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ORIGINAL PAPER

Asymmetric Epoxidation of α,β-Unsaturated Ketones over Heterogenized Chiral Proline Diamide Complex Catalyst in the Solvent-Free Condition

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Abstract Chiral copper proline diamide complex has been immobilized on surface of mesoporous silica. These heterogenized complex catalysts were examined as asymmetric catalysts for the epoxidation of α,β-unsaturated carbonyl compounds with hydrogen peroxide, *tert*-butyl hydroperoxide and urea hydroperoxide as the oxidants under solvent-free condition. Enantiomeric excesses of up to 84% can be achieved conveniently with a good conversion using these promising catalysts.

Keywords Chiral catalysis · Epoxidation · Heterogeneous catalyst · Prolinamide

1 Introduction

Chiral oxidation reaction is a crucial chemical transformation in the chemistry and pharmaceutical industries. Particularly, the asymmetric epoxidation of α,β-unsaturated carbonyl compounds is very important reaction because of its usefulness of the corresponding α,β-epoxy carbonyl compounds [1–3]. The α,β-epoxy ketone could play a important role as it can convert to β-hydroxyl ketones for prostaglandins and α-hydroxy ketones which can be used as biologically active antitumor agents and drugs [4]. Shibasaki et al. [5] have developed chiral Lewis acid complexes for catalysing this reaction. The use of organocatalyst was introduced by Jorgensen et al. [6] by employing L-proline derivative catalyst and later Schore et al. [7] further modified the catalyst by prolinol. However, the development of heterogenized asymmetric catalyst of this reaction is currently under way.

Catalysis via biomolecules including enzymatic catalysts received much attention due to propensity to be the core of numerous biological transformations such as hydrogenation, oxidation, and polymerization [8–13]. It is also well known that enzymatic biological transformation would provide a high yield and selectivity. In the epoxidation reaction, Lau et al. [14] performed an epoxidation reaction using enzyme as a catalyst, employing a clean and inexpensive oxidant such as hydrogen peroxide in ionic liquid. However, it requires long process to produce the enzyme catalyst and even some time difficult to handle the reaction system in the laboratory. With this regard, we would like to bring such biological important transformations to be a simple catalytic process but efficient too. In this contribution, particularly, we introduce immobilized amino acid derivative onto the direct synthesis amino functionalized mesoporous silica and zeolitic material for this particular purpose. Amino group on mesoporous silica surface is a useful functionality for many practical applications such as catalyst for base-catalyzed condensation reactions, support for delivery of bisphosphonates drug with controlled release into the bone tissue [15], support for enzyme immobilization [16, 17], stabilizer for metallic nanoparticles [18], and absorbent for the removal of heavy metals from the environment, spacer for further chemical modification, etc. Besides offering efficient catalytic performance, this catalyst system have various properties like recyclability, easy handling and easy preparation [19, 20].

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2 Experimental

2.1 Synthesis of Amino Functionalized Mesoporous Silica

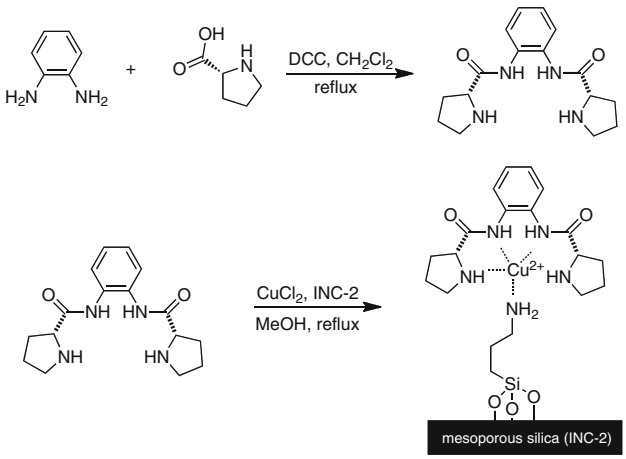
The amino functionalized mesoporous silica was synthesized according to our previous reported method [21]. For the direct synthesis of amino-functionalized SBA-15, a Pluronic P123 triblock copolymer (EO20PO70EO20, MW. 5800) was used as a structure-directing agent, a sodium metasilicate ($Na_2SiO_3{\cdot}9H_2O$) was used as a silica source and a 3-aminopropyl triethoxysilane/APTES ($NH_2(CH_2)_3Si(OEt)_3$) was used as a amino propyl group source. The initial synthesis mixtures were carried out according to the following procedures, 16 g of 10% (w/w) aqueous solutions of P123 were poured into 26.6 g distilled water and then 0.016-$\times$ moles of sodium metasilicate were added to the reaction mixtures followed by x moles of APTES ($\times = 7.5$ to obtain NH_2 to SiO_2 M ratios = 7.5). The mixtures were vigorously stirred by using mechanical stirrers at room temperature until homogenous solutions were obtained. To the vigorously stirred solutions, 13 g of concentrated hydrochloric acid (37.6%) was quickly added. The final mixtures were stirred for 1 h at 313 K before subjected to the microwave digestion system (CEM Corporation, MARS-5). The microwave condition for crystallization was set under a static condition at 373 K for 2 h with operating power of 300 W (100%). The crystallized products were filtered, washed with warm distilled water and ethanol and finally dried at 333 K. The surfactant was then removed by Soxhlet extraction over ethanol for 24 h. The sample was denoted as INC-2.

