Tetrahedron: *Asymmetry* 22 (2011) 857–865

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric Henry reaction of aldehydes catalyzed by recyclable an MCM-41 supported copper(II) salen complex

Karuthamohamed Dhahagani [a], Jegathalaprathaban Rajesh [b], Ramanujam Kannan [c], Gurusamy Rajagopal [a,*]

[a] *Department of Chemistry, Government Arts College, Melur 625 106, Madurai, India*
[b] *Department of Chemistry, Madurai Institute of Engineering and Techonology, Sivagangai 630 611, India*
[c] *Centre for Research in Nanotechnology, Karunya University, Coimbatore 641 114, India*

ARTICLE INFO

Article history:
Received 24 March 2011
Accepted 17 April 2011
Available online 14 June 2011

ABSTRACT

A chiral modified MCM-41-Cu(salen) complex has been prepared and characterized by SEM, powder XRD, and EDX techniques as well as FT-IR and EPR spectroscopic methods. This new catalytic system was examined in the asymmetric Henry reaction between various aldehydes and nitromethane at room temperature. Aromatic, aliphatic, and heterocyclic aldehydes have been converted into the corresponding nitro alcohols in 60–92% yields with 60–90% ee. Several factors concerning the reactivity and enantioselectivity are also discussed. This catalyst was separated by filtration and reused several times without a significant loss of reactivity or enantioselectivity.

1. Introduction

The importance of chirality in life science and new materials has been growing rapidly, which makes the manufacturing of chiral molecules an important topic in the modern fine chemical industry. Asymmetric synthesis, under certain conditions, allows the production of enantiomerically pure compounds, which have a wide range of applications in the chemical industry.[1] There is also increasing interest in developing catalytic asymmetric C–C bond forming processes.[2] The nitroaldol (Henry) reaction is a valuable and atom economic C–C bond-formation reaction between a nitroalkane and a carbonyl compound to furnish a 1,2-nitro alcohol.[3] Since the nitro group can be easily transformed into an amino group as well as into carbonyl or carboxylic compounds via a Nef reaction, the asymmetric Henry reaction has attracted much attention. Shibasaki et al. reported the first asymmetric nitroaldol reaction catalyzed by a BINOL derived heterometallic complex.[4] Since then, much effort has been devoted to this area because the facile reduction of the enantioenriched 1,2-nitro alcohols readily provides chiral 1,2-amino alcohols, which are ubiquitous segments in natural products, pharmaceuticals, synthetic intermediates, and chiral ligands.[5] A highly enantioselective nitroaldol reaction using nitromethane as a nucleophile has been achieved via organocatalysis[6] and biocatalysis.[7] Various chiral catalysts involving Zn, Cu, Co, Mg, and Cr metal ions have also been studied.[8]

Heterobimetallic lanthanoid catalysis has stimulated the successful development of various types of asymmetric catalysts. Amongst them, the Cu-catalyzed Henry reaction performed at room temperature has received much attention in recent years. A highly *syn*-selective nitroaldol reaction of nitroethane with both aromatic and aliphatic aldehydes catalyzed by a Cu(II)–bisimidazoline system has been reported by Lan et al.[9] *N*,*N*′-Bis(isobornyl)ethylenediamine–copper complex has been found to be an efficient catalyst in the enantioselective Henry reaction between nitromethane and various aldehydes.[10] A unique chiral skeleton based on bis(sulfonamide)–diamine-copper and amino-functionalized sulfonimidamide-copper systems has been employed in Henry reactions.[11] Although the Cu-catalyzed nitroaldol reaction is one of the most explored due to its low cost, non-toxic nature, and high catalytic activity under homogeneous reaction conditions, the separation and recycling of the catalyst still remains a serious issue under these conditions. As chiral catalysts are very expensive, their recyclability is an important aspect from an economical and industrial point of view.

Supported metal complexes have continuously attracted increasing interest because of the advantages that they offer with respect to their soluble counterparts.[12] Some of these advantages are their robustness, increased air and moisture stability, ease of separation, and the potential recyclability, when used as heterogeneous catalysts. Ordered mesoporous materials are very attractive as solid catalysts for fine chemicals synthesis that involve bulky reactants and products due to their large pore openings and high surface areas.[13] As a support, MCM 41 silicas have been widely used since the performance of this material in catalysis is directly related to a structure possessing hexagonally packed arrays of one dimensional cylindrical pores, with pore diameters ranging between 20 and 100 Å, large surface areas of upto 1500 $m^2 g^{-1}$ and pore volumes up to 1.3 $cm^3 g^{-1}$. These properties of the MCM 41 support ensure the easy accessibility of the reactants to the active

* Corresponding author. Tel.: +91 452 2416002; fax: +91 452 2415467.
E-mail address: rajagopal18@yahoo.com (G. Rajagopal).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.04.020

sites, and the functionalization of the bulky catalytic sites within the pores.

Abdi et al. reported[14] a chiral BINOL ligand covalently anchored on silica and mesoporous MCM-41 catalytic system for a Henry reaction. Khan et al. have reported the synthesis of copper complexes of (*S*)-amino alcohol-supported silica as chiral stationary phase and chiral ligand exchange stationary phase for the chromatographic separation of racemic compounds.[15] Mayani et al. successfully used a chiral copper complex supported on SBA-15 and MCF silicas for asymmetric nitroaldol reactions in the presence of chiral imine as an additive.[16]

While there are many studies on the asymmetric nitroaldol reactions under homogeneous conditions, only a limited number of recyclable homogeneous and heterogeneous catalysts have been reported. Furthermore, while several salen based metal complexes have been used for asymmetric organic transformations,[2b] no work has been reported using the MCM-41 supported copper salen complex for asymmetric Henry reactions.

