomer] and 25.91 min [minor (*S*)-enantiomer].

2.3.4 (R)-2-Nitro-1-(4-Chlorophenyl)Ethanol

Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.89$ (brs, 1H), 4.50–4.46 (m, 2H), 5.42–5.40 (m, 1H), 7.40–7.47 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 69.67$, 84.00, 127.30, 129.24, 134.80, 136.61 ppm. $[\alpha]_D^{25} = -28.5$ ($c = 1.0$, CH_2Cl_2) HPLC analysis (Chiracel OD-H column, 0.8 mL/min, n-hexane/i-PrOH 90:10, $\lambda = 210$ nm). Retention times: 20.25 min [major (*R*)-enantiomer] and 26.73 min [minor (*S*)-enantiomer].

2.3.5 (R)-2-Nitro-1-(4-Methoxyphenyl)-Ethanol

Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.39$ (brs, 1H), 3.74 (s, 3H), 4.41–4.37 (m, 2H), 5.30 (m, 1H), 6.77–7.22 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 54.99$, 70.37, 81.20, 114.39, 127.20, 130.21, 159.78 ppm.$[\alpha]_D^{25} = -38.0$ ($c = 1.02$, CH_2Cl_2). HPLC analysis

(Chiracel OD-H column, 0.8 mL/min, n-hexane/i-PrOH 90:10, $\lambda = 210$ nm). Retention times: 30.63 min [major (*R*)-enantiomer] and 40.28 min [minor (*S*)-enantiomer].

2.3.6 (R)-3-Methyl-1-Nitrobutan-2-ol

Colourless oil, ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 0.97–1.00 (m, 6H), 1.77–1.81 (m, 1H), 2.57 (s, 1H), 4.10 (s, 1H), 4.37–4.48 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.4, 18.4, 31.7, 73.3, 79.2 ppm. $[\alpha]_D^{25} = -15.8$ ($c = 0.95$, CH_2Cl_2) HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*-PrOH 97:3, 0.6 mL/min, 23 °C, $\lambda = 220$ nm). Retention times: 27.6 min [minor] and 30.0 min [major].

2.3.7 (R)-1-Nitro-2-Phenyl-But-3-en-2-ol

Yellow solid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37–7.26 (m, 5H), 6.75 (dd, $J = 15.9$ Hz, $J = 1.2$ Hz, 1H), 6.13 (dd, $J = 15.9$ Hz, $J = 6.3$ Hz, 1H), 4.47–4.45 (m, 1H), 4.13–4.06 (m, 2H), 3.50 (bs, 1H) ppm; ^{13}C NMR (50 Hz, $CDCl_3$) δ 0.1, 78.7, 125.0, 125.9, 127.8, 128.2, 132.8, 135.1 ppm. $[\alpha]_D^{25} = -12.3$ ($c = 1.0$, CH_3Cl) HPLC analysis (Chiracel OD-H column, 1.0 mL/min, n-hexane/i-PrOH 99:1, $\lambda = 205$ nm). Retention times: 19.26 min [minor (*S*)-enantiomer] and 21.55 min [major (*R*)-enantiomer].

2.3.8 (R)-(-)-1-Nitroheptan-2-ol

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.46–4.28 (m, 3H), 2.68 (b, 1H), 1.57–1.47 (m, 3H), 1.39–1.31 (m, 5H), 0.90 (t, $J = 6.72$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 80.85, 68.89, 33.86, 31.63, 25.01, 22.63, 14.01 ppm. $[\alpha]_D^{25} = -10.4$ ($c = 1.11$, CH_2Cl_2) HPLC analysis (Chiracel AD-H column, 0.9 mL/min, n-hexane/i-PrOH 90:10, $\lambda =$ 210 nm). Retention times: 8.9 min [minor (*S*)-enantiomer] and 11.6 min [major (*R*)-enantiomer].

