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ARTICLE

# Chiral copper-salen complex grafted over functionalized mesoporous silica as an efficient catalyst for the asymmetric Henry reactions and synthesis of potent drug *(R)*-isoproterenol

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Synthesis of enantiomerically pure drug molecules by using functionalized mesoporous materials bearing chiral moiety is a long standing goal in heterogeneous catalysis. Herein, we report an efficient and enantioselective one-pot Henry reaction over highly ordered functionalized mesoporous silica supported chiral copper-salen catalyst, Cu(II)@AFS-1 in DCM at RT. The catalyst has been characterized by UV-Vis, FT-IR spectroscopy, PXRD, $N_2$ adsorption/desorption, HR-TEM, EPR, thermogravimetric and elemental analyses. The diastereoselective Henry reaction of nitroethane has been carried out by using this catalyst to obtain good yields (up to 96%) and ee (up to 95%) of β-nitroalcohols with acceptable dr (3.2:1). Additionally, enantiomerically pure drug *(R)*-(-)-isoproterenol can be synthesized through asymmetric Henry reaction of 3,4-dimethoxybenzaldehyde over this chiral mesoporous Cu-catalyst as a key step.

## Introduction

Asymmetric Henry (nitro aldol) reaction comprises one of the most constructive and atom-economical methodologies to generate enantiomerically pure β-hydroxy nitroalkanes[1] through the construction of new C-C bond. A growing interest has been paid to the resulting β-nitro alcohols due to its multipurpose applications for the synthesis of chiral ligands, various pharmaceutically important structural gibbets, biologically potent compounds,[2] etc. Besides, due to the chemical versatility of the nitro group,[3] the newly formed β-nitro alcohol can easily be transformed into other chiral building blocks by oxidation, reduction, Nef reaction,[4] and nucleophilic displacement. Further, it can also be used for the synthesis of poly amino alcohols, natural products and poly hydroxylated amides[5] etc., which are used for the synthesis of more complex compounds.[6] Therefore, continuous and substantial efforts have been paid to develop a simple and novel asymmetric catalytic system for this reaction.[7] In the year 1992, Sasai et. al. have reported the pioneering work on the asymmetric version of the nitro aldol (Henry) reaction.[8] Thereafter, a large number of organocatalysts bearing reactive organic functionalities[9] as well as heterogeneous chiral catalysts[10] have been developed for the Henry reaction with uneven accomplishment. The majority of these catalytic systems provide good to brilliant yields and enantioselectivities but require low temperatures and high catalyst loadings. As a fallout, further modifications are necessary in pursuit to mitigate these obstacles, high expenditure of chiral catalysts and to recycle the catalyst through immobilization of the metal-complex on to the solid support for scaling-up. Moreover, as compared to other metal complexes, the chiral copper(II) complexes are found to be the most effective in catalysing the asymmetric Henry reaction[11] with good to marvellous product yield and enantioselectivity. In this regard, a range of non-immobilized copper containing chiral catalysts (Cu(II)-chiral *C*1-symmetric dinitrogen ligand,[12a] $(CuOTf)_2.C_6H_5CH_3$-chiral tetrahydrosalen ligand,[12b] Cu(II)-pyridinylmethyl diphenyl prolinolsilyl ether,[12c] trans-N, N'-bis-biphenyl-4-ylmethyl-cyclohexane-1,2 diamine $CuCl_2$ complex)[12d] have been reported in the literature. Besides, Kureshy *et al.*[13a,b] Dhahagani *et al.*[13c] Khan *et al.*[13d,e,f] Jones *et al.*[13g] and Bhosale *et al.*[13h] also reported immobilized copper salen complexes for the asymmetric Henry reaction with moderate to good yield and enantioselectivity. Additionally, environment friendly nature, no need of additives and mild reaction conditions could make the chiral metal complex bound to mesoporous support as highly demanding heterogeneous catalyst.[14] Due to high specific area, ordered pore arrangement, high thermal and mechanical stability, and possibility of recycling, the immobilization of a reactive metal complexes or functional moieties over mesoporous materials could be an ideal strategy in catalysis.[15] In this context, functionalization of the 2D-hexagonally ordered mesopore surface with organic moieties, especially immobilization of chiral complexes is very challenging for carrying out sustainable asymmetric catalysis over a long period of time.[16] Recently, we have reported acid functionalized mesoporous silica bearing the chiral metal complexes for catalytic epoxide ring opening reactions.[17]

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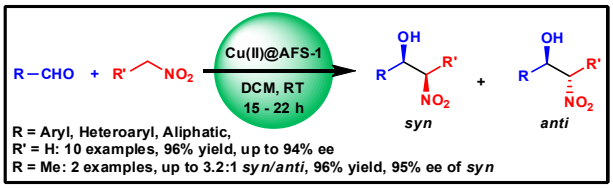
Herein, we report the synthesis of a new chiral Cu(II)-salen complex grafted over acid functionalized periodic mesoporous material to obtain Cu(II)@AFS-1 material (Fig. 1), which successfully catalyses the asymmetric Henry reaction to furnish a library of *β*-nitro alcohols in excellent yields along with good ee at RT in DCM (Scheme 1). Moreover, our synthetic protocol has been efficiently employed for the synthesis of a clinically potent drug (R)-Isoproterenol, which is used intensively for the treatment of heart blockage, bronchitis, asthma and emphysema.[18] It is pertinent to mention that (R)-form of this drug is around 90 times more effectual than the (S)-form.[17]




