

Enantioselective addition of diethylzinc to benzaldehyde over mesoporous SBA-15 functionalized with chiral proline derivatives

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ABSTRACT

Chiral proline derivative was anchored on mesoporous SBA-15 materials by nucleophilic substitution of chloropropyl-functionalized SBA-15 with (*S*)-(–)- α,α -diphenyl-2-pyrrolidinemethanol. Chloropropyl-functionalized SBA-15 prepared by co-condensation of tetraethyl orthosilicate and 3-chloropropyltrimethoxysilane using P123 copolymer as the pore directing agent in strong acidic environment was found to lead to derivatives with chiral centers more homogeneously distributed in the mesopores than that prepared by post-grafting. The resultant materials were very active and selective as catalysts in enantioselective addition of diethylzinc to benzaldehyde to form (*S*)-1-phenyl-propanol with ca. 66% of enantiometric excess (e.e.). The e.e. value was further improved to 75% by adding a small amount of *n*-BuLi. The reaction rate and the enantioselectivity increased with the accessibility of the chiral proline species in the mesopores and the hydrophobicity around the active sites. Moreover, the catalytic activity was well retained after the used catalyst was regenerated by filtration, washing with 0.2 M HCl and then neutralization by TMAOH.

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1. Introduction

Asymmetric synthesis is very important in the pharmaceutical industry [1–3]. Secondary alcohols with optical activity are important intermediates for preparing many molecules that mimic natural products and pharmaceutical compounds [4]. One of the well-known routes to prepare secondary alcohols with high optical activity is the asymmetric addition to an aldehyde with dialkyl zinc. The secondary alcohol with higher than 99% enantiometric excess (e.e.) has been obtained by asymmetric addition of diethyl zinc to benzaldehyde in the presence of a small amount of chiral β -tertiary amino alcohols as homogeneous catalysts [4–7]. The homogeneous catalysts reported in the literature include the chiral derivatives of camphor, proline, ephedrine, norephedrine, and cinchona alkaloid. The drawbacks of the homogeneous catalytic system are the difficulties involved in separation of the catalyst from the reaction solution, in purification of the products, and in reuse of the catalyst, these processes normally require tedious procedures. As a result, the cost of production is greatly increased. In contrast, the reactions through a heterogeneous catalytic pathway have the advantages of easy

purification of the products and easy recycling of the catalyst, making the catalytic processes more environmentally friendly and industrially applicable.

The asymmetric addition to benzaldehyde with diethyl zinc in heterogeneous phase has attracted great attention in recent years [8–13]. Watanabe and Soai [9,10] showed that diphenyl-(1-methylpyrrolidin-2-yl) methanol (abbreviated as DPMPM) anchored on polystyrene could catalyze asymmetric ethylation of aldehydes to form the resultant alcohols with 68% yield and 24% e.e. in about 77 h. By lengthening the tether between the polymer support and DPMPM with a hexyl group, they could increase the yield and e.e. value to 91% and 61%, respectively, after 24 h reaction. However, the thermal stability and swelling of the polymer matrix in solvents may seriously hinder the diffusion of reactants, which have been the major concerns for polymer supports [11].

In search of thermally stable and redeemable solid catalysts, chiral *N*-alkylnorephedrines anchored on alumina and amorphous silica [12,13] have been investigated. However, the reaction rate and enantioselectivity of immobilized homogeneous catalysts are generally much lower than those of the pristine system. That is attributed to that the chiral selective sites may change their conformation or may be hindered when the catalysts are anchored onto the solid supports. Moreover, the loading and the accessibility of the chiral selective catalyst are dependent on the preparation

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method and are limited by the openings of the surfaces. Mesoporous silica materials of large surface areas and tunable pore diameters are good candidates for immobilization of chiral selectivity catalysts [14–19]. Several groups have immobilized (1*R*,2*S*)-ephedrine on MCM-41-type mesoporous aluminosilicate [20–23]. However, the observed rate ($k_{\text{obs}} = 0.17 \text{ h}^{-1}$) and the e.e. value (47%) in enantioselective addition to benzaldehyde with diethyl zinc were still lower than those of homogeneous catalyst [22]. Moreover, surface silanol groups of MCM-41 were found to catalyze the racemization. Significant increases in the reaction rate and e.e. selectivity were observed when MCM-41 aluminosilicates of larger average pores (5.8 nm vs. 1.7 nm) were used as the catalysts [24]. Up to now, the highest catalytic activity (95% yield) and enantioselectivity (96% e.e. of (*S*)-1-phenyl-propanol) in the addition of diethylzinc to benzaldehyde were obtained over Ti(IV)-TADDOL ($\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) complex covalently anchored on controlled-pore glasses (CPGs) [25]. However, a stoichiometric amount of tetraalkoxytitanium was consumed during the reaction, and refilling of titanium species after every reaction cycle was inevitable.

