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Chiral enhancement in the confined space of zeolites for the asymmetric synthesis of β-hydroxy nitroalkanes

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ABSTRACT

(1*S*,2*S*)-N^1,N^2-Bis(3-chlorobenzyl)cyclohexane-1,2-diamine **1a**′ and (1*S*,2*S*)-N^1,N^2-bis(4-chlorobenzyl) cyclohexane-1,2-diamine **1b**′ were used to prepare chiral Cu(II) complexes **Cu-Y-1a**, **Cu-Y-1b**, **Cu-mZSM5-1a**, and **Cu-mZSM5-1b** by a flexible ligand method using copper exchanged zeolite Y and mesoporous ZSM-5. The characterization of zeolite supported complexes was performed by microanalysis, IR-, diffuse reflectance spectroscopy (DRS), EPR spectroscopy, specific rotation and thermogravimetric analysis (TGA). The catalytic activity of these supported complexes was explored for the asymmetric nitroaldol reaction of various aldehydes with nitromethane at 0 °C. Excellent yields (up to 99%) of β-hydroxy nitroalkane with an ee of up to 94% were achieved in the case of benzaldehyde as substrate. Significantly, the performance of the supported catalyst was better in terms of enantioselectivity than the complex under homogenous conditions. The supported catalysts were recycled four times with no observable loss in performance and no leaching of the catalytically active complex during the nitroaldol reaction.

1. Introduction

The asymmetric Henry reaction has emerged as a powerful synthetic tool for preparing β-hydroxynitroalkanes[1] that provides ready access to valuable bifunctional compounds, such as β-amino alcohols, α-hydroxy ketones, aldehydes, α-hydroxy carboxylic acids, azides and sulphides for pharmaceutical applications.[1–3] Shibasaki reported the first asymmetric version of the nitroaldol reaction in 1992 using a BINOL-derived heterometallic complex.[4–12] Since then various chiral catalysts involving Zn,[13–16] Cu,[17–32,2,33–35] Co,[36] Mg[37] and Cr[38–40] metal ions and organo-catalysts[41–47] have been studied. However, most of these methods suffer from limitations, such as high catalyst loading, low reaction temperatures, non-recyclability of an expensive catalyst, multistep synthetic procedures for ligand preparation, or demanding the use of additives, such as molecular sieves, potassium hydroxide,[48,49] cetyltrimethyl ammonium hydroxide[50] sodium carbonate,[1] triethylamine,[1] 2,6-lutidine,[29] pyridine[29] and aromatic imines.[18] Notably, the Cu-catalysed nitroaldol reaction is the most explored one due to its low cost, non-toxic nature, and high catalytic activity under homogeneous reaction conditions.[17–32,2,33–35] However, the separation and recycling of the catalyst is still a serious issue under homogeneous condition. As chiral catalysts are very expensive, their recyclability is an important aspect from an economical and industrial point of view.

Heterogenization of homogeneous catalysts, endows attributes of homogeneous systems with attractive features of a heterogenous catalyst, such as easy product separation and catalyst recovery by simple filtration.[51–54] This strategy has expanded rapidly for various asymmetric organic transformations; however, there are only few reports[30,50,55,56] available on asymmetric nitroaldol reaction. With our ongoing interest in asymmetric heterogeneous catalysts,[55–58] we herein report for the first time the use of Cu exchanged zeolite Y and mesoporous ZSM-5 of different porosity with chiral C_2-symmetric ligands (1*S*,2*S*)-N^1,N^2-bis(3-chlorobenzyl)cyclohexane-1,2-diamine **1a**′ and (1*S*,2*S*)-N^1,N^2-bis(4-chlorobenzyl)cyclohexane-1,2-diamine **1b**′ for the asymmetric nitroaldol reaction of aldehydes. The catalyst system developed demonstrates excellent yield (>99%) of β-hydroxynitroalkanes with high enantioselectivity (ee, 94%) as compared to a homogeneous counterpart.

2. Results and discussion

The encapsulation of C_2-symmetric chiral ligands (1*S*,2*S*)-N^1,N^2-bis-(3-chlorobenzyl)-cyclohexane-1,2-diamine **1a**′ and (1*S*,2*S*)-N^1,N^2-bis-(4-chlorobenzyl)-cyclohexane-1,2-diamine **1b**′ in Cu exchanged zeolite Y and mesoporous ZSM-5 was carried out by flexible ligand method[59] (Scheme 1) to obtain chiral heterogeneous