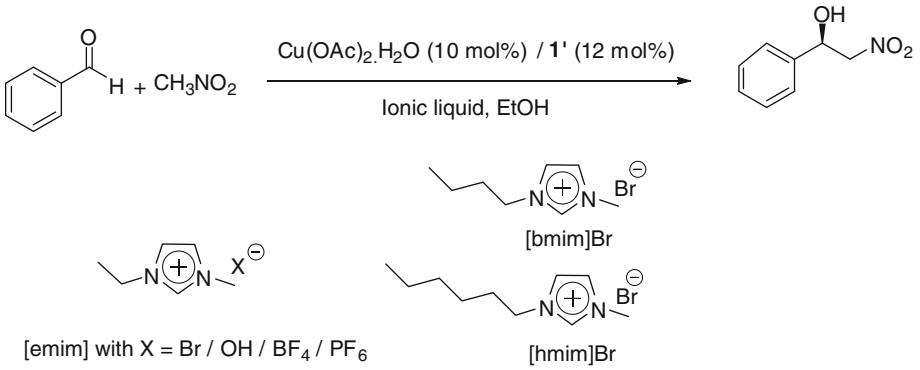
3 Results and Discussion

The chiral ligands **1′**–**4′** (Fig. 1) were synthesized by the reduction of respective diimines with $NaBH_4$ which in turn were synthesized by the condensation of benzaldehyde, 4-chloro benzaldehyde, 3-ethoxy salicylaldehyde and 3,5 di-*tert*-butyl salicylaldehyde with (1*S*,2*S*)-(+)-1,2-diamino-cyclohexane. The characterization of the ligands was accomplished by ^{1}H NMR-, IR-, UV/Vis. Spectroscopy, and optical rotation.

Chiral ligand **1′** (12 mol.%) and copper acetate (10 mol.%) were allowed to react in ethanol and the resulting complex was directly used as catalyst for nitroaldol reaction of benzaldehyde with nitromethane as a model substrate at 0 °C for 30 h, which gave the product in 55% yield and 84% ee (Table 1, entry 1). However, in this reaction the catalyst was not recyclable. In order to make the system recyclable, we conducted this reaction in the presence of readily available 1-ethyl 3-methylimidazolium bromides ([emim][Br]) as representative ionic liquid (entry 2). After 30 h there was an improvement in the product yield (65%), however there was a marginal drop in ee (78%). When the same reaction was conducted at RT ($\sim$27 °C) there was a marginal increase in product yield (69%) but with decreased ee (68%) (entry 3). On conducting this reaction in the absence of ethanol, there was a further drop in ee (61%) however the product yield remained the same (67%) (entry 4). Only a marginal increase in the product yield was observed for extended time (up to 48 h) for this reaction with minor increase in the product yield (70%) with no improvement in enantioselectivity (ee 60%, entry 5). We further explored the use of other solvents viz., THF and toluene (entries 6 and 7) for nitroaldol reaction under the similar reaction condition, however, there was a significant drop in the ee (48 and 34% respectively) of the product. Therefor, it was concluded that ethanol as a co-solvent with the ionic liquid is the reaction phase of choice.

To evaluate the effect of increasing the carbon chain length in ionic liquids n = 3 and 5 the nitroaldol reaction was carried out with benzaldehyde as representative substrate in 30 h (optimized condition). Unfortunately, the decrease in product yield as well as ee was observed (Table 1, entries 8 and 9). It is reported in the literature that the counter anion [X^-] in the ionic liquids [emim][X] greatly influences the catalytic activity and enantioselectivity of the reaction [33, 34]. Therefore, we have carried out the nitroaldol reaction under the optimized reaction conditions (Table 1, entry 3) in the presence of ionic liquids having different anions viz., OH, BF_4 and PF_6 (Table 1, entries 8–12). Basic anions like OH^- adversely effected the enantioselectivity (ee 42%, entry 10), whereas flurorinated anions like BF_4 and PF_6 gave better results in terms of product yield and enantioselectivity, BF_4 being the best among the two (entries 11 and 12). It should be noted here that nitroaldol reaction requires a delicate balance between acidity and basicity in the catalytic system in order to activate the starting materials aldehyde and nitromethane respectively. Therefore, high basicity (as in the case of OH^- counterion) of the ionic liquid might cause the lowering of product yield and enantioselectivity. On the other hand, moisture-resistant neutral counter ions like PF_6 and BF_4 may not alter the acidity or basicity of the reaction media, but could help in the polarisation of nitromethane due to highly electronegative character of fluorine atom. This in turn would increase activity of the reactant as evidenced by higher product yield in the same reaction time (for comparision please see entries 10–13). On conducting the nitroaldol reaction of benzaldehyde with nitromethane at 0 °C in