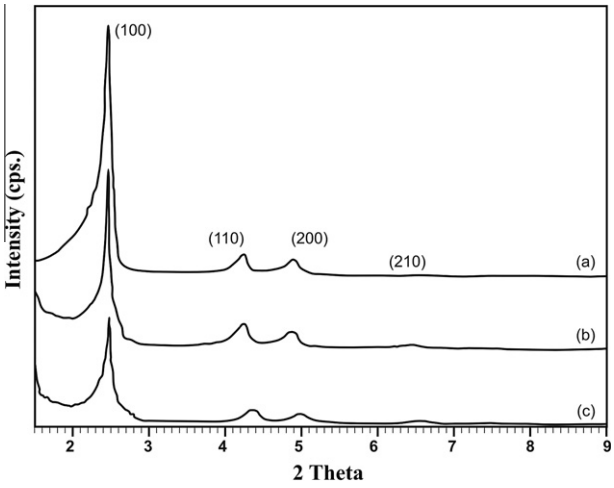
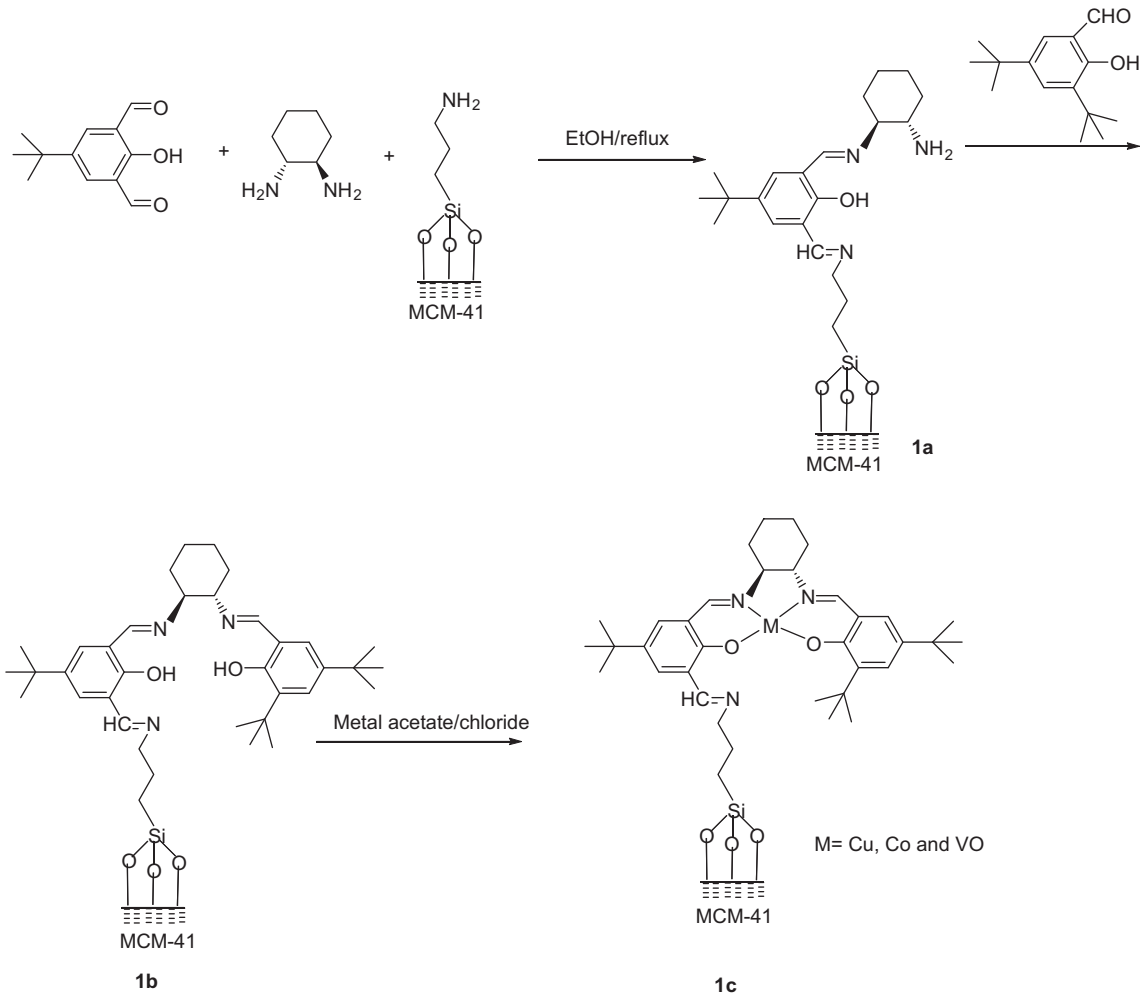


Figure 1. Powder XRD patterns of (a) MCM-41, (b) **1a** and (c) **1b**.

2. Results and discussion

The surface modification of compounds **1a** and **1b** (Scheme 1) were characterized by powder X-ray diffraction. The X-ray diffraction pattern for MCM-41 given in Figure 1a shows the presence of the four reflection peaks corresponding to 1 0 0, 1 1 0, 2 0 0 and 2 1 0 typically reported for MCM-41, which confirms the presence of ordered hexagonal mesoporous structure.[17] After the formation of **1a** [Fig. 1b] and **1b** [Fig. 1c], the intensities of the peaks at 1 0 0, 1 1 0, and 2 0 0 were reduced. This is due to the formation of a fine layer of modified salen ligand over MCM-41, which masks the original crystal structure of MCM-41. The XRD spectrum of copper



Scheme 1. Synthetic route of MCM-41 supported metal catalysts.

included MCM-41 modified salen ligand does not show any appreciable differences in the spectrum, except for a change in the increased d_{001} plane, which signifies the conservation of the mesoporous texture during the immobilization process. The presence of copper was also confirmed by the EDX spectrum (Fig. 2). Therefore, it can be concluded that the formation of the modified salen based copper catalyst takes place preferentially inside the pore system of the MCM-41.

Scanning electron microscopic images of MCM-41, modified salen moieties **1a** and **1b** and catalyst **1c** are shown in Fig. 3a–d. The particle sizes of **1a** and **1b** are different; the modified composite shows agglomerate particle. The effect was clearly seen in the SEM images. MCM-41-Cu(salen) shows a smaller particle size due to the complex formation between copper and **1b**. The ligands fitted perfectly with the pores resulting in no significant changes in the surface morphology. However, when copper was added, the ligands were thrown out from the inner core of the MCM-41 micropores and reorientate both within and outside the MCM-41. Such a complex further aggregated/agglomerated into smaller size clusters on the entire MCM-41. This 'house of cards' arrangement confirms the smaller particles in comparison to its precursor.

The FT-IR spectra of modified amine functionalized MCM-41 showed the characteristic bands at 1082 cm^{-1} of Si–O–Si and 3436 cm^{-1} of Si–OH bond (Fig. 4a). The salen anchored moiety shows characteristic peaks at 3300 cm^{-1} for $-NH_2$, and 1650 for CH═N, which suggest the successful anchoring of the salen moiety on MCM-41 (Fig. 4b). The characteristic band for the azomethane group of copper(II) complex moiety appears at ca. 1629 cm^{-1} in the IR spectrum of Cu-MCM-41 (Fig. 4c). The IR band of free CH═N group appears at 1650 cm^{-1} while in Cu-MCM-41 this band is shifted to a lower frequency, thus indicating the coordination of the azomethane nitrogen with copper.

The X-band EPR spectrum of the copper complex was recorded in acetonitrile solution. The representative EPR spectrum of Cu(II) complex is given in Figure 5. The EPR spectrum of the copper complex in solution exhibits a set of four well resolved peaks in the high field region. The 'g' tensor values of the copper(II) complexes can be used to derive the ground state. The observed 'g' values ($g_{\|} = 2.2522$; $g_{\perp} = 2.0751$) suggest that the unpaired electron lies predominantly in the $d_{x^2-y^2}$ orbital. The observed α^2 (0.7678) value indicates a good degree of metal–ligand covalency.[18]

To test the catalytic efficiency of the present catalyst, benzaldehyde was chosen as a test substrate to determine the best conditions for the nitroaldol reaction. The reactivity and enantiose lectivity of the nitroaldol reaction is strongly dependent upon the nature of the solvent used. Therefore, a catalytic enantioselective Henry reaction was conducted in different solvents, such as toluene, 1,2-dichloroethane, THF, CH_3CN, ethanol, and methanol, with catalyst **1c** under identical reaction conditions. As can be seen in Table 1, C_2H_5OH was the most appropriate solvent (Table 1, entries 1–6). CH_3OH also acts as a good solvent for this system with a slightly longer reaction time (Table 1, entry 5). CH_3CN and THF gave moderate yields and ee (Table 1, entries 3 and 4). The use of toluene and CH_2Cl_2 afforded low yield of nitroalcohols with longer reaction time.