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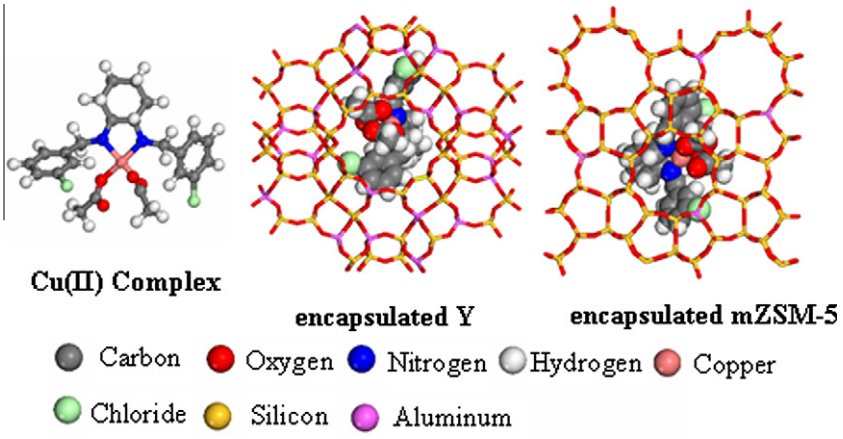


Scheme 1. Schematic representation of copper(II) complexes encapsulated in two different zeolites.

complexes **Cu-Y-1a**, **Cu-Y-1b**, **Cu-mZSM5-1a** and **Cu-mZSM5-1b.** The basic framework of zeolite Y and mesoporous ZSM-5 remained unchanged upon copper exchange as well as after encapsulation of the chiral ligands **1a**′ and **1b**′ as evidenced by XRD measurements that showed no significant change in the position and relative intensity of the diffraction lines (Fig. 1). However, the surface area and pore volume of the copper exchanged zeolite Y and mesoporous ZSM-5 showed a significant decrease after encapsulation of the complexes (Table 1) due to the presence of complexes inside the zeolite cavity which was further confirmed by FTIR, DRS and EPR spectroscopy.

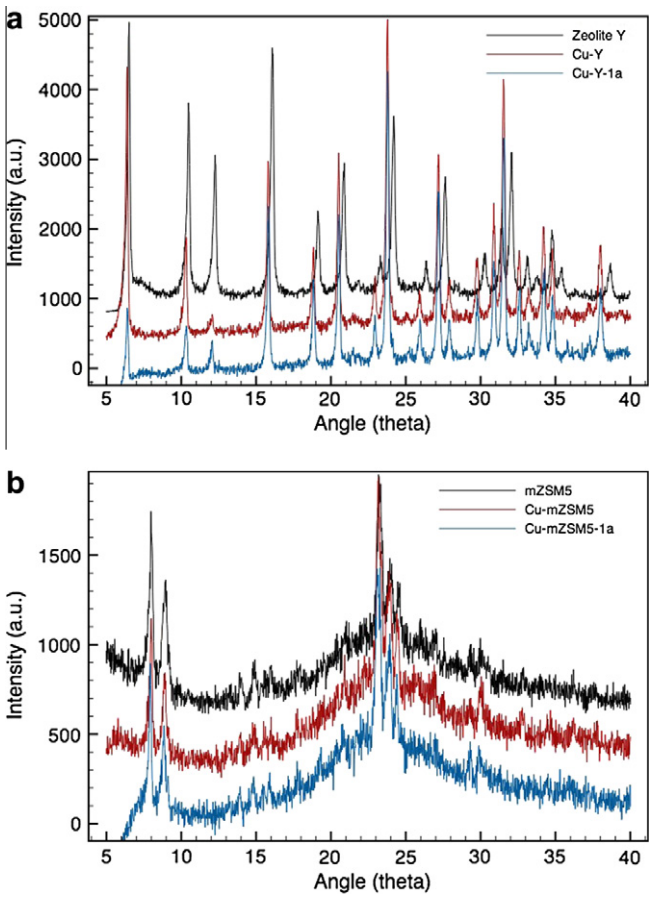


Figure 1. XRD patterns of: **Cu-1a** complex, **Cu-mZSM5-1a** and **Cu-Y-1a**.

The FTIR spectra of **Cu-Y** and **Cu-mZSM-5** show characteristic bands below 1200 cm^{-1} while their encapsulated analogues **Cu-Y-1a, Cu-Y-1b, Cu-mZSM-5-1a** and **Cu-mZSM-5-1b** show characteristic peaks of the neat complexes in the 1200–1600 cm^{-1} region along with C–H stretching and 2900–3000 cm^{-1} confirming the encapsulation of **1a** and **1b** in **Cu-Y** and **Cu-mZSM-5**. Representative IR spectra for the neat complex **1a**, supported complex **Cu-mZSM-5-1a** and **Cu-mZSM-5** are shown in Figure 2. Similar observations were also made by Jin et al.[58] for the encapsulation of Cu-[H_4]salen/Y samples.