**Scheme 1** Cu(II)@AFS-1 catalysed synthesis of chiral *β*-nitro alcohols.

## Results and discussion

### Synthesis of chiral Cu(II)AFS-1 catalyst:

Fig. 1 represents the stepwise synthetic pathway for the chiral catalyst Cu(II)@AFS-1. The chiral Schiff base ligand (1) was prepared through the stepwise functionalization of 3-tert-butyl-2-hydroxy-benzaldehyde following our previously reported literature.[16b] Then the metalation of the chiral ligand 1 furnish the homogeneous copper(II)-salen complex 2. Besides, the surface modification of SBA-15 produced the solid support AFS-1.[16b] Thereafter, the metal salen complex 2 was grafted at the surface of AFS-1 to generate the final chiral catalyst Cu(II)@AFS-1. The foremost possible structure of the functionalized Schiff base ligand (1) was studied by $^1$H NMR analysis (Fig S1, ESI). The spectroscopic data was in full agreement with the literature report.

### Porosity and nanostructure:

The small angle powder X-ray diffraction pattern of Cu(II)@AFS-1 material is shown in Fig 2a. Three significant characteristic peaks were observed at 2θ value of 0.92°, 1.60° and 1.84°, corresponding to the diffraction planes of 100, 110 and 200, respectively for the ordered 2D hexagonal mesoporous materials.[19] To measure surface area and pore size distribution, nitrogen sorption analysis has been carried out and $N_2$ adsorption/desorption isotherm is given in Fig 2b. The material exhibits typical type IV isotherm with a large hysteresis loop of type H1 in the high-pressure region i.e. 0.59 to 0.87 relative pressure of nitrogen.[20] As seen from Fig 2b the appearance of large hysteresis loop in high $P/P_0$ region suggested the presence of uniform cylindrical mesopores in the material.[18d] The BET (Brunauer-Emmett-Teller) surface area and pore volume of this material were 174 $m^2$ $g^{-1}$ and 0.2395 cc $g^{-1}$, respectively. By employing Non-Local Density Functional Theory (NLDFT), pore size of the material has been calculated, which suggested a peak at 7.02 nm from the pore size distribution plot (inset of Fig 2b). The De Boer statistical thickness (*t*-plot) suggested that the surface area of Cu(II)@AFS-1 was mostly obtained due to mesoporosity and there is very low contribution of microporosity in total BET surface area.

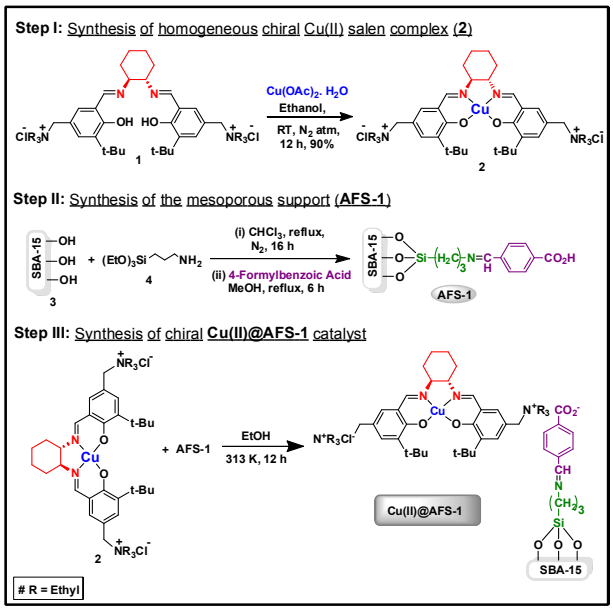



**Figure 1.** Outline for the synthesis of chiral Cu(II)AFS-1 catalyst (Supporting information Section I, Fig. S1)

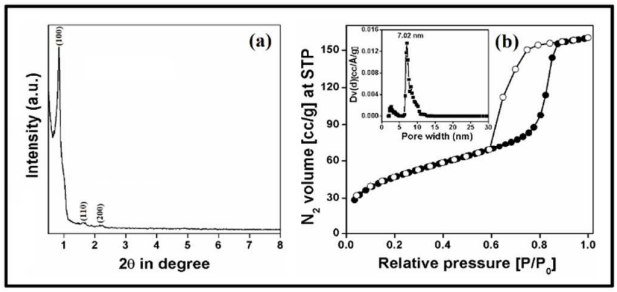



**Figure 2.** (a) Small angle powder XRD pattern of the Cu(II)@AFS-1 catalyst. (b) The nitrogen adsorption-desorption isotherm of Cu(II)@AFS-1. The pore size distribution estimated by NLDFT method is shown in inset.