2.2 Synthesis of Chiral Proline Diamide Ligand

The chiral proline diamide ligand was prepared by coupling of chiral l-proline with the phenylene diamine in the presence of DCC (*N,N′*-dicyclohexylcarbodiimide). The ratio of the mixture 2 l-Proline:1phenyl:2DCC ratio. The mixture was refluxed in the methylene chloride for 6 h. Further, product was purified using column chromatography before being used for the next step.

2.3 Heterogenization of Chiral Proline Diamide Complex Onto Amine Functionalized Mesoporous Silica

Typically, to the suspension of 1 g amino functionalized mesoporous silica (INC-2) in the methanol, solution of 1.5 mmol chiral prolinamide ligand and copper salt ($CuCl_2{\cdot}6H_2O$) was added. The mixture was vigorously stirred under reflux for 10 h. Then the resulting suspension was cooled and filtered through a Buchner funnel supplied with a fine-porous filter paper. The collected powder was washed using equivalent alcohol and acetonitrile to remove the homogeneous complexes adsorbed on the surface of support, and then the solid was dried in air at 80 °C. The complete reaction pathway to produce heterogeneous catalyst was shown in Scheme 1.



Scheme 1 Synthesis pathway to obtain heterogenized chiral proline diamide complex

2.4 Characterization

Mesostructures of the synthesized materials were identified by powder X-ray diffractions. The XRD patterns were obtained by using a Rigaku Multiflex diffractometer with a monochromated high-intensity Cu Kα radiation ($\lambda = 1.54$ Å). Scanning was performed under ambient conditions over the 2θ region of 0.6–4.5 ° at the rate of 0.1 °/min (20 kV, 10 mA). The N_2 adsorption–desorption isotherms and pore characterization were obtained by using a Micromeritics ASAP 2020 apparatus at liquid N_2 temperature. Pore distributions were calculated by using BJH method from the adsorption branches. For the observation of the synthesized INC-2 by TEM, 1 mg of the materials was dispersed in 50 mL of ethanol and a drop of suspension was then spread on a holey amorphous carbon film deposited on Ni grid (JEOL Ltd.). The prepared samples were then examined in a high-resolution transmission electron microscopy (HR-TEM; JEOL JEM-2010, 200 kV). The near infrared (NIR) diffuse reflectance spectra (DRS) were measured with a Solidspec 3700 UV–Vis–NIR spectrometer.

2.5 Catalytic Reactions

Liquid phase asymmetric epoxidation reaction of α,β-unsaturated ketones was carried out at atmospheric environment with 1 mmol of substrate (chalcone, 4-Phenyl-3-buten-2-one, Cyclohex-2-enone or naphthalene-1,4-dione)

and 10 w% of catalyst using Pyrex batch reactor in thermal reactor system (Eyela Chemi Station). The reaction was carried out at 40 °C for 24 h in presence of 2 mmol H_2O_2. The reaction mixture was analyzed by a chiral HPLC (Agilent 1200 series, Chiracel OD-H column) for enantiomeric excess determination. When catalysts were subject of recyclability test, used catalysts were washed several times by ethanol before reused again. As comparison, same reaction was done in the present of molecular urea hydroperoxide (UHP) or *tert*-butyl hydroperoxide (TBHP) as oxidant.