EPR spectra of polycrystalline neat complex **Cu-1a** showed typical unresolved hyperfine features due to copper ($S = 1/2$ and $I = 3/2$) due to nearest neighbour intermolecular spin–spin exchange interactions[60] at 298 K (Fig. 3a). However, zeolite Y and ZSM-5-encapsulated metal complex **Cu-1a** (Fig. 3b and c) showed well-resolved metal hyperfine features similar to spectra in dilute frozen solutions indicating the encapsulation of monomeric salen complexes in zeolite and ZSM-5 cavities.[61]

The UV–vis absorption spectra of the neat complex **Cu-1a**, **Cu-Y-1a**, and **Cu-mZSM5-1a** samples are shown in Figure 4. The metal complex **Cu-1a** showed broad MLCT bands in the region 360, 370 and 500 nm. Upon encapsulation of **Cu-1a** in zeolite-Y and ZSM-5 the spectra remained largely unchanged in the region of ~370 nm indicating that the structure of the homogneous complex is retained on encapsulation. However, the band at 500 nm in the neat complex, was blue shifted to 480 nm, possibly due to the interaction of Cu(II) with the zeolite framework. These results are consistent with those reported earlier.[62]

For catalytic activity measurements at first we conducted the asymmetric nitroaldol reaction of benzaldehyde as a model substrate with nitromethane in the presence of catalyst **1a** and **1b** (10 mol %) under homogeneous conditions (in ethanol) at 0 °C that gave excellent product yield (83–96%) and ee (86%) in 48 h (Table 2, entries 1 and 2). These results are in accordance with values reported by Skarzewski et al.[63,64] The same reactions when conducted under heterogeneous conditions with catalysts supported on zeolite-Y and mZSM-5 (100 mg containing ~10 mol % of **1a**/**1b**) showed an increase in ee (~94%), however, the reaction took 72 h to attain the product yield that was equivalent with the homogeneous conditions (entries 3–6). This increase in reaction time is expected due to diffusional constraints, whereas the increase in ee might be due to the confinement effect of the support or catalytic site-isolation inside mesopores. To optimize the nitroaldol reaction of benzaldehyde under heterogeneous condition, we next evaluated the effect of the solvent using **Cu-Y-1a** as a representative catalyst. Among all the solvents used (entries 7–10), ethanol was found to be the solvent of choice which is in accordance

Table 1
Physicochemical data of the catalysts

Support	Cu content[a] (mmol g^{-1})	N content[b] (mmol g^{-1})	SBET(m^2 g^{-1})	Pore Vol (cm^3 g^{-1})
Na-Y zeolite	–	–	840	0.44
mZSM-5	–	–	649	1.06
CuY	0.94	–	472	0.25
Cu-mZSM-5	0.38	–	423	0.87
CuY-1a	0.91	1.76	393	0.23
CuY-1b	0.92	1.79	387	0.24
Cu-mZSM-5-1a	0.36	0.71	346	0.76
Cu-mZSM-5-1b	0.35	0.7	342	0.74

[a] Determined by ICP-OES method.
[b] Determined by elemental analysis method (w%).

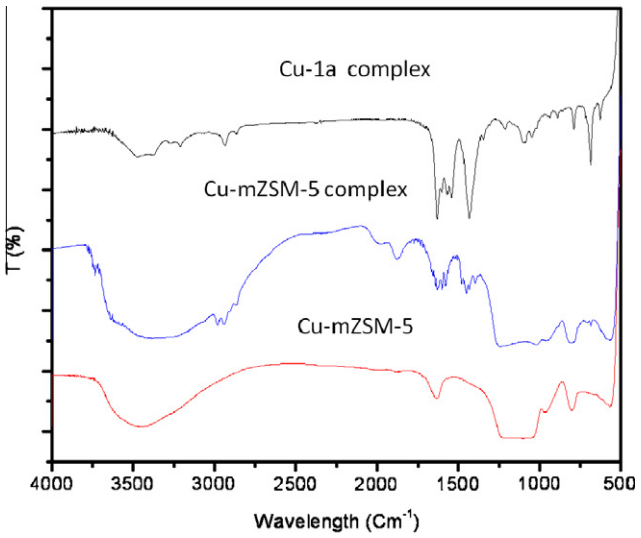


Figure 2. FTIR spectra of **Cu-1a** complex, **Cu-mZSM5-1a** and **Cu-Y-1a**.