Temperature also plays an important role in the yield and ee of the reaction. When we conducted the nitroaldol reaction of benzaldehyde as the model substrate at rt and −40 °C, there was a decrease in the yield (92% and 76%) (Table 2; entries 1 and 6) and no significant change in the ee values.[11b,16]

Since the Henry reaction is considered to employ basicity to generate the nitronate, a base was added to the reaction system in order to increase the reactivity of the catalyst. A series of bases were tested in a model reaction between nitromethane and benzaldehyde in the presence of catalyst **1c**. The results are summarized in Table 3. As expected, the reactivity of the catalyst and the yield of the nitroaldol products were significantly changed when a series of bases were added. Amongst the screened bases, morpholine gave excellent results (Table 3, entry 4). Bulky amines, such as Et_3N, DMAP, 2,6-DAP gave the nitroaldol adduct in

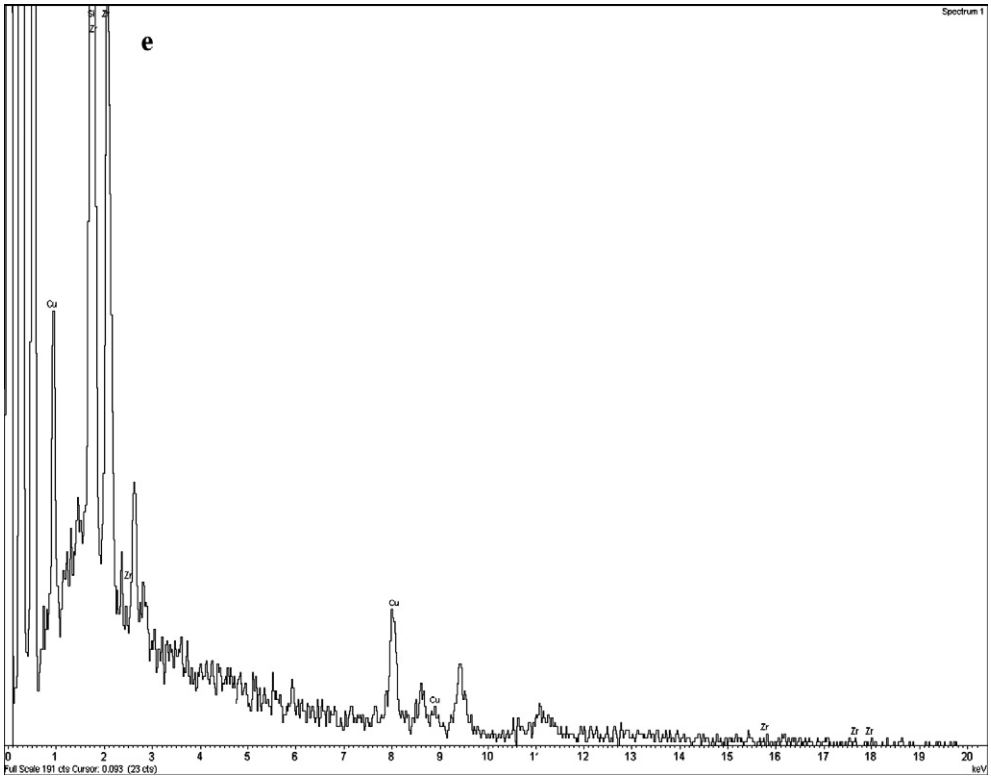


Figure 2. EDX pattern of pattern of **1c**.

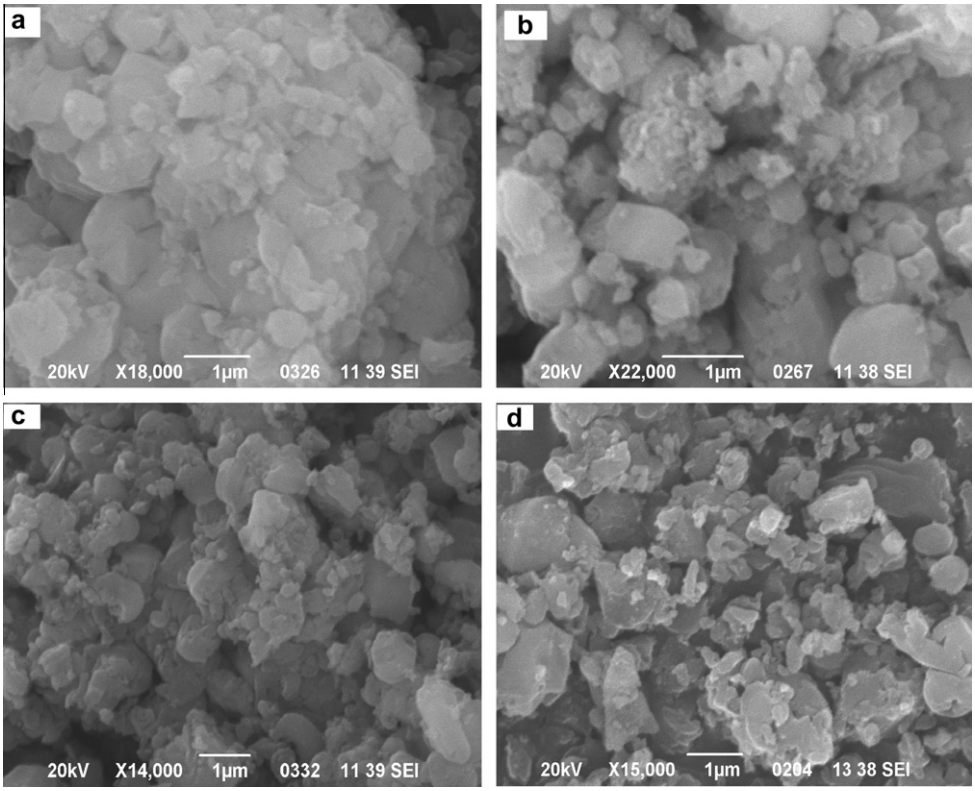


Figure 3. SEM images of (a) MCM-41, (b) **1a**, (c) **1b** and (d) **1c**.

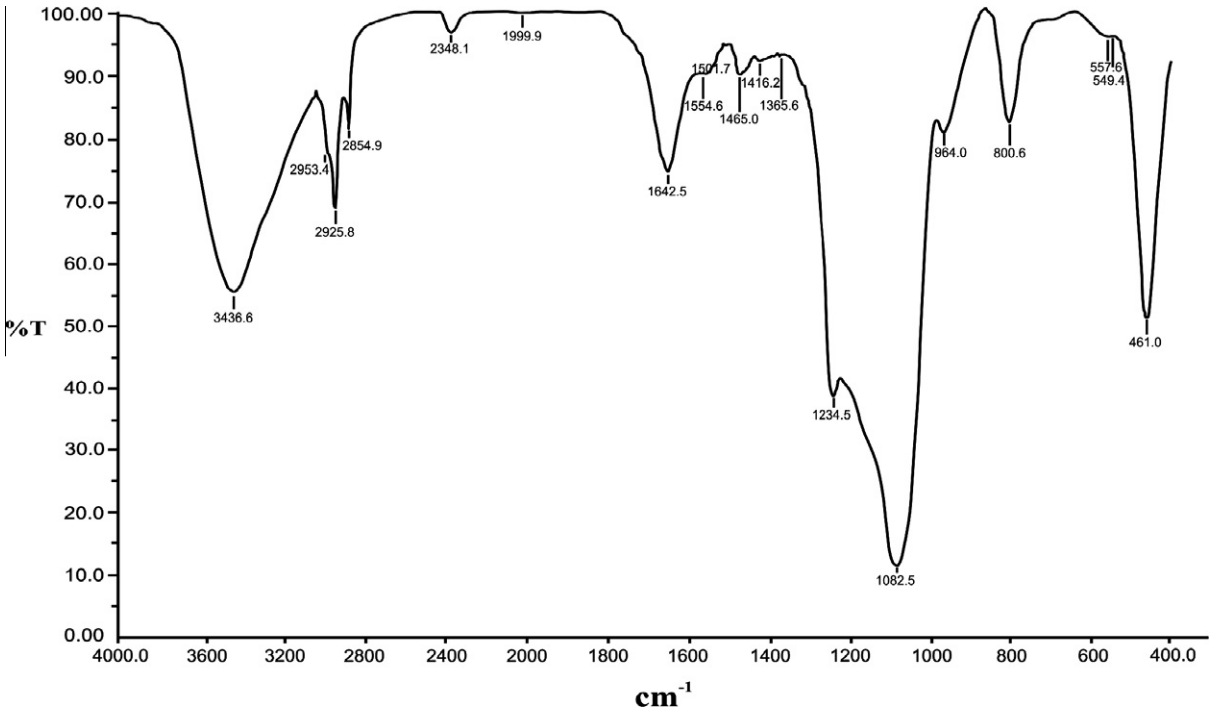


Figure 4a. IR spectrum of amino functionalized MCM-41.

moderate to good yields with moderate enantioselectivities (Table 3, entries 1–3). 4-Methylpyrimidine and *N*-methylmorpholine exhibited less reactivity with a longer reaction time (Table 3, entries 5 and 6). When pyridine was employed, the enantioselectivity and yield decreased (Table 3, entry 7).

