DOI: 10.1002/adsc.200505354

Filtration-Free Recyclable Catalytic Asymmetric Dihydroxylation Using a Ligand Immobilized on Magnetic Mesocellular Mesoporous Silica

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Received: September 9, 2005; Accepted: November 21, 2005

Abstract: A new magnetic mesocellular mesoporous silica support featuring a 3D open-pore structure has been developed for highly efficient, filtration-free recycling of chiral ligands for catalytic asymmetric dihydroxylation. Reactions using the ligand immobilized on this magnetic silica system exhibited almost the same reactivity and enantioselectivity as those obtained in the homogeneous reaction. Magnetically recovered ligand could be recycled eight times with good to excellent conservation of reaction rates and enantioselectivities.

Keywords: asymmetric dihydroxylation; filtration-free; magnetic separation; mesoporous silca; recycling

Much effort has been focused on the recycling of catalysts through immobilization for the purpose of developing practical catalytic systems.[1] Although catalysts grafted on heterogeneous supports allow for recycling and simplify purification steps, they often suffer from reduced reactivity and lower stereoselectivity. Furthermore, in many instances recovery of heterogenized catalysts through filtration is cumbersome, especially in the case of air-sensitive catalysts. In this regard, magnetic separation of catalysts could be an attractive alternative to the filtration.[2] Recently, the development of uniformly sized magnetic nanoparticles has been intensively pursued[3] and they have been exploited in the immobilization of proteins, enzymes, bioactive agents,[4] and Pd catalysts.[5] Very recently, magnetic nanoparticle-incorporated mesoporous silica and carbon materials have been reported.[6] However, efficient chiral ligand recycling through magnetic separation for asymmetric synthesis has rarely been documented.[5,7]

The Sharpless catalytic asymmetric dihydroxylation (AD) is one of the most efficient asymmetric transformations generating enantiomerically enriched vicinal diols.[8] To achieve repetitive use of the catalytic osmium-ligand system, several approaches have been documented in regard to the immobilization of the alkaloid ligand,[9,10] or osmium.[11] In recycling of the ligand-catalyst system through immobilization, filtration of the heterogenized catalyst-ligand complex is often tricky due to the high toxicity and volatility of the osmium component.

Herein we report on the preparation of a new type of magnetically separable, hierarchically-ordered mesocellular mesoporous silica (M-HMMS) and its application towards a filtration-free, recyclable AD reaction. Hierarchically ordered mesocellular mesoporous silica (HMMS), which is mesocellular silica foam[12] with ordered mesoporous walls, was synthesized using a single template as reported recently from one of these laboratories.[13] Then, magnetic nanoparticles were grafted on the pore surface of HMMS through the thermal decomposition of an iron propionate complex (Figure 1).[14]

Several peaks typical for γ-Fe_2O_3 were observed from the XRD pattern (Figure 1). The large peak widths are attributed to the formation of nanosized particles. Mean particle size calculated by Debye–Scherrer equation using the (311) peak is 5.4 nm. It is also found that about 5 nm-sized nanoparticles are homogeneously distributed all over the pores of HMMS as shown by subsequent transmission electron microscopy studies. The magnetization curve of M-HMMS exhibited typical superparamagnetic behavior, showing no observed hysteresis at room temperature. The saturation magnetization value at room temperature is 15.12 emu/g, which