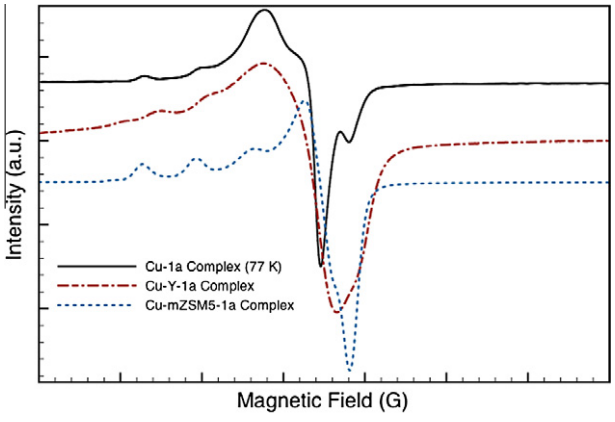


Figure 3. EPR spectra of **Cu-1a** complex, **Cu-mZSM5-1a** and **Cu-Y-1a**.

with earlier reports.[65] Temperature is one of the most sensitive parameters in enantioselective reactions, therefore, we varied the temperature of the nitroaldol reaction keeping other parameters as per entry 3. On increasing the reaction temperature from 0 °C to room temperature 92% product yield was obtained in 48 h but there was a drop in ee (70%). A further increase in the reaction temperature (50 °C) caused a further increase in the product yield (99%) but the ee dropped considerably (entry 12, ee 57%). On conducting this reaction with a decreased amount of catalyst 50 mg and 25 mg at 0 °C, there was a gradual decrease in product yield as well as ee (entries 13 and 14). In all the reactions conducted

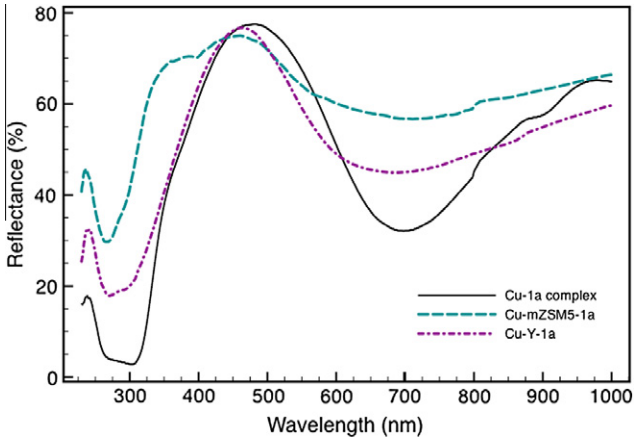


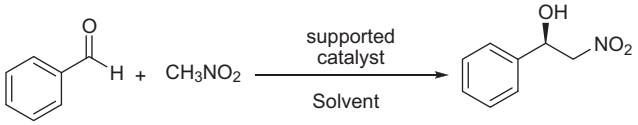
Figure 4. Diffuse reflectance UV–vis absorption spectra of: **Cu-1a** complex, **Cu-mZSM5-1a** and **Cu-Y-1a**.

above, the absolute configuration of the β-hydroxy nitroalkane was assigned as (*R*) by comparison of the specific rotation with the literature data.[18]

After optimization of the solvent, temperature and amount of the catalyst, the scope of the nitroaldol reaction with supported catalysts **Cu-Y-1a/1b** and **Cu-mZSM-5-1a/1b** was extended to various other substituted benzaldehydes and aliphatic aldehydes under the above optimized reaction condition (Table 3, entries 1 and 15). At a glance, all the chiral complexes encapsulated into zeolites cavities and mZSM-5 used in the present study faired well as catalysts in terms of product yield and ee in the nitroaldol reaction of a wide range of substrates. The substrates with electron-withdrawing groups for example, 3-nitrobenzaldehyde gave lower ee values (~51%) when zeolite-Y was used as a support as compared to the ee (~81%) obtained with the mZSM-5 supported catalysts. For other substrates, both supports gave similar enhancement in the performance of homogenous catalysts, however, mZSM-5 as a support had some edge over zeolite-Y. Possibly, a confined environment of zeolite supercage provided chiral enhancement due to the so called confinement effect (Scheme 2). Whereas, in mZSM-5 its channel like structure allowed the substrates to travel freely, thereby minimizing diffusional constraints. In any case, it is reported[57,66,67] that by anchoring or immobilizing the catalysts onto mesoporous materials, there is a significant increase in ee as compared to its homogenous analogue. Apparently, the steric features, aliphatic or aromatic nature of the substrates did not play a major role in the product yield or ee.