Table 1 Optimization of reaction conditions for asymmetric nitroaldol reaction in ionic liquids for in situ generated chiral $Cu(Oac)_2{\cdot}H_2O$/ **1′** as catalyst



Entry	Ionic liquid	Solvent	T (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	–	EtOH	0	30	55	84
2	[emim]Br	EtOH	0	30	65	78
3	[emim]Br	EtOH	RT	30	69	68
4	[emim]Br	–	RT	30	67	61
5	[emim]Br	–	RT	48	70	60
5	[emim]Br	THF	RT	30	57	48
6	[emim]Br	Toluene	RT	30	47	34
8	[bmim]Br	EtOH	RT	30	60	48
9	[hxmim]Br	EtOH	RT	30	41	27
10	[emim]OH	EtOH	RT	30	30	42
11	$[emim]BF_4$	EtOH	RT	30	71	79
12	$[emim]PF_6$	EtOH	RT	30	57	77
13	$[emim]BF_4$	EtOH	0	30	82	86
14[c]	$[emim]BF_4$	EtOH	0	30	40	84
15[d]	$[emim]BF_4$	EtOH	0	40	52	–
16[e]	$[emim]BF_4$	EtOH	0	40	Trace	–
17[f]	$[emim]BF_4$	EtOH	0	40	–	–

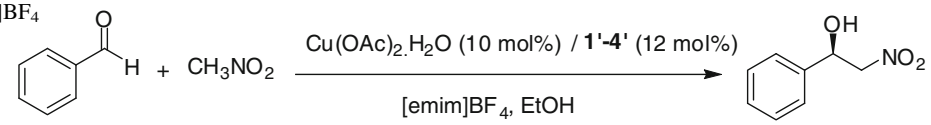
All reactions were performed with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of in situ generated complex **1** from ligand **1′**(12 mmol and $Cu(OAc)_2{\cdot}2H_2O$ (10 mol.%) in 0.125 mL of solvent and 250 mg ionic liquid at 0 °C. [a] Isolated yields by the column chromatography. [b] Determined by HPLC on a OD-H column. [c] Reaction was conducted with isolated complex (10 mol.%) from ligand **1′** and $Cu(OAc)_2{\cdot}2H_2O$). [d] The reaction was conducted in the absence of chiral ligand **1′**. [e] The reaction was conducted in the absence of $Cu(OAc)_2{\cdot}2H_2O$. [f] The reaction was conducted in the absence of chiral ligand **1′**and $Cu(OAc)_2{\cdot}2H_2O$

$[emim]BF_4$ along with ethanol as co-solvent 82% yield of chiral *β*-nitroalcohol with high ee (86%) under optimized reaction condition was obtained (Table 1, entry 13).