3 Results and Discussion

Amino-functionalized SBA-15 having short perpendicular 1D channel (INC-2) have been synthesized from the co-condensation of APTES and sodium metasilicate in the presence of P123 triblock copolymer and under a strong acidic condition [21]. Powder XRD patterns and N_2 adsorption–desorption full isotherms (not shown) clearly showed that the obtained NH_2pr-SBA-15 catalysts have typical mesostructure of hexagonal symmetry with high surface area, narrow distributed large pore size, and large pore volume [21–23].

The amino functionalized mesoporous silica (INC-2) was further modified by immobilization of chiral proline amide complex. The presence of complex inside of mesoporous cavity of INC-2 was further confirmed by FTIR and UV DRS spectroscopy analysis (not shown). This process has no strong influence on the structure of mesoporous silica, as evidenced by XRD measurements that no obvious change in the position and the relative intensity of diffraction before and after the immobilization of the complex. In high angle XRD measurement, no diffractions lines attributable to copper clusters were observed. It means that all copper ions are highly dispersed to form complex between chiral ligand and amino group on the surface. The N_2 adsorption–desorption isotherms for all samples exhibited well-defined type-IV isotherms with H1-type hysteresis loops, characteristic of mesoporous materials having uniform cylindrical mesoporous that facilitate the condensation of N_2 [24]. The structural parameters such as BET surface area, pore size and pore volume of the further chemically modified samples were decreased due to the addition of bulky chiral ligands and their complexes (Table 1). TEM and SEM analyses revealed that the obtained amino functionalized mesoporous silica (INC-2) catalysts have uniform hexagonal platelet morphology with short pore channels in 150–300 nm length, which were perpendicularly arranged to the platelet morphologies Fig. 1. This pore arrangement would be helpful to overcome diffusion limitation of the reaction substrates [25].

Table 1 Physicochemical data of the catalysts

Sample	N content[a] (mmol g^{-1})	Cu content[b] (mmol g^{-1})	Pore size (nm)	S_{BET} (m^2 g^{-1})	Pore Vol. (cm^3 g^{-1})
INC-2	1.17	–	9.0	680	0.94
Cu-Pro-INC2	3.21	0.98	8.1	432	0.65

[a] Determined by elemental analysis method, [b]Determined by ICP-OES analysis method

The obtained catalyst (Cu-Pro-INC2) was used for the chiral epoxidation of series α,β-unsaturated ketones. In the first set of experiments, the dependence of the epoxidation on various reaction parameters was analyzed with chalcone as the model substrate (Fig. 2). Here, hydrogen peroxide (H_2O_2) was employed as green oxidant as the by-product after oxidation is water. Further, the epoxidation of unsaturated ketones was conducted in the absence of solvent. The hydrogen peroxide is sufficient to make homogeny reaction mixture, while further addition of organic solvent may not help to increase the activity as reported earlier [26]. As shown in Fig. 2, the heterogenized copper proline diamine catalysts oxidized chalcone with nearly similar enantiomeric excess towards epoxide from the first hour of the reactions. No induction periods was observed, which implies that the metal centers were already in their active forms before the reactions or the transformation into the active forms which took place rapidly during the initial reaction time.

The chiral epoxidation of series of α,β-unsaturated ketones requires a basic condition in order to achieve high conversion and selectivity [26]. Although the nature of the solid support possesses basicity due to the presence of amino functional groups [25, 27], though this basicity is not strong enough to give optimum conversion and enantioselectivity since the maximum conversion at 24 h was observed only 64%. It has been reported in the literature that the use of additives can improve the reactivity and enantioselectivity [28–30]. To further see the role of additives in catalytic activity, we have used several additives on the course of the epoxidation reaction Table 2. Our investigation showed that the addition triethyl amine (TEA) was able to increase the conversion up to 88% with 83% enantiomeric excess. These experiments suggest the existence of synergy between the catalyst and the additive during the transfer of chirality in the ring epoxidation of chalcone. However the addition of chiral S or R-Benzyl amine, which is expected to give better effect, failed to enhance both the conversion and enantioselectivity. The addition of strong inorganic base such as KOH or NaOH in the presence of water is not suggested because it leads the formation of alcohol product (-diols) rather than expected