Finally, catalyst recyclability was carried out with **Cu-Y-1a** and **Cu-mZSM-5-1a** for the asymmetric nitroaldol of benzaldehyde as a model substrate with nitromethane. Both the catalysts were easily recovered by centrifugation from the reaction system and thoroughly washed with ethanol before use. The recovered catalysts

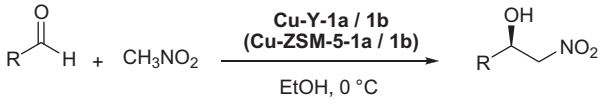
Table 2
Optimization of reaction conditions for the asymmetric Henry reaction with heterogeneous catalysts[a]



Entry	Catalyst	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**[d]	Ethanol	0	48	83	86
2	**1b**[d]	Ethanol	0	48	96	86
3	**Cu-Y-1a**	Ethanol	0	72	96	93
4	**Cu-Y-1b**	Ethanol	0	72	97	94
5	**Cu-mZSM-5-1a**	Ethanol	0	72	98	93
6	**Cu-mZSM-5-1b**	Ethanol	0	72	98	94
7	**Cu-Y-1a**	Nitromethane	0	72	32	85
8	**Cu-Y-1a**	Toluene	0	72	29	87
9	**Cu-Y-1a**	CH_2Cl_2	0	72	35	85
10	**Cu-Y-1a**	THF	0	72	19	79
11	**Cu-Y-1a**	Ethanol	rt	48	92	70
12	**Cu-Y-1a**	Ethanol	50	48	99	57
13	**Cu-Y-1a**	Ethanol[e]	0	72	73	80
14	**Cu-Y-1a**	Ethanol[f]	0	72	57	76

[a] All reactions were performed with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of 100 mg **Cu-Y-1a** catalyst in 2 ml of solvent at the specified temperature.
[b] Isolated yields by column chromatography.
[c] Determined by HPLC on a OD-H column. Reactions were conducted with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of 0.10 mmol of the catalyst (10 mol %).
[e] 50 mg **Cu-Y-1a** catalyst was used.
[f] 25 mg **Cu-Y-1a** catalyst was used.

Table 3
Asymmetric Henry reaction of nitromethane with various aldehydes catalysed by chiral **Cu-Y-1a, Cu-ZSM-5-1a/Cu-Y-1b, Cu-ZSM-5-1b**[a]



Entry	R	Chiral supported complexes	Yield[b] (%)	ee[c] (%)
1 (15)	Ph	**Cu-Y-1a (Cu-ZSM-5-1a)**	96 (98)	93 (93)
2 (16)	3-NO_2Ph	**Cu-Y-1a (Cu-ZSM-5-1a)**	96 (96)	51 (81)
3 (17)	3-ClPh	**Cu-Y-1a (Cu-ZSM-5-1a)**	95 (98)	90 (90)
4 (18)	4-ClPh	**Cu-Y-1a (Cu-ZSM-5-1a)**	94 (96)	93 (90)
5 (19)	4-MeOPh	**Cu-Y-1a (Cu-ZSM-5-1a)**	56 (75)	89 (83)
6 (20)	$PhCH_2CH_2$	**Cu-Y-1a (Cu-ZSM-5-1a)**	80 (87)	74 (68)
7 (21)	C_5H_{11}	**Cu-Y-1a (Cu-ZSM-5-1a)**	82 (90)	77 (80)
8 (22)	Ph	**Cu-Y-1b (Cu-ZSM-5-1b)**	97 (98)	94 (93)
9 (23)	3-NO_2Ph	**Cu-Y-1b (Cu-ZSM-5-1b)**	99 (99)	53 (80)
10 (24)	3-ClPh	**Cu-Y-1b (Cu-ZSM-5-1b)**	96 (99)	90 (90)
11 (25)	4-ClPh	**Cu-Y-1b (Cu-ZSM-5-1b)**	95 (97)	91 (91)
12 (26)	4-MeOPh	**Cu-Y-1b (Cu-ZSM-5-1b)**	88 (78)	65 (88)
13 (27)	$PhCH_2CH_2$	**Cu-Y-1b (Cu-ZSM-5-1b)**	81 (88)	77 (70)
14 (28)	C_5H_{11}	**Cu-Y-1b (Cu-ZSM-5-1b)**	81 (93)	79 (84)

[a] All reactions were performed with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of 100 mg **Cu-Y-1a**/**1b** catalyst in 2 ml of solvent at the appointed temperature.
[b] Isolated yields by the column chromatography.
[c] Determined by HPLC on a OD-H column.

were effectively used 4 times without any noticeable loss in their activity and enantioselectivity (Table 4). In order to detect leaching of the complex, the reaction mixture obtained after the separation of the catalyst was subjected to ICP, which showed no trace of Cu metal. Also there was no trace of the chiral ligand on TLC. These experiments clearly demonstrate that the active catalyst is well secured inside the cavity/channel of the solid support.