### HR-TEM and EPR study:

The UHR-TEM images of Cu(II)@AFS-1 material is shown in Fig 3. From Fig 3a and 3b, it is noticed that regularly arranged ordered hexagonal pores perpendicular to the pore axis are spread over the whole specimen. Fig 3a, 3b and 3c represent the UHR-TEM images of Cu(II)@AFS-1 material at three different resolutions in different positions. The Fast Fourier Transform (FFT) pattern is shown in the inset of Fig 3b, suggesting the presence of highly ordered hexagonal pores in this material. Also, the channel like structural patterns are seen parallel to the pore axis in Fig 3c. To know the definite coordination environment changes of metal (copper) centre, electron paramagnetic resonance (EPR) analysis has been performed at room temperature (298 K) using freshly prepared copper grafted acid functionalized solid catalyst Cu(II)@AFS-1. As shown in Fig 3e, the material exhibits sharp and clear four splitting component in low magnetic field region due to hyperfine coupling between nuclear spin of copper and unpaired electrons, which are −3/2, −1/2, +1/2, +3/2. From EPR spectrum other three parameters has been obtained where $g_{\parallel}$ =2.40, average $g_{\perp}$ = 2.11, suggesting the distorted tetrahedral square planar geometry of Cu(II) ions.[21]

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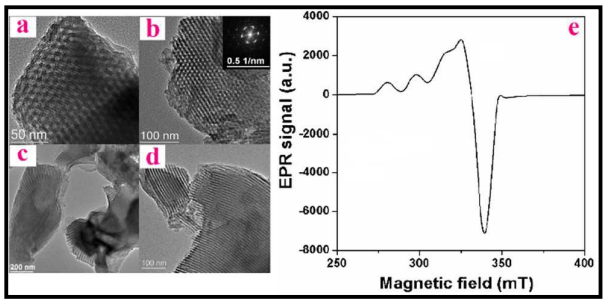


**Figure 3.** The UHR-TEM images of Cu(II)@AFS-1 material (a, b) perpendicular to the pore axis, (c) different resolution and (d) parallel to the pore axis. The FFT pattern is shown in the inset of figure 3b. (e) EPR spectrum of Cu(II)@AFS-1 material.

**Spectroscopic studies:**

In Fig. 4 the UV-Vis DRS absorption spectra of AFS-1 and Cu(II)@AFS-1 are shown. The appearance of a new broad band near 345-450 nm indicated the presence of surface bound Cu(II) sites in the chiral catalyst. Fig. 5 represented the FT-IR spectra of SBA-15 (a), 3-aminopropyl triethoxysilane functionalized SBA-15 (b), carboxylic acid functionalized mesoporous material AFS-1 (c), and heterogeneous chiral catalyst Cu(II)@AFS-1 (d) respectively. The broad peak (a, Fig. 5) near about 3000 $cm^{-1}$ signifies the aliphatic C–H stretching vibrations. The intensity of this peak raises gradually with the surface modification of SBA-15 to Cu(II)@AFS-1. Besides the broad peak near 1084 $cm^{-1}$ (for Si-O-Si bond) and 3444 $cm^{-1}$ (Si-OH bond) undoubtedly indicate the existence of SBA-15 material. In the spectrum 'b' (Fig. 5) the peak near 1556 $cm^{-1}$ could be ascribed for the deformed N-H vibrations of amido-groups of 3-APTES functionalized SBA-15. Again, the peaks near 1350-1600 $cm^{-1}$ in the figure (c, d, Fig. 5) suggested the presence of -C=N- starching vibrations of the surface modified catalyst. Thus, the FT-IR spectra revealed the successful step by step modification of SBA-15 to the chiral catalyst Cu(II)@AFS-1.

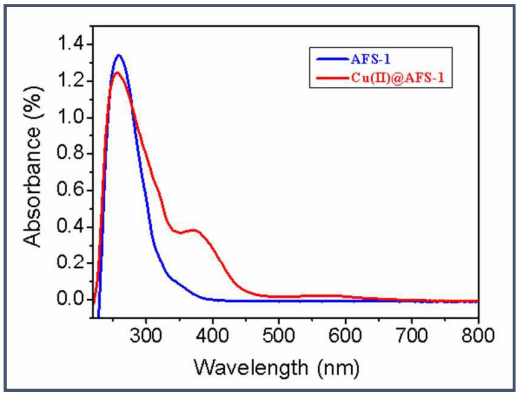


**Figure 4.** The DRS-UV-Vis absorption spectrum of AFS-1 and chiral Cu(II)@AFS-1 catalyst.

**Thermal stability:**

To measure the thermal stability of Cu(II)@AFS-1 we have carried out TGA/DTA analysis with temperature ramp of 10 °C per min. As seen from Fig. 6 the first weight loss up to 102 °C could be attributed to the evaporation of surface adsorbed moisture and second weight loss is observed 187 to 530 °C due to the decomposition of organic part of the material.

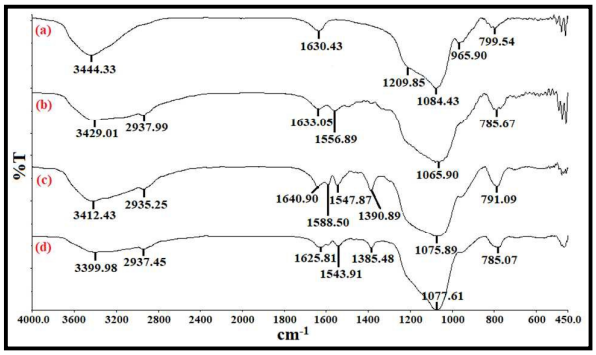


**Figure 5.** FT IR spectra of (a) SBA-15, (b) 3-APTES functionalized SBA-15, (c) acid functionalized mesoporous material AFS-1 and (d) heterogeneous chiral catalyst Cu(II)@AFS-1.