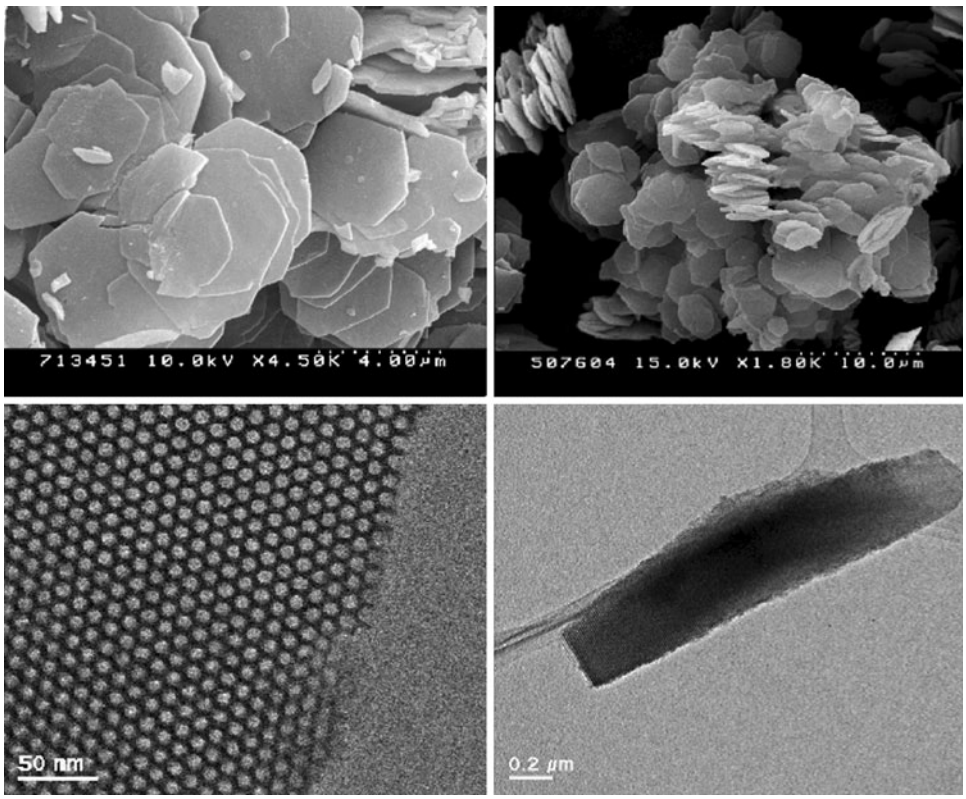


Fig. 1 SEM and TEM images of amino functionalized mesoporous silica (INC-2)

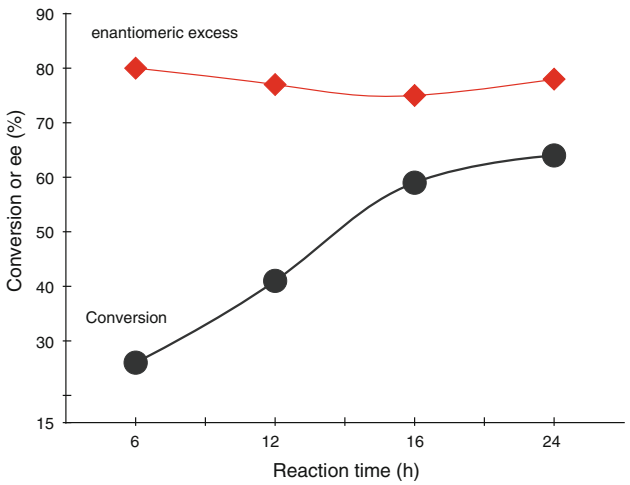
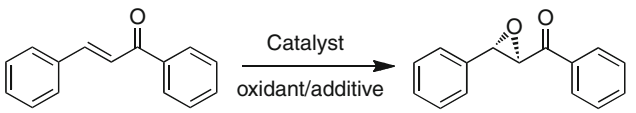


Fig. 2 Conversion profile of chalcone (*circle*) and enantiomeric excess of the product (*diamond*) of asymmetric epoxidation reaction of chalcone

Table 2 Effect of additive and oxidant in the liquid phase asymmetric epoxidation reaction of chalcone



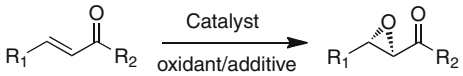
Entry	Substrate	Time (h)	Oxidant	Additive	Conv. (%)	ee[a] (%)
1	Chalcone	24	H_2O_2	TEA	88	83
2	Chalcone	24	H_2O_2	S-Benzylamine	52	65
3	Chalcone	24	H_2O_2	R-Benzylamine	54	79
4	Chalcone	24	UHP	TEA	72	84
5	Chalcone	24	TBHP	TEA	75	83
6	Chalcone	24	H_2O_2	–	61	72

[a] Enantioselectivity estimated by HPLC

chiral epoxide [30]. Also, replacing the hydrogen peroxide by TBHP and UHP also does not helpful in the conversion but due to their accessibility though it gave slightly higher enantioselectivity.