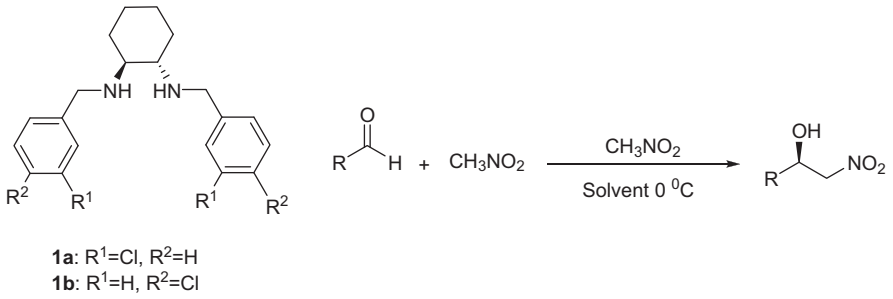
3. Conclusion

We have demonstrated the usefulness of chiral diamine complexes immobilized into a zeolite cavity and mZSM-5 as truly heterogeneous catalysts for the asymmetric nitroaldol of various aldehydes to give the desired β-nitroalcohols in high yield and ees. The immobilized catalysts worked well four times with retention of their activity and enantioselectivity during the nitroaldol reaction.

4. Experimental

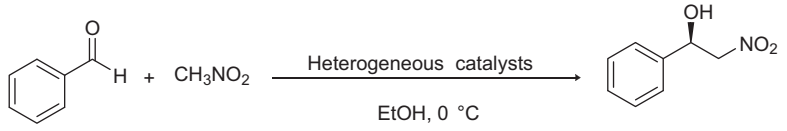
4.1. Materials and characterization

Solvents were dried according to standard procedures and distilled prior to use. (1*S*,2*S*)-(+)-1,2-Diaminocyclohexane, nitromethane (TCI), various aldehydes, benzaldehyde, 3-NO_2-, 3-Cl-, 4-Cl-, 4MeO-benzaldehyde, hydrocinnamaldehyde, heptanaldehyde, copper acetate monohydrate (Aldrich) were used as recieved. Zeolite Y was obtained from commercial source (ZEOLYST), while mesoporous ZSM-5 zeolites was synthesized according to our standard procedure.[68,69] All the reactions were carried out under specified reaction conditions. ^{1}H NMR spectra were recorded at 200 MHz (JEOL) in $CDCl_3$ as solvent and tetramethylsilane as an internal standard. X-ray powder diffraction (XRD) patterns have been recorded on a Rigaku, D-Max III VC model, with nickel-filtered Cu Kα radiation. A glass holder was used to support the catalyst samples. The samples were scanned in the 2θ range of 2–60° with a scanning rate of 4°/min. Fourier transform infrared (FTIR) spectra were obtained from KBr pressed pellets using a Nicolet 6700 (Thermo Electron Corporation) infrared spectrometer. The diffuse reflectance (UV DRS) spectra of the solid samples were recorded in the region 200–800 nm using a spectrophotometer (Shimadzu UV2101 model) with $BaSO_4$ as the reference material. The electron spin resonance (ESR) spectra were measured in a JEOL FA200



Scheme 2. Chiral diamine ligand employed for the asymmetric Henry reaction after encapsulation to copper zeolites.

Table 4
Recyclability data on the asymmetric Henry reaction using a supported catalyst[a]



Entry	Catalyst	Catalytic runs	Time (h)	Yield[b] (%)	ee[c] (%)
1 (5)	**Cu-Y-1a (Cu-ZSM-5-1a)**	1	72	96 (98)	93 (93)
2 (6)	**Cu-Y-1a (Cu-ZSM-5-1a)**	2	72	96 (98)	93 (93)
3 (7)	**Cu-Y-1a (Cu-ZSM-5-1a)**	3	72	96 (98)	93 (93)
4 (8)	**Cu-Y-1a (Cu-ZSM-5-1a)**	4	72	96 (97)	94 (93)

[a] All reactions were performed with 1 mmol of benzaldehyde and 5 mmol of nitromethane in the presence of 100 mg catalyst in 2 mL of ethanol.
[b] Isolated yields by the column chromatography.
[c] Determined by HPLC on a OD-H column.

spectrometer at 9.06 GHz. Elemental analyses were performed with an EA-1112 (CE Instruments). In order to determine the copper content in the heterogeneous complexes, samples were analysed by the PE optima 7300 DV ICP-OES equipped with S-10 autosampler. Thermogravimetric analyses (TGAs) were performed on Perkin-Elmer TGA-7 analyzer at a 10 °C/min scan rate in a nitrogen atmosphere.