Beyond this temperature the weight loss could be assigned due to the further condensation in the material. Thus, TGA analysis revealed the good thermal stability of material, which is good enough to conduct the heterogeneous catalytic reactions.

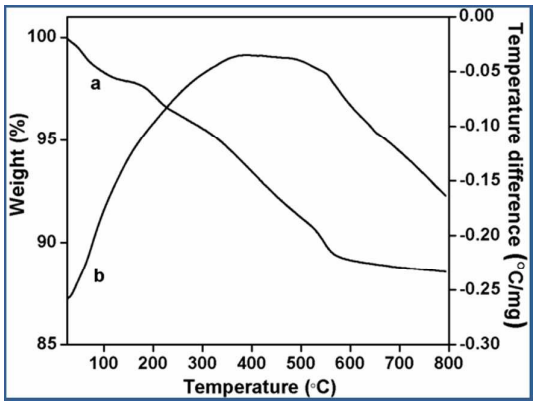


**Figure 6.** The TG-DTA profile diagram of Cu(II)@AFS-1.

**Elemental data of the Cu(II)@AFS-1:**

The CHN analysis data revealed the carbon, hydrogen and nitrogen content in the material framework, where C = 11.22 %, H = 2.74 % and N = 2.77 %, respectively. AAS analysis revealed the copper content in freshly prepared Cu(II)@AFS-1 material, which was estimated as 0.178 $mmolg^{-1}$. FT-IR: 3399, 2937, 1625, 1544, 1385, 1077, 874 $cm^{-1}$.

**Enantioselective Henry Reaction:**

Taking the aforesaid benefits of a heterogeneous catalytic system in mind, our preliminary study was to evaluate the optimum reaction conditions for the reactivity of the Cu(II)@AFS-1 catalyst. For this purpose, 4-nitro benzaldehyde (**1a**) and nitromethane were chosen as the model substrates. Table 1 briefly delivers this result. The reaction is not possible without addition of catalyst (Table 1, Entry 1). Even though, a range of solvents viz. ethanol, THF, benzene,

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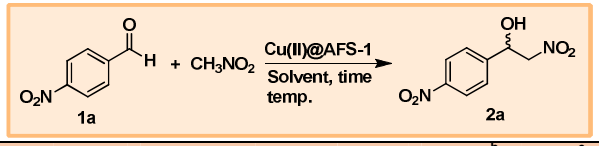
chloroform etc. were used but DCM has furnished the best outcomes in terms of yield and enantioselectivity of the product 2a (Table 1, Entry 2-7). Next, we screened the amount of the catalyst and reaction temperature (Table 1, Entry 7-13). For 5 mg catalyst loading the product yield value is very low (Table 1, Entry 8), while for 10 mg catalyst the reaction took place with good product yield and ee. Next we have increased the catalyst loading from 10 to 12 mg. Here, product yield negligibly increases but improvement in the ee value was observed (Table 1, entries 7 and 9). With 15 mg catalyst, no further improvement of the ee value was observed, but decreases slightly. Normally, lower temperatures are beneficial in asymmetric synthesis because enantioselectivity of the product is enhanced.

**Table 1.** Optimization table for the asymmetric Henry reaction over Cu(II)@AFS-1[a]

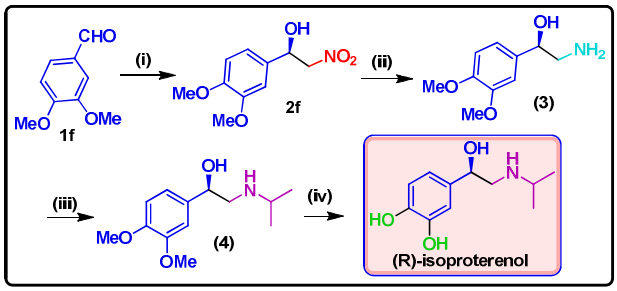



| Entry | Cat. (mg) | Solvent | T [ºC] | t [h] | Yield[b] [%] | ee[c] |
|---|---|---|---|---|---|---|
| 1 | - | - | RT | 72 | 00 | - |
| 2 | 12 | - | RT | 15 | 91 | 87 |
| 3 | 12 | EtOH | RT | 15 | 79 | 80 |
| 4 | 12 | THF | RT | 15 | 60 | 64 |
| 5 | 12 | PhH | RT | 15 | 41 | 52 |
| 6 | 12 | $CHCl_3$ | RT | 15 | 69 | 79 |
| **7** | **12** | **DCM** | **RT** | **15** | **95** | **91** |
| 8 | 5 | DCM | RT | 15 | 64 | 84 |
| 9 | 10 | DCM | RT | 15 | 94 | 88 |
| 10 | 15 | DCM | RT | 15 | 96 | 89 |
| 11 | 12 | DCM | 10 | 15 | 75 | 84 |
| 12 | 12 | DCM | 0 | 15 | 48 | 80 |
| 13 | 12 | DCM | 40 | 15 | 90 | 75 |

[a]**Conditions: 1a** (1.0 mmol), $CH_3NO_2$ (6.0 mmol), Cu(II)@AFS-1 (5-15 mg), solvent (2 mL), RT (25 °C). [b]Isolated yield. [c]Determined by HPLC using Chiralcel OD-H column