Further, the isolated complex (10 mol.%) as synthesized by the reaction of ligand **1′** with $Cu(OAc)_2{\cdot}H_2O$, was tested for its efficacy in the nitroaldol reaction of benzaldehyde under the above optimized reaction condition (as per entry 13). The result showed a decrease in product yield (40%) however the enantioselectivity (ee, 84%) was retained (entry 14). This result is in consonance with the earlier report [75]. The blank experiment conducted in the absence of chiral ligand **1′** keeping other conditions as per entry 13 yielded 52% racemic nitroalcohol (entry 15) indicates that copper metal is active for nitroaldol reaction but to impart enantioselctivity in the product a chiral ligand is essential. Further, the same reaction in the absence of copper acetate failed to perform nitroaldol reaction (entry 16). Furthermore, when the nitroaldol reaction was carried out in presence of only ionic liquid with no chiral ligand and copper acetate the reaction at all does not occur (entry 17).

Under the optimized reaction condition (Table 1, entry 13) we further explored the efficacy of the in situ generated complexes derived from chiral ligands **2′**–**4′** (12 mol.%) and $Cu(OAc)_2{\cdot}H_2O$ (10 mol.%), in the nitroaldol reaction of benzaldehyde as representative substrate in $[emim]BF_4$ as ionic liquid at 0 °C (Table 2, entries 1–4). The results clearly indicate that bidentate ligands **1′** and **2′** (entries 1, 2) fared better in terms of product yield (82–84%) and ee (86–88%) than tetradentate ligands **3′** and **4′** (entries, 3, 4; yield, 23–36%; ee, 11–38%). A possible reason for this

Table 2 Effect of chiral Cu(II) complexes generated in situ using the chiral ligands (**1′–4′**) for asymmetric nitroaldol reaction in presence of the Ionic Liquid [emim]BF_4



Entry	Ionic liquid	Ligand	T (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	[emim]BF_4	**1′**	0	30	82	86
2	[emim]BF_4	**2′**	0	30	84	88
3	[emim]BF_4	**3′**	0	30	36	38
4	[emim]BF_4	**4′**	0	30	23	11

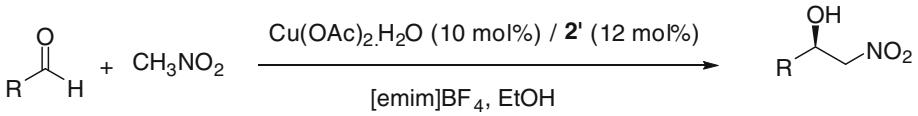
All reactions were performed with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of in situ generated complexes **1–4** from ligand **1′–4′**(12 mmol and $Cu(OAc)_2{\cdot}2H_2O$ (10 mol.%) in 0.125 mL of solvent and 250 mg ionic liquid at 0 °C. [a] Isolated yields by the column chromatography. [b] Determined by HPLC on a OD-H column

behaviour can be the ready access of catalytically active metal centre to the reactants in the case of bidentate ligands than relatively more rigid tetradentate ligands **3′** and **4′**. Moreover, mechanistically it is reported that in order to show high activity and enantioselectivity the two reactants should position themselves parallel to each other while coordinating to the catalytically active metal centre [34]. The possibility of such an alignment is relatively higher in the case of bidentate/tridentate ligands than in tetradentate ligands due to steric and electronic considerations [61].

The above optimized reaction protocol for nitroaldol reaction was further extended to various aromatic and aliphatic aldehydes using the in situ generated complex (having 12 mol.% ligand **2′** and 10 mol.% $Cu(OAc)_2{\cdot}H_2O$ in the presence of [emim]BF_4 as represented ionic liquid and data is given in Table 3. Overall, all the substrates used in the present study showed only marginal difference in the ee and yield of the products chiral β-nitroalcohols irrespective of the electron withdrawing (nitro) or electron donating (OMe) substituents on the phenyl ring of aldehyde. Nevertheless, among all the substrate used here, the best results in term of activity (yield, 89%) and enantioselectivity (ee, 94%) (Table 3, entry 6) was achieved with 4-methoxy benzaldehyde. The catalytic system also worked well in terms of good yields and enantioselectivity of nitroalcohol with aliphatic aldehyde (Table 3 entry 9).