4.2. Synthesis of chiral ligands 1a′ and 1b′

The chiral ligands **1a**′ and **1b**′ were synthesized by the modified reported procedure.[62,63] In a 100 ml round bottom flask aldehyde/substituted aldehydes (1 mmol) was taken in ethanol (20 ml), to which (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (0.5 mmol) was added at 0 °C. The reaction mixture was then stirred at this temperature for 1 h, and then refluxed for 10–12 h. After completion of the reaction (checked on TLC), the reaction mixture was cooled to room temperature and sodium borohydride (4 mmol) was added in small fractions with stirring. The resulting solution thus obtained was refluxed for 10 h. Subsequently, the solvent was removed on a rotary-evaporator. The resulting mass was dissolved in dichloromethane (10 ml), washed with distilled water, dried over anhydrous sodium sulphate and evaporated to give the desired ligand as a semi-solid. The characterization of the ligands was accomplished by different physicochemical techniques and the data obtained were well matched with the earlier reports.[63,64]

4.2.1. (1*S*,2*S*)-*N*,*N*-bis(3-Chlorobenzyl)cyclohexane-1,2-diamine 1a′

Pale yellow solid; mp = 60–64 °C; ^{1}H NMR (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 (KBr): 3300, 3045, 2919, 2840, 1590, 1560, 1450, 1220, 1110, 860, 770 cm^{-1}.

4.2.2. (1*S*,2*S*)-*N*,*N*-bis(4-Chlorobenzyl)cyclohexane-1,2-diamine 1b′

Colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90–1.70 (m, 8H), 1.80 (br s, 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 (KBr): 3280, 3010, 2900, 2815, 1575, 1460, 1410, 1200, 1135, 810, 765, cm^{-1}.

4.2.3. Preparation of Cu exchanged zeolites

For the preparation of copper exchanged zeolite, copper acetate monohydrate (3.5 g) was dissolved in 700 ml of warm distilled water and 7.5 g Na-Y/mesoporous ZSM-5 zeolite were added while stirring the solution. The resultant mass was further stirred for 8 h. The solids were filtered and washed thoroughly with demineralised water until the washing became colourless. The solid Cu-Y obtained after the third exchange was dried at 383 K overnight in air. The same procedure was applied for Cu-mZSM-5 sample.

4.2.4. Preparation of heterogeneous catalysts

Heterogeneous catalysts **Cu-Y-1a**, **Cu-Y-1b**, **Cu-mZSM5–1a** and **Cu-mZSM5-1b** were prepared by encapsulating the chiral ligands **1a**′ and **1b**′ on to **Cu-Y zeolite** and **Cu-mZSM-5** via flexible ligand method.[59] The chiral ligands **1a**′ or **1b**′ were dissolved in ethanol and copper exchanged zeolite **Cu-Y** and **Cu-mZSM-5** were then added to it. The resulting solution was allowed to stir for 24 h followed by filtration to give heterogeneous complexes **Cu-Y-1a**, **Cu-Y-1b**, **Cu-mZSM5-1a** and **Cu-mZSM5-1b.** The unreacted chiral ligands **1a**′ and **1b**′ were removed by Soxhlet extraction in methylene chloride.

4.2.5. Typical procedure for the asymmetric nitroaldol reaction

Asymmetric nitroaldol reactions were carried out in magnetically stirred glass reactor under dry and inert conditions. Zeolite supported chiral copper (II) complexes, **Cu-Y-1a**, **Cu-Y-1b**, **Cu-mZSM-5-1a** and **Cu-mZSM-5-1b** (100 mg) were taken in absolute

ethanol (0.5 ml) and the resulting slurry was cooled to 0 °C. To the cold slurry an appropriate aldehyde (1 mmol) was added with stirring and after a lag of 15 min, nitromethane (0.6 ml) was added through a syringe. The resulting suspension was stirred for 72 h at 0 °C. The progress of the reaction was monitored by TLC. After 72 h, the cold reaction mixture was centrifuged and washed with ethanol. The solid residue was dried in vacuum and kept for reuse experiments. The solvent from the combined supernatant was removed and the resultant residue was chromatographed on silica gel column using hexane/ethyl acetate as eluent to give the desired β-nitroalcohol. The products were analyzed by ^{1}H NMR ($CDCl_3$), specific optical rotations (CH_2Cl_2 or $CHCl_3$) and their enantiomeric excess (ee) was determined by HPLC using an OD-H column with 2-PrOH/hexane (90:10) as the eluent. HPLC traces of products were compared with the respective racemic samples.

4.3. Characterization of the products

4.3.1. (*R*)-2-Nitro-1-phenylethanol

HPLC analysis (Chiralcel OD-H column, 0.8 mL/min, hexane/*i*-PrOH 90:10, λ = 210 nm), Retention time: 21.03 min [major (*R*)-enantiomer] and 25.99 min [minor (*S*)-enantiomer]; Colourless oil with ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.89 (br s, 1H; OH), 4.39 (dd, *J* = 3.2, 9.4 Hz, 1H; CH_2NO_2), 4.43 (dd, *J* = 3.2, 9.5 Hz, 1H; CH_2NO_2), 5.34 (2d, *J* = 3.1, 3.2 Hz, 1H; CHOH), 7.13–7.33 (m, 5H; ArH) ppm; ^{13}C NMR (500 MHz, $CDCl_3$): δ = 69.00, 79.19, 125.10, 128.94, 129.01, 138.11 ppm.