To determine the efficiency of supported copper salen complexes, we carried out Henry reactions of benzaldehyde in the presence of morpholine as an additive under identical reaction conditions and the results are summarized in Table 4. It is evident that the copper supported catalyst performed well in terms of yield and ee.

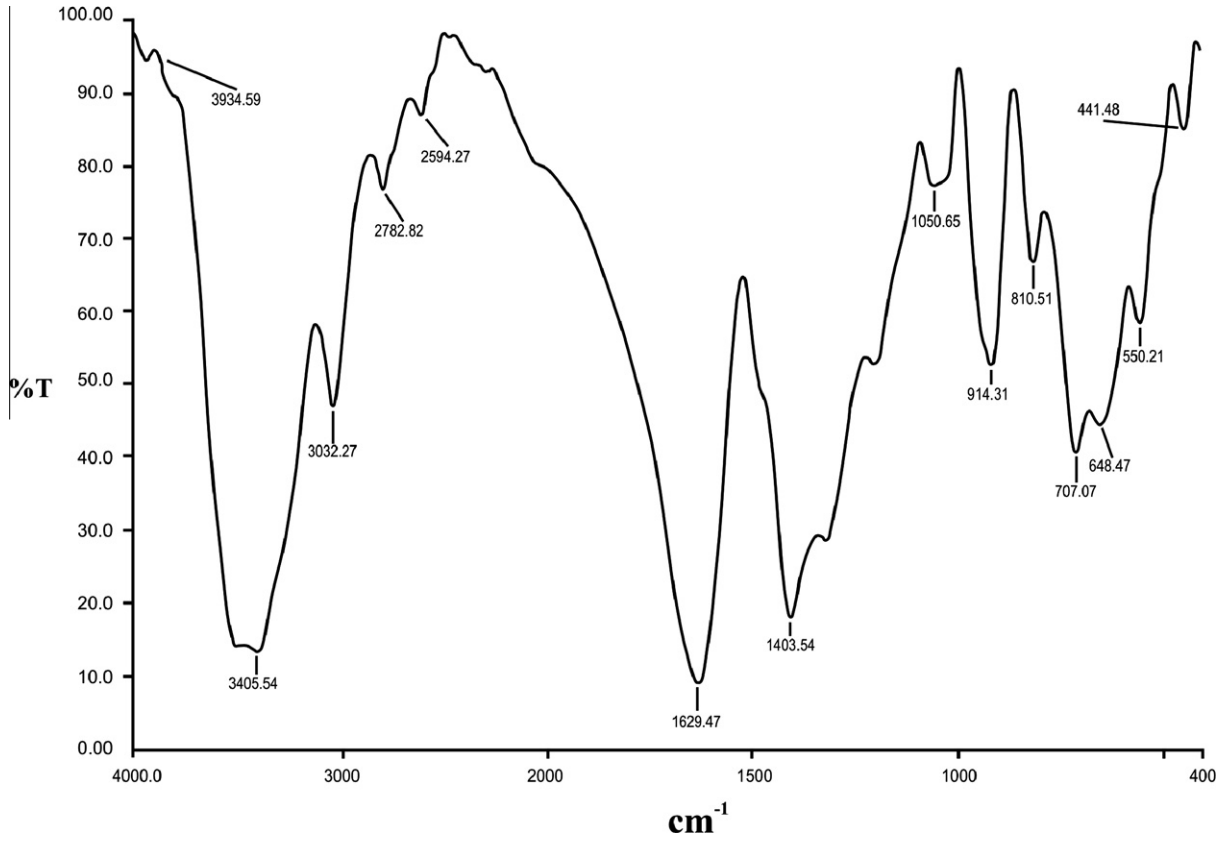


Figure 4b. IR spectrum of **1b**.

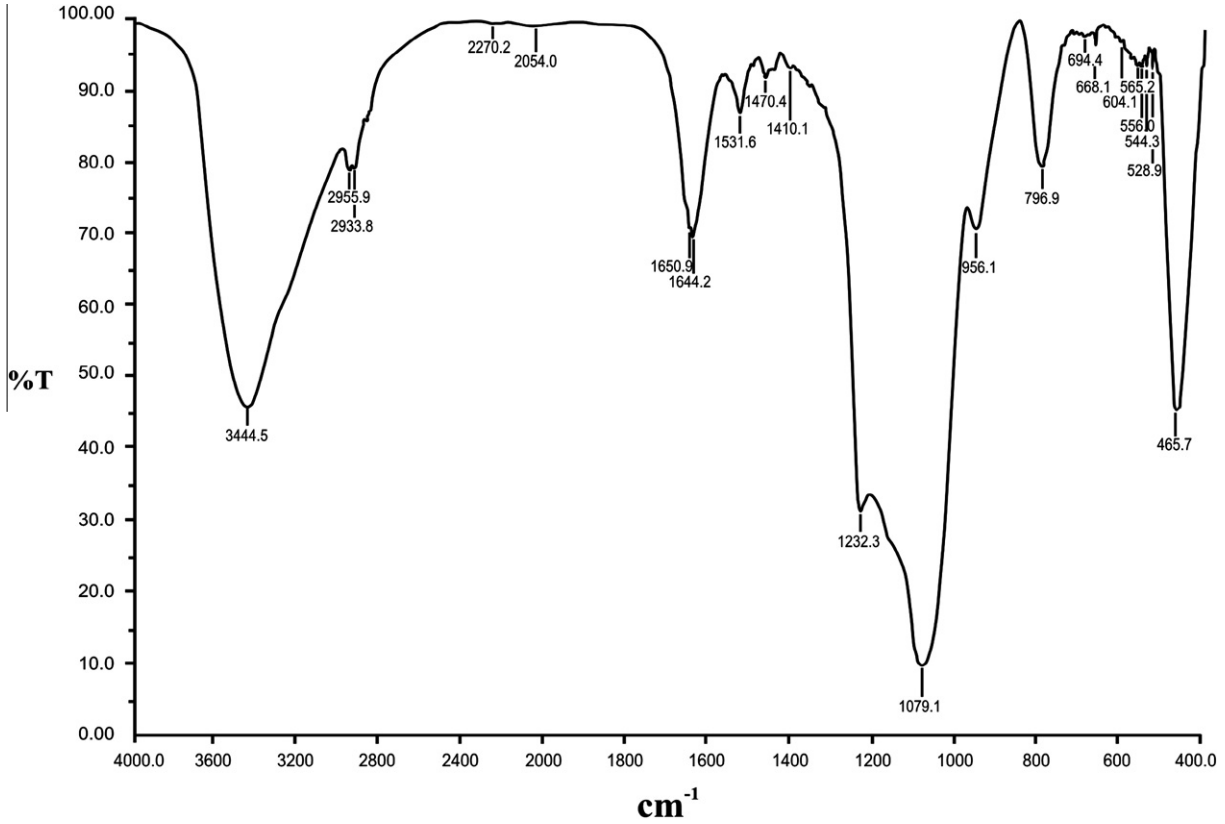


Figure 4c. IR spectrum of **1c**.