To understand the scope of this reaction, we studied various α,β-unsaturated ketones under the optimized conditions (40 °C for 24 h in presence of 2 mmol H_2O_2 and TEA), and the results are summarized in Table 3. Acyclic enones other than chalcone are also good substrates. 4-phenyl-3-buten-2-one gives the epoxide product in an 89% conversion and 82% enantioselectivity (entry 2). Some cyclic enones were also studied. 2-Cyclohexenone produced the epoxide in a 92% conversion and 83% enantioselectivity. 1,4-naphthalenedi-one (enedione) was also successfully epoxidized, and the product was obtained in an excellent yield (89% conversion with 82% ee, entry 4).

Table 3 Epoxidation of α,β-unsaturated ketones using heterogenized prolinamide complex under the optimized conditions



Entry	Substrate	Time (h)	Oxidant	Additive	Conv. (%)	ee[a] (%)
1	Chalcone	24	H_2O_2	TEA	88	83
2	4-phenyl- 3-buten-2-one	24	H_2O_2	TEA	89	82
3	Cyclohex-2-enone	24	H_2O_2	TEA	92	83
4	Naphthalene-1,4-dione	24	H_2O_2	TEA	89	82

[a] Enantioselectivity estimated by HPLC

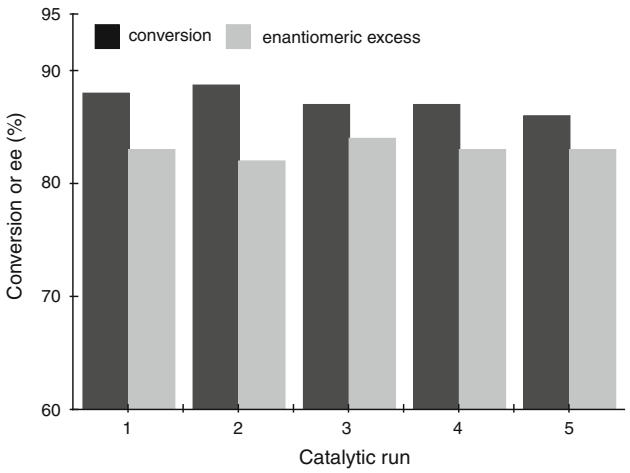


Fig. 3 Recyclability test of the catalyst in the liquid phase asymmetric epoxidation reaction of chalcone

The catalyst used in the reaction is recyclable as evidenced by the recycling experiments (Fig. 3). The recyclability experiments were carried out using chalcone as a representative substrate. After completion of the catalytic reaction the products mixture were separated by centrifugation. The product mixture was concentrated and purified by column chromatography. The recovered catalyst was washed by ethanol and dried in vacuum and was used for the subsequent catalytic runs. The recycled catalyst worked well up to five catalytic runs with marginal loss in yield. However, the enantioselectivity of the product was retained. In here, the strength point of this catalyst is the present of diamide bond between chiral proline with the phenylene diamine rather than C=N double bond in commonly reported Schiff base chiral ligands which is easily hydrolyzed [31, 32].

4 Conclusions

In summary, we have modified amine functionalized mesoporous silica to be chiral proline diamide complex. This heterogenized complex catalysts were examined as asymmetric catalysts for the epoxidation of α,β-unsaturated carbonyl compounds with hydrogen peroxide, *tert*-butyl hydroperoxide and urea hydroperoxide as the oxidants under solvent-free condition. This novel catalyst can effectively catalyse a highly enantioselective chalcone epoxidation without any pre-activation. Furthermore, the better catalytic efficiency of this catalyst was shown when TEA was used as additive. Enantiomeric excesses of up to 84% can be achieved conveniently with a good conversion using these promising catalysts. Interestingly, the recycled catalyst worked well up to five catalytic runs with marginal loss in yield.

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