4.3.2. (*R*)-2-Nitro-1-(3-nitrophenyl)ethanol

HPLC analysis (Chiralcel OD-H column, 0.5 ml/min, hexane/*i*-PrOH 85:15, λ = 210 nm), Retention time: 41.97 min [major (*R*)-enantiomer] and 49.10 min [minor (*S*)-enantiomer]; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 2.89 (br s, 1H; OH), 8.30–7.29 (m, 4H), 5.62–5.60 (m, 1H), 4.60–4.57 (m, 2H), 3.20 (d, *J* = 4.2 Hz, 1H) ppm.

4.3.3. (*R*)-2-Nitro-1-(3-chlorophenyl)ethanol

HPLC analysis (Chiralcel OD-H column, 0.8 ml/min, hexane/*i*-PrOH 90:10, λ = 210 nm), Retention time: 20.26 min [major (*R*)-enantiomer] and 25.91 min [minor (*S*)-enantiomer]; Colourless oil with ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.47–7.28 (m, 4H), 5.45–5.40 (m, 1H), 4.60–4.47 (m, 2H), 3.44 (d, *J* = 4.1 Hz, 1H) ppm; ^{13}C NMR (50 Hz, $CDCl_3$) δ = 69.2, 83.0, 123.0, 124.1, 126.9, 129.2, 134.8, 142.0 ppm.

4.3.4. (*R*)-2-Nitro-1-(4-chlorophenyl)ethanol

HPLC analysis (Chiralcel OD-H column, 0.8 mL/min, hexane/*i*-PrOH 90:10, λ = 210 nm), Retention time: 20.25 min [major (*R*)-enantiomer] and 26.73 min [minor (*S*)-enantiomer]; Colourless oil with ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.89 (br s, 1H; OH), 4.46 (dd, *J* = 3.3, 9.2 Hz ,1H; CH_2NO_2), 4.50 (dd, *J* = 3.3, 9.3 Hz, 1H; CH_2NO_2), 5.42 (2d, *J* = 3.3, 3.3 Hz, 1H; CHOH), 7.40–7.47 (m, 4H; ArH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 69.67, 84.00, 127.30, 129.24, 134.80, 136.61 ppm.

4.3.5. (*R*)-2-Nitro-1-(4-methoxyphenyl)ethanol

HPLC analysis (Chiralcel OD-H column, 0.8 mL/min, hexane/*i*-PrOH 90:10, λ = 206 nm), Retention time: 30.63 min [major (*R*)-enantiomer] and 40.28 min [minor (*S*)-enantiomer]; Colourless oil with ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39 (br s, 1H; OH), 3.74 (s, 3H; CH_3), 4.37 (dd, *J* = 3.2, 9.5 Hz, 1H; CH_2NO_2), 4.41(dd, *J* = 3.2, 9.5 Hz, 1H; CH_2NO_2), 5.30 (2d, *J* = 3.2, 3.2 Hz, 1H; CHOH), 6.77–7.22 (m, 4H; ArH) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.99, 70.37, 81.20, 114.39, 127.20, 130.21, 159.78 ppm.

4.3.6. (*R*)-(+)-1-Nitro-4-phenylbutan-2-ol

HPLC analysis (Chiralcel AD-H column, 1.0 mL/min, *n*-hexane/*i*-PrOH, 90:10, λ = 215 nm), Retention time: 11.69 min [major (*R*)-enantiomer] and 14.88 min [minor (*S*)-enantiomer]. Off-white solid with ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.87–1.77 (m, 2H), 2.78–2.69 (m, 2H), 2.85–2.82 (m, 1H), 4.40–4.27 (m, 3H), 7.25–7.19 (m, 3H), 7.32–7.28 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 34.51, 35.29, 67.95, 80.74, 126.52, 128.61, 128.84, 140.79 ppm.

4.3.7. (*R*)-(−)-1-Nitroheptan-2-ol

HPLC analysis (Chiralcel AD-H, 1.0 mL/min, *n*-hexane/*i*-PrOH, 97:3, λ = 215 nm), Retention time: 20.29 min [major (*R*)-enantiomer] and 29.66 min [minor (*S*)-enantiomer]; Colourless oil with ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.72 Hz, 3H), 1.39–1.31 (m, 5H), 1.57–1.47 (m, 3H), 2.68 (br, 1H), 4.46–4.28 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 14.01, 22.63, 25.01, 31.63, 33.86, 68.89, 80.85 ppm.

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