In some cases, however, better results are achieved at ambient or higher temperatures since the catalyst requires activation.[22] In our present study, we used heterogeneous chiral mesoporous material as an active catalyst with which an extensive study was done varying the temperature from 0 to 40 °C (Table 1, Entry 7, 11-13). We observe that at lower temperatures (Table 1, Entry 11-12) the enantioselectivities are better but the yield is very low, because of the lower activity of the catalyst. While at higher temperature (Table 1, Entry 13) the amount of yield is improved but the enantioselectivity decreases enormously. But at RT (25 °C) (Table 1, Entry 7) both yield and enantioselectivity are improved. Hence an appropriate temperature is required to gain a minimum amount of activation energy for the production of the corresponding product with high yield and enantioselectivity. We found that, our Cu(II)@AFS-1 chiral catalyst exhibits the best catalytic activity for carrying out the Henry reaction at RT in DCM for 15 h using just 12 mg (0.2136 mol % of Cu) of the Cu(II)@AFS-1 catalyst (Table 1, entry 7).

Having established the applicability of chiral Cu(II)@AFS-1 catalyst in Henry reaction as per entry 7 (Table 1), we have further extended this optimized reaction conditions for a number of aromatic aldehydes viz, 4-$NO_2$ benzaldehyde, 4-Cl benzaldehyde, benzaldehyde, 4-Me benzaldehyde, 4-MeO benzaldehyde, and 3-Cl benzaldehyde etc., and the results are summarized in Table 2. In terms of yield and enantioselectivity the catalyst displayed high efficiency in most of the cases. Both electron donating or withdrawing groups attached to the benzene ring of the corresponding aldehydes (Table 2) have a little effect towards the conversion (90 - 96 %) as well as enantioselectivity (85 - 94 %). Furthermore, together with the aromatic aldehydes, heteroaromatic aldehydes viz, furan-2-carbaldehyde and thiophene-2-carbaldehyde were also the promising partners in this work providing the desired *β*-nitro alcohols in 92-93% yields and 88 - 90 % ee (Table 2, Entry 8, 9). Additionally, aliphatic aldehydes, heptanal (**1j**) and cyclohexanecarbaldehyde (**1k**) also underwent this reaction following our optimized reaction conditions giving 84% and 82% yields and 81% and 85% ee, respectively (Table 2, entries 10 and 11). In all these cases, Cu(II)@AFS-1 with (S, S) selectivity afforded the (R)-nitro alcohols, except for furan-2-carbaldehyde and thiophene-2-carbaldehyde. The latter two compounds are (S)-configured, but just for formal reasons of the CIP notation (Table 2). A similar observation was reported by Zulauf et al. using chiral chromium thiophene-salen complexes.[23] The selectivity and ee values of the corresponding products have been examined by the $^1$H-NMR and HPLC analyses (ESI†).




**Scheme 2** Synthesis of (R)-isoproterenol. Reaction conditions: (i) Cu(II)@AFS-1, DCM, RT, 15h, (ii) $H_2$, 10% Pd/C, EtOH, (iii) (a) EtOH, acetone, (b) $NaBH_4$ (iv) $AlCl_3$, EtSH, DCM, RT. ($^1$H NMR and HPLC chromatograms of the products are provided in Figures S3-S6)

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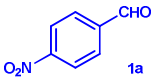
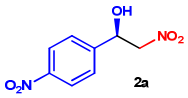
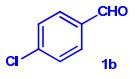
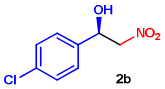
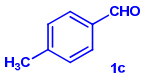
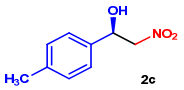
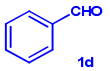
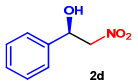
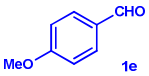
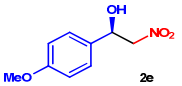
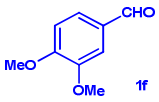
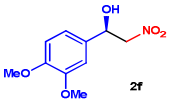
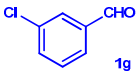
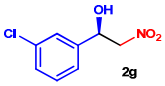
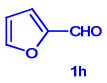
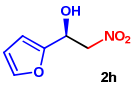
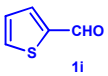
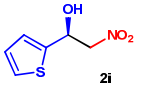
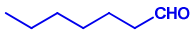
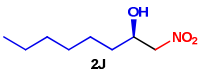
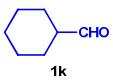
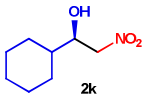
**Table 2.** Variation of substrates in asymmetric nitro aldol reaction[a]

| Entry | Aldehyde | Product[b] | *t* (h) | Yield[c] (%) | ee[d] (%) | TON[e] |
|---|---|---|---|---|---|---|
| 1 |  1a |  2a | 15 | 95 | 91 | 445 |
| 2 |  1b |  2b | 16 | 94 | 90 | 440 |
| 3 |  1c |  2c | 15 | 90 | 87 | 421 |
| 4 |  1d |  2d | 15 | 96 | 94 | 449 |
| 5 |  1e |  2e | 15 | 94 | 85 | 440 |
| 6 |  1f |  2f | 15 | 96 | 93 | 449 |
| 7 |  1g |  2g | 15 | 93 | 93 | 435 |
| 8 |  1h |  2h | 16 | 93 | 88 | 435 |
| 9 |  1i |  2i | 16 | 92 | 90 | 430 |
| 10 |  1J |  2J | 22 | 84 | 81 | 393 |
| 11 |  1k |  2k | 22 | 82 | 85 | 384 |

