Preparation of Mesoporous Silica-Supported Chiral Amino Alcohols for the Enantioselective Addition of Diethylzinc to Aldehyde and Asymmetric Transfer Hydrogenation to Ketones

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Received 10 October 2014; Revised 17 December 2014; Accepted 18 December 2014

1. Introduction

Synthesis of optically active secondary alcohols through the asymmetric addition of organozinc reagent to aldehydes and transfer hydrogenation of ketones is an important chemical process in industry and drugs’ synthesis research [1–10]. Reduction of carbonyl group into alcohols involves a number of reducing reagents including addition of alkyl group, molecular hydrogen, metal hydrides, and dissolving metals [11]. The use of the hydrogen donor has some advantages over the use of molecular hydrogen since it avoids risks and constraint associated with hydrogen gas as well as the necessity of pressure controlling vessels and other equipment [12]. In the recent years, covalent immobilization of chiral catalysts onto insoluble supports has attracted much interest [13–17] since it provides an easy separation of products from the catalysts without tedious experimental workup, enabling an efficient recovery of the spent catalyst. It prevents the intermolecular aggregations of the active species because of their rigid structures, which do not swell or dissolve in organic solvents and often exhibit superior thermal and mechanical stability under the catalytic conditions. However, the examples of immobilized catalysts for the asymmetric transfer hydrogenation of ketones have been rare [18,19]. Further, the immobilization of catalysts onto inorganic supports has been poorly reported [20–22]. The successful development of homogeneous catalysts has sometimes been followed by attempts to attach the catalysts on an insoluble inorganic support [23]. The discovery of ordered mesoporous materials opened a new field for catalyst synthesis. Ordered mesoporous material is one of the attractive inorganic supports in preparing immobilized catalysts. The use of well-defined nanostructured mesoporous materials [24–26], magnetic materials [27], zeolites [28], organic polymers [29], or high surface area carbon [30] for catalytic transformations of organic substrates is an exciting and rapidly growing area. Recently, mesoporous MCM materials with uniform nanosized pore diameters and high specific surface areas have got intense interest as inorganic supports [31–33]. Such immobilization offers practical advantages such as ease of separation and reuse of the catalysts and catalysis within the microenvironment of nanopores. MCM-41 silica has recently been used as a mesoporous support for the immobilization of Au, Pt, Pd, Ni, Co, and Cu catalysts [34, 35]. On the other hand, cubic-structured mesoporous MCM-48 silica has received...
less attention due to difficulties in synthesis [36–39]. Owing to its unique three-dimensional pore structure, MCM-48 may be more advantageous than MCM-41. MCM-48 with three-dimensional nanosized pore networks and high specific surface areas would be of high interest in this area. Moreover, organic groups can be robustly anchored to the surface. Attachment of optically active ligands onto the pores of MCM-48 silica can create heterogeneous chiral ligands [40]. Our interest in the field led to prepare MCM-48-supported chiral ligands.

Our interest in the field led to prepare MCM-48-supported chiral ligands for asymmetric addition of diethylzinc to aldehydes and asymmetric transfer hydrogenation of ketones. Herein, we describe our results for the asymmetric addition of diethylzinc reagent to aldehydes and transfer hydrogenation to the ketones catalyzed by MCM-48-supported chiral amino alcohol Ru-complex.

2. Experimental

2.1. Preparation of the MCM-48 Silica. MCM-48 silica was prepared according to the procedure described in bibliography [39]. The resultant silicate mixture was stirred for 1 h at room temperature and the samples were then collected by filtration and transferred to a Teflon lined steel vessel. The sample was then heated at 100 °C for 4 days. After the mixture was cooled, the precipitated product was washed with DI water and calcinated at 500 °C for 8 h. The MCM-48 was characterized by XRD and TEM analyses.

2.2. Preparation of the Chloropropylated MCM-48 Silica. To a stirred solution of (3-chloropropyl)triethoxysilane (1.2 g, 4.98 mmol) in toluene (25 mL) was added fresh calcinated MCM-48 silica (2.4 g) and the mixture was stirred at 105 °C for 12 h. The reaction was cooled and filtered. The powder was washed several times with methylene chloride and dried under vacuum at 70 °C to give 3-chloropropylated MCM-48 silica. Weight gain showed that 1.1 mmol of (3-chloropropyl)triethoxysilane was immobilized onto 1.0 g of mesoporous MCM-48 silica.