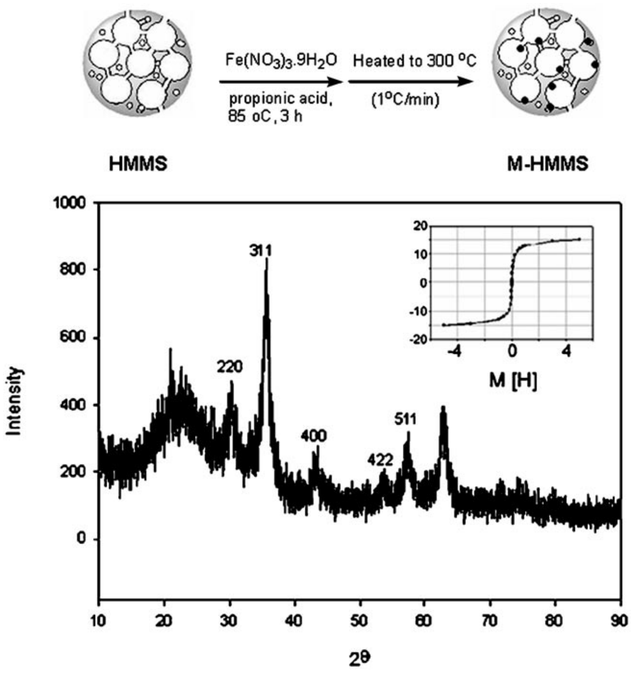


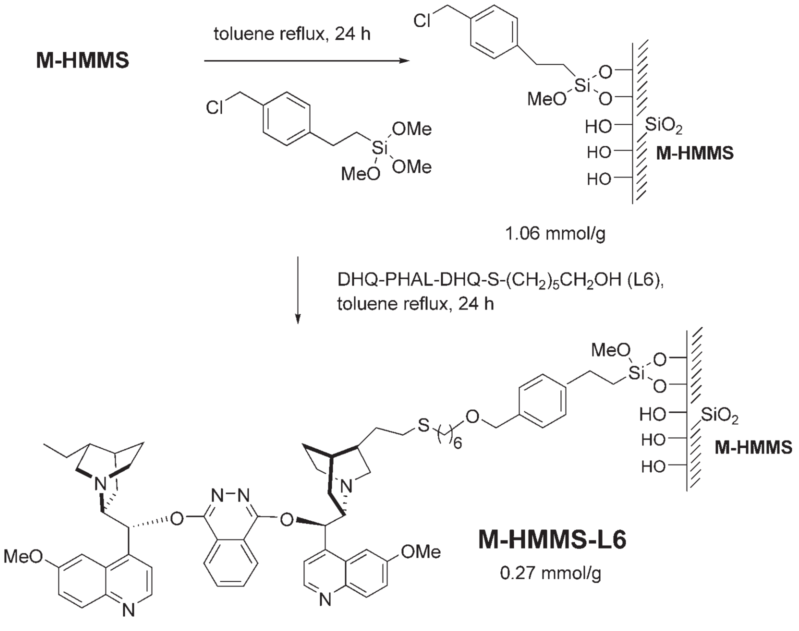
Figure 1. Preparation of iron-nanoparticle encapsulated mesostructured material and physical data: wide-angle XRD pattern of M-HMMS and magnetization curve of M-HMMS.

is sufficiently high for magnetic separation (Figure 1) and much higher than those of previously reported magnetic nanoparticles loaded onto MCM-41[15a] and Cab-o-Sil.[15b] We envisioned that the fact that M-HMMS has a high magnetization value with a high ligand loading capability would warrant its general applicability for efficient catalyst/ligand recovery.

Reaction of M-HMMS functionalized with a chlorobenzyl linker and the previously reported *Cinchona* alkaloid DHQ-PHAL-DHQ-S-$(CH_2)_5CH_2OH$ monomer ligand **L6**[10a] (Figure 2b) in refluxing toluene for 24 h followed by extensive washing provided the silica loaded with the ligand (**M-HMMS-L6**, Scheme 1). Elemental analysis of M-HMMS-L6 indicated a ligand loading of 0.27 mmol/g, which was higher than that obtained with the mesoporous SBA-15 (0.17 mmol/g),[10a] in spite of the lower surface area (Figure 2c, below 253 m^2/g) of the M-HMMS than that of SBA-15 ($>600\ m^2/g$). The loading of the organic linker and the ligand renders the surface of the M-HMMS-L6 hydrophobic, a desirable feature for the AD reaction, which requires the ligand to be well dispersed in organic (*t*-BuOH) layer.