[a]**Reaction condition** aldehyde (1 mmol), nitromethane (6 mmol), Cu(II)@AFS-1 (12 mg, 0.2136 mol% of Cu), DCM, RT. [b]Absolute configurations were allocated through comparing the HPLC retention time and the sign of optical rotation with the literature data. [c]Isolated yield. [d]Determined by HPLC using Chiralcel OD-H column. [e]TON = moles of substrate converted per mole of active site. ([1]H NMR and HPLC chromatograms of the products are given in ESI, Fig. S7-S27)

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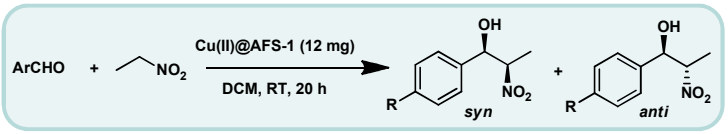
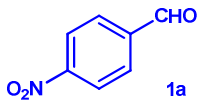
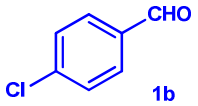
**Table 3.** Substrate scope of aldehydes and nitroethane in the asymmetric henry reaction[a]




| Entry | Aldehyde | Product[b] | Yield[c] (%) | syn/anti (%)[d] | ee(%)[e] (syn/anti) | TON[f] |
|---|---|---|---|---|---|---|
| 1 |  1a | **3a** | 96 | 3.2:1 | 95/84 | 449 |
| 2 |  1b | **3b** | 95 | 3:1 | 95/66 | 445 |

[a]**Reaction conditions**: aldehyde (1 mmol), nitroethane (6 mmol), Cu(II)@AFS-1 (12 mg, 0.2136 mol% of Cu), DCM, 20h, RT. [b]Absolute configurations were allocated through comparing the HPLC retention time. [c]Isolated yield. [d]Determined from NMR data. [e]Determined by HPLC using Chiralcel OD-H column. [f]TON = moles of substrate converted per mole of active site. ([1]H NMR and HPLC chromatograms of the products are given in ESI, Fig. S28-S31)

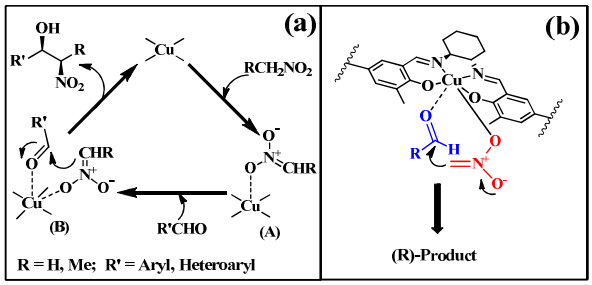
Further, in order to perceive the best ability of our chiral catalyst, diastereoselective Henry reaction[24] between 4-Nitro benzaldehyde (**1a**) and 4-Cl-benzaldehyde (**1b**) with nitroethane has been carried out under the optimal reaction conditions. The results are listed in Table 3. Both aldehydes provide the corresponding products with 96% and 95% yield in addition with good ee for syn isomers. Probably a very week intramolecular hydrogen-bonding interaction helps to furnish the syn isomer as major one.[25] The diastereomeric ratio (dr) of the product **3a** and **3b** was found to be 3.2:1 and 3:1 (syn/anti).

The synthetic importance of our current catalytic protocol was further scrutinized through the synthesis of medicinally and pharmaceutically potent drug molecule (R)-isoproterenol[26] (Section I, ESI). The Cu(II)@AFS-1 catalyzed asymmetric Henry reaction between 3,4-dimethoxybenzaldehyde and nitromethane was the key step for this synthesis (Section II, ESI). Next, following the procedure established by G. Blay *et al.*[26c] and Kureshy *et al.*[26d] (R)-isoproterenol was synthesized from 2f. Scheme 2 illustrates the synthetic route of this drug. The overall yield of the drug molecule is 82%. The most probable mechanistic pathway[26,13b] for the asymmetric Henry reaction catalyzed by heterogeneous chiral Cu(II)@AFS-1 catalyst is shown in Scheme 3a and respective most plausible transition state[27,12d,13b] is given in Scheme 3b.

Finally, to examine the catalytic efficiency, we have compared the reactivity of the first cycle of our heterogeneous Cu(II)@AFS-1 catalyst with the non-immobilized Cu(II)-salen complex for the model reaction between benzaldehyde (**1d**) and nitromethane under the optimized reaction conditions. The results are summarized in Table 4. From this table, it is quite evident that our heterogeneous chiral Cu(II)@AFS-1 catalyst displayed similar catalytic activity with the homogeneous counterpart (HPLC data is given in **Fig S2, ESI**).

**Recyclability and Reusability of chiral Cu(II)@AFS-1 catalyst:**

Recyclability is the most important characteristic feature of a heterogeneous catalyst due to their sustainable operation. 4-nitro benzaldehyde (**1a**) and nitromethane were taken as model substrates for the recycling experiments. The recycling efficiency of Cu(II)@AFS-1 is shown in Fig. 7. From the TEM, PXRD and BET experimental data it is quite evident that the catalyst is uniformly porous and the active centers were homogeneously distributed inside of the pore as well as on the outer surface of the support. On recycling the catalyst, the little decrease in the number of active sites could be attributed to the partial pore blockage. But the chiral environment of the residual active centers remains unaltered. As a result, the catalytic activity of the catalyst gradually decreases while the enantioselectivities basically remain unchanged upon recycling of the catalyst. Thus, this result suggested that, chiral Cu(II)@AFS-1 catalyst can be recycled for eight consecutive cycles in the asymmetric Henry reaction.