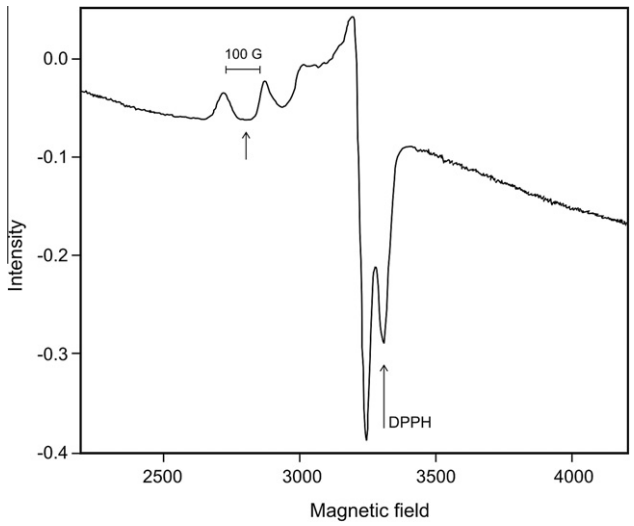
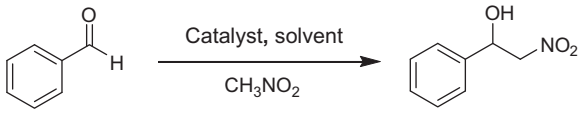


Figure 5. EPR spectrum of **1c**.

Table 1
Henry reaction of benzaldehyde under various solvent reaction conditions



Entry	Catalyst loading (mol %)	Solvent	Time (h)	Yield	ee (%)
1	10	CH_2Cl_2	36	70	65
2	10	Toluene	42	73	60
3	10	CH_3CN	18	86	71
4	10	THF	16	91	74
5	10	CH_3OH	12	90	85
6	10	C_2H_5OH	8	92	90

Table 2
Effect of temperature on the Henry reaction

Entry	Temp (°C)	Solvent	Time (h)	Yield	ee (%)
1	rt	C_2H_5OH	8	92	90
2	0	C_2H_5OH	13	84	85
3	−10	C_2H_5OH	15	84	88
4	−20	C_2H_5OH	22	80	90
5	−30	C_2H_5OH	28	80	88
6	−40	C_2H_5OH	36	76	85

Table 3
Effect of bases on Henry reaction at rt[a]

Entry	Base[b]	Solvent	Time (h)	Yield[c]	ee (%)
1	Et_3N	C_2H_5OH	13	85	80
2	DMAP	C_2H_5OH	15	82	80
3	2,6-DAP	C_2H_5OH	22	80	83
4	Morpholine	C_2H_5OH	8	92	90
5	4-Methylpyrimidine	C_2H_5OH	28	80	79
6	*N*-Methylmorpholine	C_2H_5OH	36	78	77
7	Pyridine	C_2H_5OH	18	75	65

[a] Reagents and conditions. 1.0 mmol of benzaldehyde.
[b] 10 mol % of base.
[c] Isolated yield.

To determine the effect of the catalytic loading on the yield, we performed the reaction with 3–15 mol % of catalyst **1c** in C_2H_5OH. For 10–15 mol % catalytic loading, the reactions took place with less reaction time and with high yields (Table 5, entries 1 and 2). Further reduction in the amount of catalyst from 10 to 5 mol % gave 85% yield in 16 h (Table 5, entry 3). For less than 5 mol % of catalytic loading, longer reaction times were required (Table 5, entries 4 and 5). Based on the above observations, the reaction conditions of entry 2 were chosen for the asymmetric nitroaldol reaction of aldehydes at room temperature.

Table 4
Nitroaldol reaction of benzaldehyde with various supported MCM-41 complexes

Catalyst	Mol %	Time (h)	Yield (%)	ee (%)
Cu-MCM-41	10	8	92	90
VO-MCM-41	10	72	45	30
Co-MCM-41	10	40	20	—

Given the aforementioned optimal results (Table 5, entry 2), the copper complex was used in the asymmetric addition of nitromethane to a variety of other aldehydes (Table 6). It was found that the present system worked well for various aromatic aldehydes, regardless of the substituents on the aromatic ring, that is, either the electron-withdrawing or donating group (Table 6, entries 1–11). The *o*- or *m*-position of the substituents on the phenyl ring had a limited effect on the yield and ee (entries 3–4 and 5–6). Bulkier aldehydes such as 1-napthaldehyde and 2-naphthaldehyde, could also give the corresponding adducts with good yield and ee (entries 12 and 13). A compromised yield and ee was obtained for cinnamaldehyde (entry 14). Heterocyclic aldehydes, furfuraldehye, and thiophenealdehdye, were found to be good substrates affording adducts with decent ee (entries 15 and 16).

Moderate conversions (60–89%) and ee (60–70%) were obtained when the Henry reaction was carried out with cyclic and straight chain aliphatic aldehydes (entries 17–20). The reaction appears to be catalyzed by a double activation process, which occurs via the catalysis of both chiral Lewis acid and achiral base.[8s,u,10] The supported Cu(salen) complex functions as a weak Lewis acid to activate the aldehyde oxygen while morpholine acts as a base for the activation of nitromethane (Scheme 2).

To access the recyclability of the supported Cu(salen) catalyst, the catalytic runs for the Henry reaction of benzaldehyde were taken as representative substrates by adding fresh reactants. From the data in Table 7, it is evident that the catalyst worked well for up to three cycles with only a small decrease in reactivity and enantioselectivity. With this limited success in recycling the supported catalyst, we hoped the insoluble supports would provide a more robust environment for the salen framework. The recovery of the catalyst was easily accomplished by filtration of the reaction mixture.

3. Conclusions

The MCM-41 supported Cu(salen) complex was able to promote a highly enantioselective Henry reaction between nitromethane and a wide range of aromatic and aliphatic aldehydes, providing high yields and excellent enantioselectivities. The effectiveness of this catalyst system and the simplicity of the reaction procedure make our catalyst widely applicable. The nitroaldol reaction takes place under relatively mild conditions in terms of temperature and reaction time. Further investigations to clarify the reaction mechanism and efforts to extend the use of the present catalytic system to other organic transformations are currently in progress.

4. Experimental

4.1. Materials and characterization

All chemicals were purchased from Sigma–Aldrich. ^1H and ^{13}C NMR were taken utilizing a Varian Jemini 2000 (300 MHz) or a

Table 5
Effect of catalytic loading of Cu-MCM-41 supported catalyst[a]

Entry	Catalyst loading (mol %)	Additive	Solvent	Temp	Time (h)	Yield[b]	ee (%)
1	15	Morpholine	C_2H_5OH	rt	8	96	88
2	10	Morpholine	C_2H_5OH	rt	8	92	90
3	5	Morpholine	C_2H_5OH	rt	16	85	83
4	3	Morpholine	C_2H_5OH	rt	38	78	84
5	2	Morpholine	C_2H_5OH	rt	42	77	77

[a] Reagent and condition. 1.0 mmol of benzaldehyde.
[b] Isolated yield.

Varian Unity Inova 400 (400 MHz) or a Bruker Avance 400 NMR spectrometer. Enantiomeric excess was determined by chiral HPLC column (DAICEL CHIRALCEL OJ-H, DAICEL CHIRALCEL OD-H and DAICEL CHIRALCEL OB-H). Analytical high performance liquid chromatography (HPLC) was performed on Gilson 305 series HPLC using the indicated chiral column. All data were in accordance with literature values. Absolute configurations were determined by the specific rotation. Powder X-ray diffraction (XRD) patterns of the samples were recorded with SHIMADZU Lab X-XRD600, Cu K Alpha, Japan. Scanning electron microscopic (SEM) images were recorded using JEOL JSM-6390, Japan. Energy dispersive X-ray analysis (EDX) was performed on INCApentaFETx3, Oxford Instruments, England.