To investigate the reactivity of the M-HMMS-L6/OsO_4 complex, the dihydroxylation of styrene was first investigated under the standard conditions employing $K_3Fe(CN)_6$ as a co-oxidant,[16] changing the molar ratio of ligand and OsO_4 from 1.0 to 0.2 mol %. The results were quite consistent regardless of the relative amounts of osmium and the ligand (97.3, 96.4 and 95.9% ees with 1.0, 0.4 and 0.2 mol % of OsO_4, respectively). Even with 0.2 mol % each of M-HMMS-L6 and OsO_4, the reaction proceeded almost at the same rate (less than 2 h) as the homogeneous reaction. Encouraged by this result, ADs of various olefins were investigated with M-HMMS-L6 and the results were compared with those obtained from the reactions using homogeneous ligand and ligand immobilized onto SBA-15 (Table 1).

Reactions using M-HMMS-L6 exhibited almost the same rates and enantioselectivities as those observed in the reactions using homogeneous ligand. Most reactions were complete within 8 h. The high reactivity and



Scheme 1. Immobilization of chiral ligand L6 on M-HMMS.

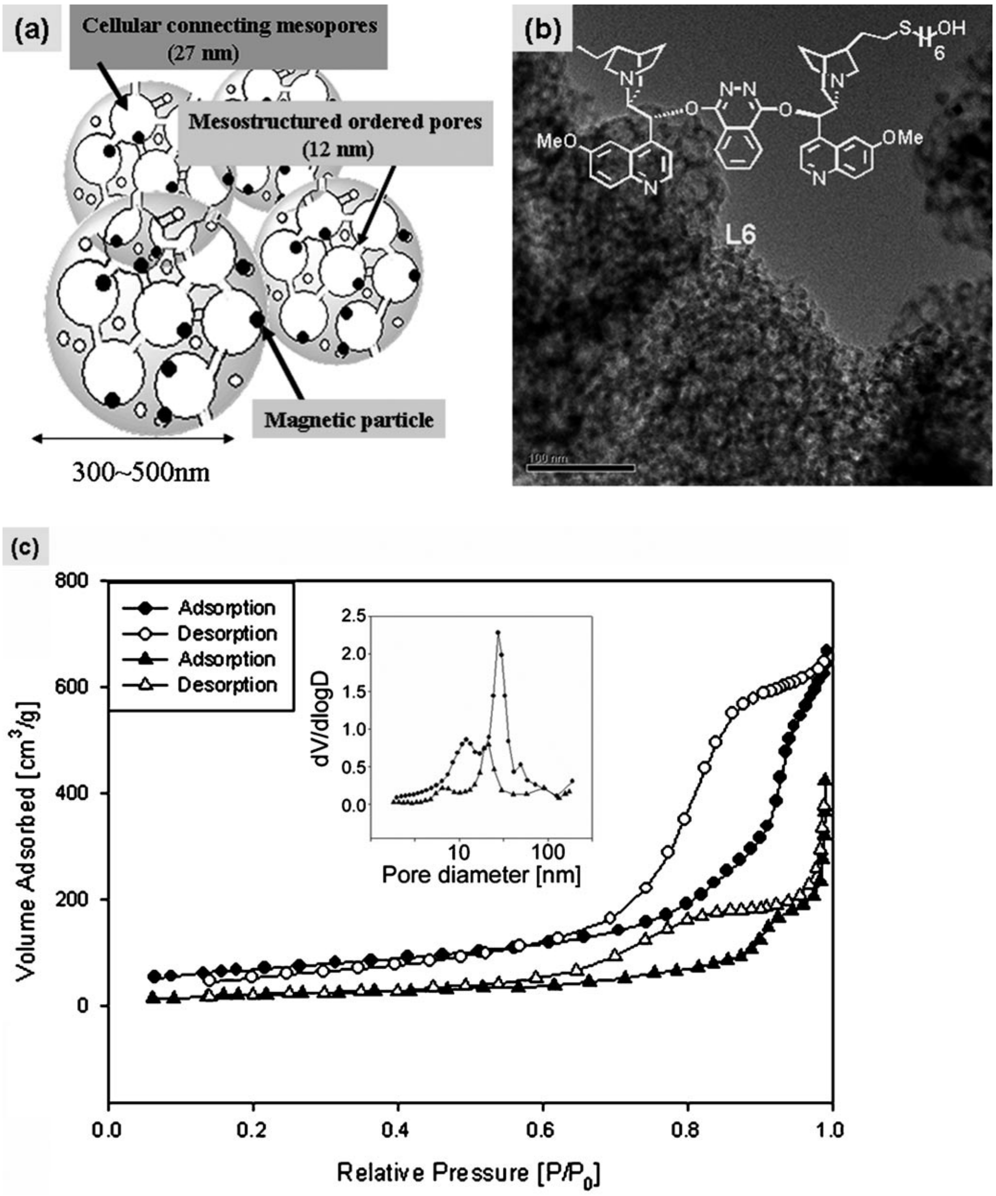
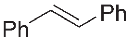
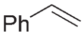
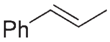
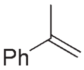
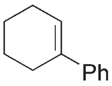