**Scheme 3.** Proposed catalytic cycle (a) and transition state (b) for the asymmetric Henry reaction over chiral Cu(II)@AFS-1 catalyst

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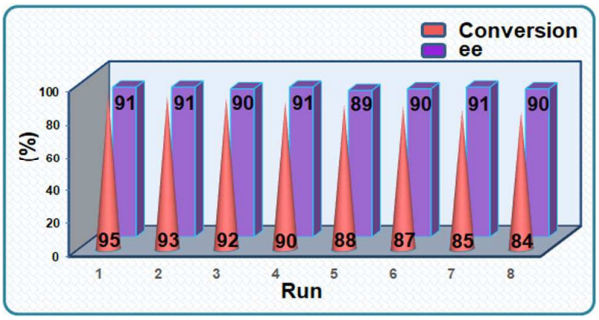


**Figure 7.** Reusability chart of chiral Cu(II)@AFS-1 catalyst.

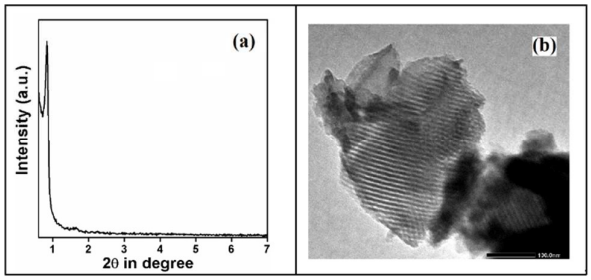


**Figure 8.** Small angle PXRD pattern (a) and UHR-TEM (b) of the reused Cu(II)@AFS-1.

To investigate the stability of the nanostructure of reused Cu(II)@AFS-1 catalyst we have carried out some key characterizations. The small angel PXRD pattern of the reused Cu-catalyst (Fig. 8a, after 6th cycle) revealed the three characteristic diffraction planes viz. 100, 110 and 200, suggesting the nanostructure of reused catalyst has been retained. On the other hand, UHR-TEM image (Fig. 8b) of reused catalyst (after 6th cycle) confirms the presence of regularly arranged ordered hexagonal pores. The FT-IR spectrum (ESI†, Fig. S32) of the reused catalyst further clarifies the organic functionalization at the surface of the mesoporous AFS-1 material has been retained during the course of reactions. The possibility of leaching of the metal ion (Cu) was estimated by the AAS analysis of the reaction mixture after the reaction. Our chemical analysis data suggested no significant leaching of copper metal during the course of catalytic reactions.

**Table 4.** Comparative study between the homogeneous Cu(II)-salen and Cu(II)@AFS-1 for the asymmetric Henry reaction[a]

| Catalyst | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| Homogeneous Cu(II) salen complex | 13.5 | 96 | 95 |
| Heterogeneous chiral Cu(II)@AFS-1 catalyst | 15 | 96 | 94 |

[a]**Conditions:** benzaldehyde (1 mmol), nitromethane (6 mmol), Cu(II) catalyst (0.2136 mol % Cu), DCM, RT; [b] Isolated Yield, [c] Determined by chiral HPLC analysis using Chiralcel OD-H column (Fig S2, ESI)

Moreover, the catalytic applicability of our heterogeneous chiral Cu(II)@AFS-1 catalyst has been compared with the previously reported homogeneous and heterogeneous catalysts (ESI†, Table S1). This comparative study clearly indicates that our heterogeneous Cu(II)@AFS-1 catalyst showed better catalytic activity in terms of yield, enantioselectivity and TON.

## Experimental

**Synthesis of homogeneous chiral Cu(II) salen complex (2):**

Notably, ethanolic solution of $Cu(OAc)_2.H_2O$ (1.25 mmol, 10 mL) was added to the ethanolic solution of the homogeneous Schiff base ligand (1) (1 mmol, 10 mL), under $N_2$ atmosphere. The as-formed bluish solution was then stirred at RT for 12 h. Thereafter, the solvent was removed and the solid mass was extracted with DCM followed by washing with water and finally drying over $Na_2SO_4$.Then after removal of the solvent the solid residue was finally precipitated from *n*-hexane to furnish the corresponding homogeneous chiral Cu(II) salen complex (2) as a bluish solid (yield 90%). The obtained m/z value for the salen complex (2) ($C_{42}H_{69}Cl_2CuN_4O_2$) was 794.4091[$(M+H)^+$, cal. 794.4094], which suggested efficient synthesis of the complex.

**Synthesis of heterogeneous chiral Cu(II) salen complex, Cu(II)@AFS-1 catalyst:**

To the ethanolic solution of homogeneous chiral Cu(II) salen complex (2) (0.03 g), carboxylic acid functionalized mesoporous solid support AFS-1 (0.20 g) was added and the resulting solution was stirred at 313 K for 12 h. Thereafter, the bluish solid was centrifuged, cleansed thoroughly and repeatedly extracted with MeOH and DCM on Soxhlet apparatus until the colourless washing was appeared. Finally, the catalyst was dried under air.