Although the loading and the accessibility of the catalytic sites are important for the performance of immobilized chiral catalysts, very few papers have addressed these issues. Moreover, most of the chiral selective catalysts reported in the literature were anchored on the mesoporous silica by post-grafting method. It is difficult to achieve a high loading of the organic groups without tampering with the mesopores due to pore blocking [20–26]. In the present study, we focused on the effects of the homogeneity and loading of the chiral selective sites on the catalytic performance. Proline was anchored onto mesoporous SBA-15 materials by nucleophilic substitution of chloropropyl-functionalized SBA-15 with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol (Scheme 1). The chloropropyl-SBA-15 was prepared via co-condensation of tetraethyl orthosilicate (TEOS) and 3-chloropropyltrimethoxysilane (CPTMS) in order to achieve high loading and homogeneous distribution of the catalytic sites. The catalytic activity and enantioselectivity of the proline functionalized SBA-15 were examined by the asymmetric ethylation of benzaldehyde. Moreover, the influence of hydrophilicity of the silica surfaces was examined by co-functionalizing the mesoporous materials with methyl and phenyl groups, which were also prepared by co-condensation.

2. Experimental

2.1. Chemicals

All chemicals and solvents of reagent grade were purchased from Janssen Chiminca, Acros, and Aldrich. They were used

without further treatments, except for benzaldehyde, which was purified by distillation.

2.2. Synthesis of 3-chloropropyl-functionalized mesoporous SBA-15 via co-condensation method

Well-ordered 3-chloropropyl-functionalized SBA-15 materials were prepared by one-pot co-condensation method with the aid of NaCl [27,28]. Four gram of pore-directing agent P123 (Aldrich, $M_n = 5800$) and 13.04 g of NaCl (Acros, 99%) were dissolved in 160 mL of 2 M HCl solution. To this solution, ca. 0.041 mol of TEOS (Acros, 98%) was pre-hydrolyzed at 35 °C for 2 h before adding CPTMS (Acros, 98+%). The molar reactant compositions in the gel were 0.0168 P123: (1 - x) TEOS: x CPTMS: 7.6HCl:185H₂O, where x denotes the CPTMS/(TEOS + CPTMS) molar ratios that vary from 5% to 20%. The synthesis solution was stirred at 35 °C for 22 h, followed by a hydrothermal treatment at 90 °C under static conditions for 24 h. Subsequently, the solid precipitates were obtained by filtration, washing, and drying at 50 °C overnight. The P123 was removed by ethanol extraction. The resultant samples are hereafter designated as x Cl-SBA-15.

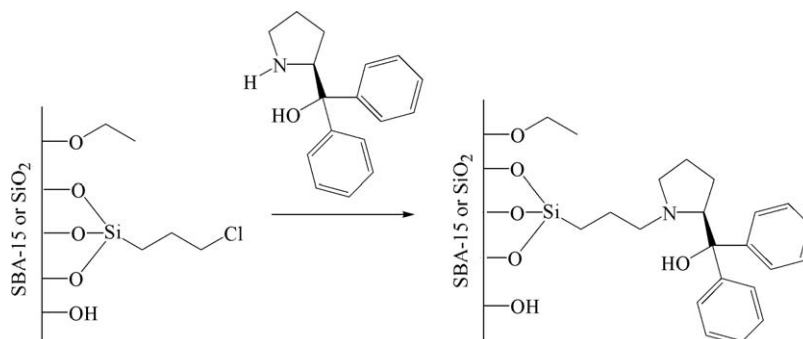
In some cases, 1 g of the ethanol-extracted sample was stirred in 50 mL toluene at 80 °C for 14 h to achieve further removal of the P123 residue. The resultant sample is designated as x Cl-SBA-15-t.

2.3. Synthesis of SBA-15 dual-functionalized with 3-chloropropyl and methyl (or phenyl) groups via co-condensation method

3-Chloropropyl and methyl (or phenyl) dual-functionalized SBA-15 materials were also prepared by the co-condensation method. The procedure was similar to that of 3-chloropropyl-functionalized SBA-15, except that methyltriethoxysilane (MTES, Acros, 98+%) or phenyltriethoxysilane (PTES, Acros, 98+%) was also added while CPTMS was introduced into the TEOS pre-hydrolyzed mixture. The resultant samples are designated as 10Me-15Cl-SBA-15 and 10ph-15Cl-SBA-15, corresponding to the respective molar reactant compositions in the gels of 0.0168P123:0.75TEOS:0.15CPTMS:0.10MTES (or PTES):7.6HCl:185H₂O. The samples were further treated with 50 mL toluene solution at 80 °C for 14 h to remove the residual P123 and are designated as 10Me-15Cl-SBA-15-t and 10ph-15Cl-SBA-15-t.

2.4. Synthesis of 3-chloropropyl-functionalized mesoporous SBA-15 and amorphous SiO₂ via grafting method

For comparison, 3-chloropropyl-functionalized mesoporous SBA-15 and amorphous SiO₂ were also prepared via the grafting method. Pure siliceous SBA-15 was synthesized according to the literature reports [16,17]. Prior to the grafting procedure, the calcined siliceous SBA-15 or commercial silica gel (Janssen Chimica, silicagel 0.060–0.200 mm, pore diameter ca. 6 nm) was



Scheme 1. Anchoring of proline derivative on SBA-15 or SiO₂ materials.

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