Notwithstanding high reactivity and enantioselectivity, the in situ generated complex (having 12 mol.% ligand **2′** and 10 mol.% $Cu(OAc)_2{\cdot}H_2O$) in ionic liquid is recyclable for the enantioselective nitroaldol reaction. To demonstrate its recyclability, experiments were carried out by using

Table 3 Enantioselective nitroaldol reaction with various aldehydes catalyzed by in situ generated complex **2** in presence of ionic liquid [emim]BF_4

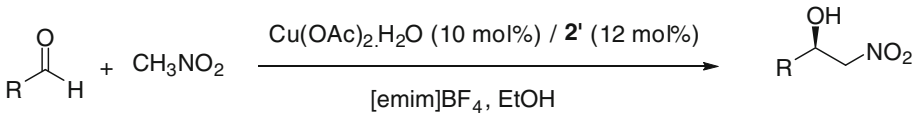


Entry	R	Ligand	Ionic liquid	Time (h)	Yield (%)[a]	ee (%)[b]
1	Ph	**2′**	[emim]BF_4	30	84	88
2	3-NO_2Ph	**2′**	[emim]BF_4	30	78	81
3	4-NO_2Ph	**2′**	[emim]BF_4	30	89	86
4	3-ClPh	**2′**	[emim]BF_4	30	88	89
5	4-ClPh	**2′**	[emim]BF_4	30	90	90
6	4-MeOPh	**2′**	[emim]BF_4	30	89	94
7	4-iPrPh	**2′**	[emim]BF_4	30	87	88
8	$PhCH_2CH_2$	**2′**	[emim]BF_4	30	90	89
9	C_5H_{11}	**2′**	[emim]BF_4	30	79	84

All reactions were performed with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of in situ generated complex **2** from ligand **2′** (12 mmol and $Cu(OAc)_2{\cdot}2H_2O$ (10 mol.%) in 0.125 mL of solvent 250 mg ionic liquid at 0 °C

[a] Isolated yields by the column chromatography, [b] Determined by HPLC on a OD-H column

Table 4 Recyclability test of the in situ generated catalyst **2** in presence of ionic liquid [emim]BF_4



Entry	Run	Ligand	T (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	1st	2	0	30	84	88
2	2nd	2	0	30	82	88
3	3rd	2	0	30	83	87
4	4th	2	0	30	82	88
5	5th	2	0	30	80	87

All reactions were performed with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of in situ generated complex **2** from ligand 2′(12 mmol and $Cu(OAc)_2{\cdot}2H_2O$ (10 mol.%) in 0.125 mL of solvent and 250 mg ionic liquid at 0 °C

[a] Isolated yields by the column chromatography, [b] Determined by HPLC on a OD-H column

benzaldehyde as a representative substrate with nitromethane in 1-ethyl-3-methylimidazolium [emim]BF_4 (as representative ionic liquid) and ethanol as co-solvent at 0 °C (Table 4). After completion of the catalytic reaction the products were extracted with n-hexane:ethylacetate (80:20). The extract was concentrated and purified by column chromatography. The recovered ionic liquid containing the catalyst was dried in vacuum and was used for the subsequent catalytic runs without any further processing. The recycled catalyst worked well up to five catalytic runs with marginal loss in yield. However, the enantioselectivity of the product was retained.

4 Conclusion

In conclusion, in situ generated chiral Cu(II) C_2 symmetric secondary bis-amines complexes having different substituents were used as catalysts for the nitroaldol reaction of benzaldehyde, substituted benzaldehydes and aliphatic aldehyde in the presence of different ionic liquids as reaction medium at 0 °C. Chiral β-nitroalcohols with high chiral purity (ee, 94%) was achieved when [emim]BF_4 with ethanol as co-solvent was used as reaction medium with the catalyst (in situ generated complex having 12 mol.% ligand **2′** and 10 mol.% $Cu(OAc)_2{\cdot}H_2O$) in case of 4-methoxybenzaldehyde in 30 h. The catalytic system worked well up to five cycles with the retention of enantioselectivity.

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