4.1.1. Synthesis of metal immobilized chiral compounds

Chiral salen metal complexes immobilized on MCM-41 were prepared according to Scheme 1. 3-Aminopropylsilyl-functionalised MCM-41, and the chiral half units of salen immobilized on MCM-41 **1a** and **1b** were prepared by reported procedure.[19] The metal catalyst was prepared by an ethanolic solution of 1.0 equiv chiral unit of salen immobilized on MCM-41 **1b** and 1.0 equiv of metal acetate in an inert atmosphere for 8 h. The resulting mixture was filtered and washed several times with methylene chloride and methanol.

4.2. General procedure for the enantioselective Henry reaction

A mixture of MCM-41-Cu(salen) complex (10 mol %) and morpholine (10 mol %) were suspended in absolute ethanol (3 ml). The aldehyde (1 mmol) was added and the reaction mixture was stirred at rt until the reaction was complete (disappearance of substrate by TLC). After evaporation of the solvent, the residue was purified by column chromatography on silica gel (10–15% EtOAc–hexane) to afford the nitroaldol product. The nitroalcohols thus obtained were identified by ^1H and ^{13}C NMR data, which are consistent with the structure.

4.2.1. 1-Phenyl-2-nitroethanol (Table 6, entry 1)

^1H NMR ($CDCl_3$) δ 3.1 (br, 1H) 4.40–4.50 (m, 2H), 5.35 (dd, J = 6.0, 3.0 Hz, 1H), 7.31–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 71.1, 81.3, 126.2, 129.1, 129.3, 138.3. $[\alpha]_D^{24} = -15.08$ (c 1.18, CH_2Cl_2) 90% ee. HRMS(MC) calcd for $C_8H_9NO_3$: 167.0583.1079; found: 167.0577. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/98, flow = 0.8 mL/min) 22.1 and 21.3 min.

4.2.2. 1-(4-Methylphenyl)-2-nitroethanol (Table 6, entry 2)

^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 2.81 (br, 1H), 4.43–4.46 (m, 2H), 5.31 (dd, J = 9.0, 3.0 Hz, 1H), 7.12–7.26 (m, 4H) . ^{13}C NMR ($CDCl_3$) δ 21.0, 69.8, 83.2, 126.0, 127.1, 131.2, 139.2 $[\alpha]_D^{24} = -16.4$ (c 1.78, CH_2Cl_2) 80% ee. HRMS (MC) calcd for $C_9H_{11}NO_3$: 182.0817; found: 182.0825. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/9, flow = 0.8 mL/min) 19.1 and 18.3 min.

4.2.3. 1-(4-Methoxyphenyl)-2-nitroethanol (Table 6, entry 3)

^1H NMR ($CDCl_3$) δ 3.10 (br, 1H), 3.80 (s, 3H), 4.42–4.62 (m, 2H), 5.36 (dd, J = 9.0, 3.0 Hz, 1H), 6.92 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.0, 69.7, 81.0, 114.0, 127.6, 130.7, 160.5. $[\alpha]_D^{24} = -22.4$ (c 1.78, CH_2Cl_2) 82% ee. HRMS (MC) calcd for $C_9H_{11}NO_4$: 198.0766; found: 198.0773. HPLC (DAICEL CHIRALCEL OB-H, *i*PrOH/hexane = 2/9, flow = 0.8 mL/min) 25.6 and 25.0 min.

4.2.4. 1-(3-Methoxyphenyl)-2-nitroethanol (Table 6, entry 4)

^1H NMR ($CDCl_3$) δ 3.02 (br, 1H), 3.71 (s, 3H), 4.31–4.48 (m, 2H), 5.21 (dd, J = 9.5, 3.0 Hz, 1H), 6.70–6.90 (m, 2H), 7.26–7.31 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 53.2, 69.8, 80.3, 95.2, 110.2, 112.3, 118.1, 129.7, 139.2, 159.0. $[\alpha]_D^{24} = -27.4$ (c 1.78, CH_2Cl_2) 85% ee. HRMS (MC) calcd for $C_9H_{11}NO_4$: 198.0773; found: 198.0783. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 19.0 and 18.5 min.

4.2.5. 1-(4-Nitrophenyl)-2-nitroethanol (Table 6, entry 5)

^1H NMR ($CDCl_3$) δ 3.06 (br, 1H), 4.51–4.68 (m, 2H), 5.63 (br 1H), 7.58 (d, J = 9 Hz, 2H), 8.21 (dd, J = 6.8, 2.0, 2H). ^{13}C NMR ($CDCl_3$) δ 69.6, 80.1, 123.8, 126.7, 145.1, 148.0. $[\alpha]_D^{24} = +37.4$ (c 1.78, CH_2Cl_2) 87% ee. HRMS (MC) calcd for $C_8H_8N_2O_5$: 213.0511; found: 213.0521. HPLC (DAICEL CHIRALCEL OB-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 21.5 and 20.8 min.

4.2.6. 1-(3-Nitrophenyl)-2-nitroethanol (Table 6, entry 6)

^1H NMR ($CDCl_3$) δ 3.71 (br, 1H), 4.60–4.65 (m, 2H), 5.6 (dd, J = 9.6, 3.3 Hz, 1H), 7.52–7.80 (m, 2H), 8.11–8.30 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 71.0, 83.8, 122.8, 127.2, 131.0, 137.2, 139.1, 147.5 $[\alpha]_D^{24} = -27.4$ (c 1.78, CH_2Cl_2) 89% ee. HRMS (MC) calcd for $C_8H_8N_2O_5$: 213.0511; found: 213.0524 HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 22.7 and 21.5 min.

4.2.7. 1-(4-Chlorophenyl)-2-nitroethanol (Table 6, entry 7)

^1H NMR ($CDCl_3$) δ 3.01 (br, 1H), 4.43–4.52 (m, 2H), 5.42 (dd, J = 9.0, 3.0 Hz, 1H), 7.30–7.37 (m, 4H), ^{13}C NMR ($CDCl_3$) δ 70.5, 83.0, 129.2, 132.0, 134.6, 140.2 $[\alpha]_D^{24} = -17.4$ (c 1.78, CH_2Cl_2) 90% ee. HRMS (MC) calcd for $C_8H_8ClNO_3$: 202.0271; found: 202.0271. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 18.3 and 6.3 min.

4.2.8. 1-(4-Bromophenyl)-2-nitroethanol (Table 6, entry 8)

^1H NMR ($CDCl_3$) δ 3.31 (br, 1H), 4.36–4.58 (m, 2H), 5.30 (dd, J = 9.0, 3.3 Hz, 1H), 7.20–7.33 (m, 4H), $[\alpha]_D^{24} = -27.4$ (c 1.78, CH_2Cl_2) 80% ee. HRMS (MC) calcd for $C_8H_8BrNO_3$: 245.9766; found: 245.9775. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 19.0 and 11.0 min.