2.3. Preparation of the MCM-48-Supported Chiral Amino Alcohols. To a stirred solution of (–)-ephedrine (0.23 g, 1.38 mmol) and diisopropylethylamine (0.12 g, 0.92 mmol) in toluene (10 mL) was added 3-chloropropylated MCM-48 silica (0.7 g, 0.77 mmol). The mixture was gradually heated at 105 °C and allowed to react for 36 h. The powder was collected by filtration and successively washed with H2O, methanol, and CH2Cl2. The MCM-48-supported ephedrine 2a was obtained after drying in vacuo at 70 °C. Elemental analysis and weight gain showed that 0.47 mmol of ephedrine was anchored onto 1.0 g of 3-chloropropyl MCM-48 silica 2a. Mesoporous MCM-48-supported norephedrine 2b and prolilol 2c were obtained by the same procedure with 0.50 mmol/g and 0.45 mmol/g, respectively.

2.4. General Procedure for the Asymmetric Addition of Diethylzinc to Aldehydes. To a stirred solution of MCM-48 silica (5 mol%) in hexane (3 mL) was added Et2Zn (3.0 mL, 1.0 M in hexane) at 0 °C. The mixture was allowed to reach room temperature and then aldehyde (1.5 mmol) was added to the reaction mixture. The mixture was stirred at room temperature for 10 h and the reaction progress was observed by TLC analysis. After disappearance of the starting material, the reaction was quenched at 0 °C by addition of saturated NH4Cl solution. The catalyst was removed by filtration and washed with CH2Cl2. The filtrate was extracted with CH2Cl2, dried over Na2SO4, and filtered, and solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel with 10% AcOEt/hexane. The enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H column, 3% of 2-propanol in hexane, 0.5 mL/min, and detection at 254 nm). Racemic comparison samples were prepared by reactions of the corresponding aldehydes with EtMgBr. Configurations were assigned by comparison with known elution order from a chiral column.

2.5. General Procedure for the Ru-Catalyzed Asymmetric Transfer Hydrogenation to the Ketones with Immobilized Ligand. A suspension was formed by the mixture of [RuCl2(p-cymene)]2 (5 mg, 0.008 mmol) and mesoporous silica-supported norephedrine 2b (0.016 mmol) in 2-propanol (5 mL). The mixture was heated at 80 °C for 30 min under nitrogen atmosphere. To this resulting solution, a degassed solution of ketone (0.83 mmol) with KOH (2.3 mg, 0.04 mmol) in 2-propanol (10 mL) was added and the mixture was stirred at room temperature for 3–4 h. The reaction was monitored by TLC analysis and after completion of the reaction it was neutralized with aqueous NH4Cl solution (1 mL). The immobilized ligand 2b was filtered on a glass filter and washed with water and ethyl acetate. The obtained ligand was dried and used for the next reaction. The excess 2-propanol was removed under reduced pressure and diluted with water and ethyl acetate. The organic layer was washed with brine and dried over MgSO4 and the crude product was purified by short-column chromatography (hexane-ethyl acetate 95/5 as eluent). Enantiomeric excess of the product was determined by HPLC analysis using Chiralcel OD-H column (3% of 2-propanol in hexane, 1 mL/min).

3. Results and Discussion

3.1. Preparation and Characterization of the MCM-48-Supported Chiral Amino Alcohols. Soai and coworkers have reported asymmetric addition of diethylzinc reagent to aldehyde catalyzed by silica gel-supported ephedrine [41]. The immobilization of optically active (–)-ephedrine, (–)-norephedrine, and (–)-prolinol onto MCM-48 silica was easily performed through two steps as shown in Scheme 1. Treatment of MCM-48 silica with (3-chloropropyl)trimethoxysilane in refluxing toluene gave chloropropylated MCM-48 silica 1 with maximum loading of chloropropyl group (1.1 mmol/g (CH3)2Cl). Reaction of the modified MCM-48 silica 1 with an excess of (–)-ephedrine, (–)-norephedrine, and (–)-prolinol in refluxing toluene under basic condition afforded MCM-48-supported ephedrine 2a (0.47 mmol/g), 2b (0.50 mmol/g), and 2c (0.45 mmol/g), respectively.
Scheme 1: Preparation of the MCM-48-supported chiral amino alcohols.