**Synthesis of the drug (R)-isoproterenol:**

Starting from 3,4-dimethoxy benzaldehyde and nitromethane, clinically potent drug (R)-isoproterenol was synthesized through stepwise modifications of the functional groups. The step by step synthetic alterations were examined through $^1$H NMR, HPLC chromatograms and optical rotation value. The detail synthetic procedures and characterization data of the compound 2f, 3, 4 and the final drug (R)-isoproterenol were given in ESI (Sections I and II).

**General procedure for asymmetric Henry reaction of aldehydes with nitromethane:**

A mixture of **1a** (1.0 mmol), nitromethane (6.0 mmol) and Cu(II)@AFS-1 catalyst (12 mg, 0.2136 mol % of Cu) in DCM were stirred at room temperature (25˚C) for 15 h. The progress of the reaction was monitored by TLC. After completion of reaction, the catalyst was removed from the reaction mixture by simple filtration and ethyl acetate was added. The organic phase was washed with water and brine, and finally dried over $Na_2SO_4$. Then the product was separated by column chromatography

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over silica gel with pet ether/ethyl acetate (85:15) as eluent. All the products were characterized based on their 1H NMR and their spectroscopic data are in agreement with those previously reported. Enantiomeric excess (ee) was determined by HPLC analysis using Chiralcel OD-H column.

**Reusability of the catalyst:**

After completion of the reaction the heterogeneous chiral catalyst was collected through centrifugation. Thereafter the catalyst was washed with distilled water and ethyl acetate followed by DCM and then dried in an oven at 80 ˚C for 2 h before reuse.

**Leaching test:**

A mixture of 4-nitro benzaldehyde (1.0 mmol), nitromethane (6.0 mmol) and Cu(II)@AFS-1 catalyst (12 mg, 0.2136 mol % of Cu) in DCM were stirred at room temperature (25 ˚C) for 7 h. Then the catalyst was separated from the reaction mixture and the filtrate was concentrated under reduced pressure. Then $HNO_3$ solution [5 mL 5% (in aq)] was added to the crude material and stirred. After that, this solution was taken in a 10 mL volumetric flask, and the volume was made up to the mark. Finally, this solution was studied using the AAS measurement to calculate the amount of leached copper metal.

## Conclusions

In conclusion, a new chiral Cu(II)-salen functionalized highly ordered mesoporous material can be synthesized by using surface functionalization route. This mesoporous chiral Cu-catalyst displayed good catalytic activity for the asymmetric Henry reaction to furnish chiral β-nitro alcohols. It also catalyses the diastereoselective Henry reactions with nitroethane giving good to excellent yields, ee and dr. Using this protocol as the key step, enantiomerically pure drug (*R*)-isoproterenol has also been prepared. In a broader context our protocol will provide a platform for the synthesis of β-nitroalcohols using chiral Cu(II)-salen complex grafted over the acid functionalized mesoporous SBA-15 support. The novelty of our observation lies in (a) comparatively good BET surface area, (b) uniform dispersion of the active sites over the support, (c) high catalytic activity, (d) good recyclability of the catalyst (e) room temperature reaction (f) use of no additives, bases, (g) comparatively shorter reaction time, (h) good enantioselectivity and (i) high TON. Thus, this work may unlock huge opportunity for asymmetric catalysis over functionalized mesoporous materials in future.

## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgements

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## Graphical Abstract

# Chiral copper-salen complex grafted over functionalized mesoporous silica as an efficient catalyst for the asymmetric Henry reactions and synthesis of potent drug *(R)*-isoproterenol

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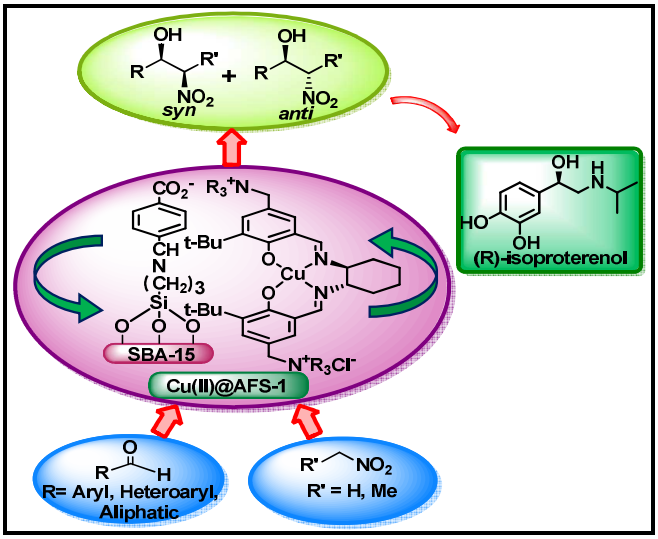


A new heterogeneous chiral catalyst Cu(II)@AFS-1 has been synthesized, which showed remarkable catalytic activity in the asymmetric Henry reaction (ee up to 94%, yield 96%) and diastereoselective Henry reaction (ee up to 95%, dr 3.2:1) of aromatic aldehydes with nitroalkane in DCM at RT. In addition, enantiomerically pure drug (R)-(-)-isoproterenol has been synthesized using this protocol.

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