4.2.9. 1-(4-Flourophenyl)-2-nitroethanol (Table 6, entry 9)

^1H NMR ($CDCl_3$) δ 3.21 (br, 1H), 4.42–4.60 (m, 2H), 5.34 (dd, J = 9.0, 3.0 Hz, 1H), 7.06–7.12 (m, 2H), 7.38–7.40 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 70.2, 82.1, 117.1, 128.0, 134.0, 161.9, 165.0 $[\alpha]_D^{24} = -28.2$ (c 1.78, CH_2Cl_2) 82% ee. HRMS (MC) calcd for

Table 6
Addition of nitromethane to aldehydes catalyzed by MCM-41 supported Cu(salen) complex

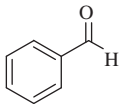
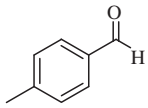
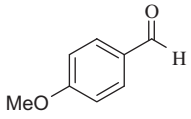
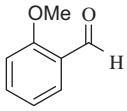
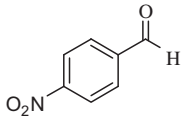
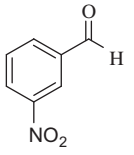
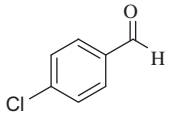
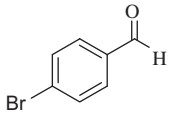
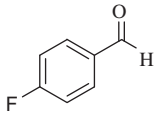
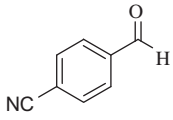
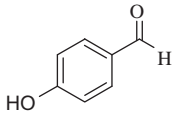
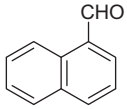
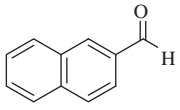
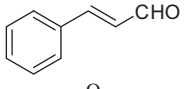
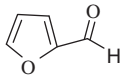
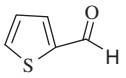
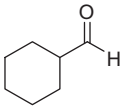
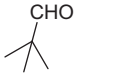
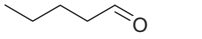
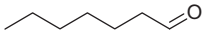
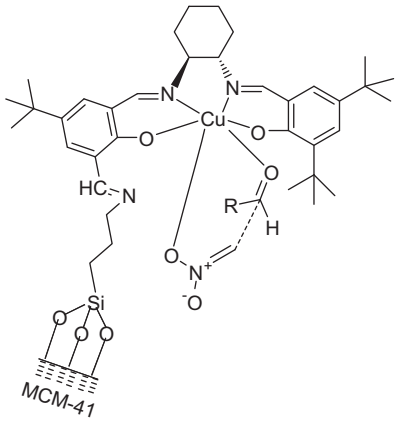
Entry	Substrate	Time (h)	Yield[a] (%)	ee (%)
1		8	92	90
2		15	88	80
3		12	91	82
4		11	90	85
5		9	85	87
6		10	87	89
7		14	90	90
8		13	85	80
9		10	88	82
10		10	90	88
11		16	87	90
12		11	85	88
13		12	83	85
14		10	81	80
15		14	83	82

Table 6 (*continued*)

Entry	Substrate	Time (h)	Yield[a] (%)	ee (%)
16		18	80	80
17		7	89	70
18		12	85	69
19		15	60	70
20		17	63	60

[a] Isolated yield.



Scheme 2. Transition state involved in the asymmetric nitroaldol reaction.

$C_8H_8FNO_3$: 185.0488; found: 185.0475 HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 19.1 and 11.1 min.

4.2.10. 1-(4-Cyanophenyl)-2-nitroethanol (Table 6, entry 10)

^{1}H NMR ($CDCl_3$) δ 3.20 (br, 1H), 4.51–4.61 (m, 2H), 5.58 (dd, J = 9.0, 3.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 70.3, 80.9, 112.2, 118.0, 126.3, 131.8, 144.0. $[\alpha]_D^{24} = -33.2$ (c 1.78, CH_2Cl_2) 88% ee; HRMS: calcd for $C_9H_8N_2O_3$: 191.0535, found 191.0545. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane =2/8, flow = 0.8 mL/min) 38.4 and 29.2 min.

4.2.11. 1-(4-Hydroxyphenyl)-2-nitroethanol (Table 6, entry 11)

^{1}H NMR ($CDCl_3$) δ 3.18 (br, 1H), 4.39–4.54 (m, 2H), 5.34 (dd, J = 9.0, 3.0 Hz, 1H), 7.15 (m, 2H), 7.50 (m, 2H) ^{13}C NMR ($CDCl_3$) δ 71.1, 82.9, 117.8, 129.0, 136.4, 155.9 $[\alpha]_D^{24} = -22.2$ (c 1.78, CH_2Cl_2), 90% ee. HRMS (MC) calcd for $C_8H_9NO_4$: 184.00610; found: 184.0621 HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 40.8 and 29.8 min.

4.2.12. 1-(1-Naphthyl)-2-nitroethanol (Table 6, entry 12)

^{1}H NMR ($CDCl_3$) δ 3.20 (d, J = 4.2 Hz, 1H), 4.46 (d, J = 6.0 Hz, 2H), 6.20 (m, 1H), 7.51 (dd, J = 8. 0 Hz, 8.0 Hz, 1H), 7.34–7.41 (m, 2H), 7.61 (d, J = 7.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.70 (dd, J = 7.2 Hz, 2.5 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 68.3, 80.1, 121.3, 123.3, 125.9, 126.1, 127.0, 129.6, 130.2, 134.2 $[\alpha]_D^{24} = -26.2$ (c 1.78, CH_2Cl_2) 88% ee; HRMS: calcd for $C_{12}H_{11}NO_3$: 217.0739, found 217.0728. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow = 0.8 mL/min) 20.2 and 13.7 min.

Table 7
Studies on the recyclability of the supported catalyst at rt

Catalyst	Run	Time (h)	Yield[a] (%)	ee (%)
Cu-MCM-41	1	8	90	92
	2	8	90	90
	3	9	88	87
	4	14	88	85
	5	15	85	85

[a] Isolated yield.

4.2.13. 1-Nitro-4-phenyl-but-3-en-2-ol (Table 6, entry 14)

^{1}H NMR ($CDCl_3$) δ 3.01 (br, 1H), 4.50 (d, J = 7 Hz, 2H), 5.12 (m, 1H), 6.20 (dd, J = 14. 0, 7.0 Hz, 8.0 Hz, 1H), 6.85 (d, J = 14. 0 Hz, 1H), 7.21–7.42 (m, 5H) ^{13}C NMR ($CDCl_3$) δ 135.1, 133.2, 128.2, 127.8, 126.0, 124.3, 80.1, 69.1 $[\alpha]_D^{24} = -22.2$ (c 1.78, CH_2Cl_2) 90% ee. HRMS (MC) calcd for $C_{10}H_{11}NO_3$: 194.0817; found: 194.0821. HPLC (DAICEL CHIRALCEL OD-H, *i*PrOH/hexane = 2/8, flow 0.8 mL/min) 16.3 and 12.3 min.

4.2.14. 1-(Furan-2yl)-2-nitroethanol (Table 6, entry 15)

^{1}H NMR ($CDCl_3$) δ 2.99 (br, 1H), 4.61–4.81 (m, 2H), 5.47 (dd, J = 9.0, 3.0 Hz, 1H), 6.31–6.41 (m, 2H), 7.41 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.1, 143.0, 110.0, 108.1, 78.2, 64.8 $[\alpha]_D^{24} = -26.2$ (c 1.78, CH_2Cl_2) 90% ee. HRMS calcd for $C_6H_7NO_4$: 157.0375; found: 157.0369; HPLC (DAICEL CHIRALCEL OB-H, *i*PrOH/hexane = 2/8, flow 0.9 mL/min) 36.5 and 36.9 min.

4.2.15. 1-Cyclohexyl-2-nitroethanol (Table 6, entry 17)

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.22 (s, 9H), 1.88 (s, 3H), 6.35–6.40 (m, 1H), 6.47–6.50(m, 1H), 7.41–7.43 (m, 1H). ^{13}C NMR ($CDCl_3$): δ = 0.49, 28.37, 65.89, 108.14, 110.68, 120.23, 143.09, 151.63. HRMS: calcd for $C_8H_{15}NO_3$: 173.1052, found 173.1060; HPLC (DAICEL CHIRALCEL OB-H, *i*PrOH/hexane = 2/8, flow 0.98 mL/min) 31.0 and 31.8 min.