Table 1: Structural characteristics of MCM-48-supported chiral amino alcohols 2.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Surface area (m²/g)</th>
<th>Pore diameter (nm)</th>
<th>Pore volume (cm³/g)</th>
<th>Loading amount (mmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCM-48</td>
<td>1250</td>
<td>3.15</td>
<td>0.71</td>
<td>—</td>
</tr>
<tr>
<td>2a</td>
<td>758</td>
<td>2.65</td>
<td>0.50</td>
<td>0.47</td>
</tr>
<tr>
<td>2b</td>
<td>767</td>
<td>2.72</td>
<td>0.54</td>
<td>0.50</td>
</tr>
<tr>
<td>2c</td>
<td>794</td>
<td>3.11</td>
<td>0.61</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Figure 1: TEM image of MCM-48-supported amino alcohol 2a.

Figure 2: XRD pattern of MCM-48-supported amino alcohol 2a.

The degrees of functionalization were determined by weight gain or elemental analysis. Some physical properties of the modified MCM-48 are summarized in Table 1. The data showed that the functionalized MCM-48 possesses characteristic pore structure of mesoporous material containing high specific surface area and high mesoporous volume. Surface area and pore diameter of MCM-48 2 decreased due to the grafting of organic functional group. HRTEM image was obtained after the modification of the parent MCM-48 silica shown in Figure 1. The 3D cubic structure and the pore arrays are conserved after the anchoring of chiral ligand onto MCM-48 silica, which is also confirmed by XRD in Figure 2. Apparently, there is no change of the lattice parameters upon the functionalization process.

3.2. Catalytic Enantioselective Addition of Diethylzinc to the Aldehyde. With the MCM-48-supported chiral amino alcohols 2 in hand, we examined their catalytic efficiency in the addition of diethylzinc to aldehydes in hexane. As shown in Table 2, satisfactory enantioselectivities and high yields were obtained in the presence of MCM-48-supported ephedrine 2a. The results are compared with those obtained using previously reported silica gel-supported ephedrine (entries 5 and 7) [42]. MCM-48-supported ephedrine 2a gave much higher reaction rate and better asymmetric induction than
Next, we did a recycling experiment using chiral ligand 2a. We successfully recovered the catalyst and reused it twice without further addition of Ru-complex (entry 6). However, poor enantioselectivity was observed when the reaction was performed with MCM-48-supported ligands 2b and c (entries 3 and 4).

### 3.3. Catalytic Asymmetric Transfer Hydrogenation of Ketones

Next, the efficiency of MCM-48-supported norephedrine 2b was assessed in ruthenium-catalyzed asymmetric transfer hydrogenation of ketones. The chiral ruthenium catalyst was generated in situ by mixing [Ru(η⁶-arene)Cl₂]₂ and supported ligand 2b (Ru : ligand = 1 : 2) in 2-propanol at 80 °C for 30 min. The catalyst afforded (R)-secondary alcohols in up to 82% enantiomeric excess with 99% conversion. The reaction conditions and results are summarized in Table 3. [Ru(hexamethylbenzene)Cl₂]₂ as a Ru(II) source gave somewhat higher enantiomeric excess than [Ru(p-cymene)Cl₂]₂. It should be noted that MCM-48-supported ligand 2b could serve as an effective enantioselective chiral ligand [43].

### 4. Conclusions

The study successfully showed that mesoporous MCM-48 silica can be used as a potential inorganic support for the synthesis of heterogeneous catalysts for the asymmetric addition of diethylzinc reagent to aldehydes and asymmetric transfer hydrogenation of ketones. Promising results were obtained with MCM-48-supported ephedrine, in which ordered structure of MCM-48 had a positive effect on the conversation (99%) enantioselectivity (82%). The synthesis of other MCM-48-supported chiral ligands for the asymmetric catalysis is underway in our laboratory.

### Conflict of Interests

All authors declare that they have agreed to publish this paper and that it does not have any contents with conflict of interests.

### Acknowledgments

This work was supported by the University of Malaya Fund no. RP005A-2013AET to Md. E. Ali and the University of Malaysia Pahang Fund no. RDU-140124 to S. M. Sarkar.

### References