4.2.16. 3,3-Dimethyl-1-nitrobutan-2-ol (Table 6, entry 18)

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.01 (9H, s); 2.41 (1H, d, J = 4.5 Hz); 4.10–4.15 (1H, m); 4.31–4.55 (2H, m). $[\alpha]_D^{24} = -28.1$ (c 1.78, CH_2Cl_2) 69% ee. HRMS: calcd for $C_6H_{13}NO_3$: 147.0895, found 147.0887; HPLC (DAICEL CHIRALCEL OB-H, *i*PrOH/hexane = 2/8, flow 0.9 mL/min) 25.5 and 26.3 min.

4.2.17. 1-Nitro-2-heptanol (Table 6, entry 19)

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.85 (t, J = 7.0 Hz, 3H), 1.30–1.43 (m, 5H), 1.39–1.51 (m, 3H), 2.80 (d, J = 5.0 Hz, 1H), 4.24–4.28 (m, 1H), 4.39 (dd, J = 13.0, 8.0 Hz, 1H), 4.32 (dd, J = 13.0, 3.0 Hz, 1H), ^{13}C NMR ($CDCl_3$) δ = 14.6, 23.1, 24.9, 31.1, 35.3, 68.1, 80.5. $[\alpha]_D^{24} = -28.2$ (c 1.78, CH_2Cl_2) 70% ee. HRMS: calcd for $C_7H_{15}NO_3$: 161.1052; found 161.1040. HPLC (DAICEL CHIRALCEL OB-H, *i*PrOH/hexane = 2/8, flow 0.9 mL/min) 33.7 and 28.2 min.

Acknowledgment

Financial support from the University Grants Commission, New Delhi [Grant No: F. No. 38-70/2009(SR)] is gratefully acknowledged.

References

1. (a) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993; (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
2. (a) Belokon, Y. N.; North, M.; Kagan, H. Novel Types of Chiral Catalysts for Asymmetric C–C Bond Formation Reactions. In *Current Trends in Organic Synthesis*; Scolastico, C., Nicotra, F., Eds.; Kluwer Academic, 1999; pp 221–228; (b) Achard, T. R. J.; Clutterbuck, L. A.; North, M. *Synlett* **2005**, 1828–1847; (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; (d) Marqus-Lopez, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401; (e) Zhang, B.; Cai, L.; Song, H.; Wang, Z.; He, Z. *Adv. Synth. Catal.* **2010**, *352*, 97.
3. Henry, L.; Hebd, C. R. *Seances Acad. Sci.* **1895**, *120*, 1265–1267.
4. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.
5. For reviews on the catalytic asymmetric Henry reaction, see: (a) Shibasaki, M.; Grçger, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, pp 1075–1090; (b) Shibasaki, M.; Grçger, H.; Kanai, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 2004; pp 131–133. Supplement 1; (c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444; (d) Boruwa, J.; Gogoi, J.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; (e) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574.
6. For selected examples, see: (a) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; (b) Marcelli, T.; Van der Haas, R. N. S.; Van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929–931; Reaction of α-ketoesters: (c) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732–733; Reaction of α-ketophosphonates: (d) Mandal, T.; Samanta, S.; Zhao, C. *Org. Lett.* **2007**, *9*, 943–945.
7. (a) Purkarthofer, T.; Gruber, K.; Gruber-Khadjawi, M.; Waich, K.; Skranc, W.; Mink, D.; Griengl, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3454–3456; (b) Gruber-Khadjawi, M.; Purkarthofer, T.; Skranc, W.; Griengl, H. *Adv. Synth. Catal.* **2007**, *349*, 1445–1450.
8. Rare-earth metals: (a) Saa, J. M.; Tur, F.; Gonzalez, J.; Vega, M. *Tetrahedron: Asymmetry* **2006**, *17*, 99–106; (b) Tur, F.; Saa, J. M. *Org. Lett.* **2007**, *9*, 5079–5082; Zinc: (c) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863; (d) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881–3884; (e) Liu, S.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831–1834; (f) Bulut, A.; Aslan, A.; Dogan, O. *J. Org. Chem.* **2008**, *73*, 7373–7375; Copper(II): (g) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881; (h) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; (i) Ginotra, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2007**, *5*, 3932–3937; (j) Selvakumar, S.; Sivasankaran, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156; (k) Ma, K.; You, J. *Chem. Eur. J.* **2007**, *13*, 1863–1871; (l) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066–4068; (m) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978–5981; (n) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595–3597; (o) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616–618; Copper(I): (p) Xiong, Y.; Wang, F.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007**, *13*, 829–833; (q) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323–9328; (r) Blay, G.; Climent, E.; Fernández, I.; Hernández, V.; Pedro, J. *Tetrahedron: Asymmetry* **2006**, *17*, 2046; (s) Blay, G.; Climent, E.; Fernández, I.; Hernández, V.; Pedro, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1603; (t) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725; (u) Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313–1316; Cobalt(II): (v) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2004**, *33*, 614–615; (w) Kogami, Y.; Nakajima, T.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1947–1950; Magnesium: (x) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171; Chromium(III): (y) Kowalczyk, R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753–756; (z) Kowalczyk, R.; Sidorowicz, L.; Skarzewski, J. *Tetrahedron: Asymmetry* **2007**, *18*, 2581; (aa) Zulauf, A.; Mellah, M.; Schulz, E. *J. Org. Chem.* **2009**, *74*, 2242.
9. Cheng, L.; Dong, J.; You, J.; Gao, G.; Lan, J. *Chem. Eur. J.* **2010**, *16*, 6761–6765.
10. Sanjeevakumar, N.; Periasamy, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1842–1847.
11. (a) Jin, W.; Li, X.; Huang, Y.; Wu, F.; Wan, B. *Chem. Eur. J.* **2010**, *16*, 8259–8261; (b) Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301–3310.
12. Mastrorilli, P.; Nobile, C. F. *Coord. Chem. Rev.* **2004**, *248*, 377–395.
13. (a) Corma, A. *Chem. Rev.* **1997**, *97*, 2373; (b) On, D. T.; Desplantier-Giscard, D.; Danumah, C.; Kaliaguine, S. *Appl. Catal. A* **2003**, *253*, 545; (c) Taguchi, A.; Schusth, F. *Microporous Mesoporous Mater.* **2005**, *77*, 1.
14. Bhatt, A. P.; Pathak, K.; Jasra, R. V.; Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R. *J. Mol. Catal. A: Chem.* **2006**, *244*, 110–117.
15. (a) Mayani, V. J.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Agrawal, S.; Jasra, R. V. *J. Chromatogr., A* **2008**, *223*, 1191; (b) Mayani, V. J.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Agrawal, S.; Jasra, R. V. *J. Chromatogr., A* **2006**, *186*, 1135; (c) Mayani, V. J.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Agrawal, S.; Jasra, R. V. *Chirality* **2008**, *21*, 255.
16. Mayani, V. J.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Das, A.; Bajaj, H. C. *J. Org. Chem.* **2010**, *75*, 6191–6195.
17. (a) Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710; (b) Brieler, F. J.; Grundmann, P.; Fröba, M.; Chen, L.; Klar, P. J.; Heimbrodt, W.; Krug von Nidda, H. A.; Kurz, T.; Loidl, A. *J. Am. Chem. Soc.* **2004**, *126*, 797.
18. Swett, V. C.; Dudek, E. J. *J. Phys. Chem.* **1968**, *72*, 1244–1249.
19. Kim, G. J.; Shin, J. H. *Catal. Lett.* **1999**, *63*, 205–212.