Figure 2. (**a**) Pictorial representation of M-HMMS, (**b**) structure of the modified ligand L6 and the TEM image of M-HMMS-L6, (**c**) N_2 adsorption-desorption isotherm of magnetic M-MMS (●) and M-MMS-L6 (▲) including calculated pore diameter by the BJH method.

enantioselectivity of M-HMMS-L6 were attributed to the well-connected three-dimensional (3D) pore structures and small particle size of the mesostructured silica support (~500 nm), which render the active sites well dispersed on the surface and readily accessible. Finally, to explore the repetition capability of the magnetically separable ligand, we performed reactions consecutively using the recycled ligand. The filtration-free M-HMMS-L6 was almost quantitatively recovered through simple magnetic separation (Figure 3) and then reused for the next reaction employing a new batch of $K_3Fe(CN)_6$. Reactions of styrene using the recycled M-HMMS-L6 proceeded with 95, 81 and 19% yields for three consecutive runs, respectively, thus a precipitous yield drop was observed at the third run, indicating a significant loss of osmium. The quick drop in reactivity was similarly observed with other types of ligand immobilization from this and other laboratories.[10] For this reason, a new batch of OsO_4 was employed in each recycling experiment to obtain a reasonable reaction rate.

As shown in Table 1, the recovered chiral ligand could be recycled eight times with good to excellent conservation of reaction rates and enantioselectivities. In the case of *trans*-stilbene, the enantioselectivity remained within

Table 1. Results of AD using M-HMMS-L6 in comparison with those using homogeneous and SBA-15 immobilized ligand, and recycling results.

Entry	Olefin	% ees with homogeneous reagent[a]	% ees with SBA-15[b]	% ees with consecutive use of M-HMMS-L6[c]							
				1st	2nd	3rd	4th	5th	6th	7th	8th
1		>99.5	>99.5	**>99.5**	99.2	98.8	98.8	98.8	98.6	>99.5	98.5
2		97	96	**97.3**	95.2	94.7	94.4	94.0	93.8	93.5	94.1
3		97	98	**96.9**	93.1	93.2	93.5	95.2	93.1	96.2	93.8
4		93	90	**92.7**	87.9	81.5	81.5	80.1	81.2	80.7	80.9
5		97	94	**95.5**	93.0	91.8	92.0	90.6	91.5	92.2	91.9

[a] Ref.[8a]

[b] Ref.[10a]

[c] All reactions were carried out with molar ratio of olefin/OsO_4/M-HMMS L6 = 1/0.01/0.015 under standard $K_3Fe(CN)_6$ conditions. Recycling experiments were performed using a new batch of OsO_4 and oxidant. The ee values were determined through HPLC analysis.

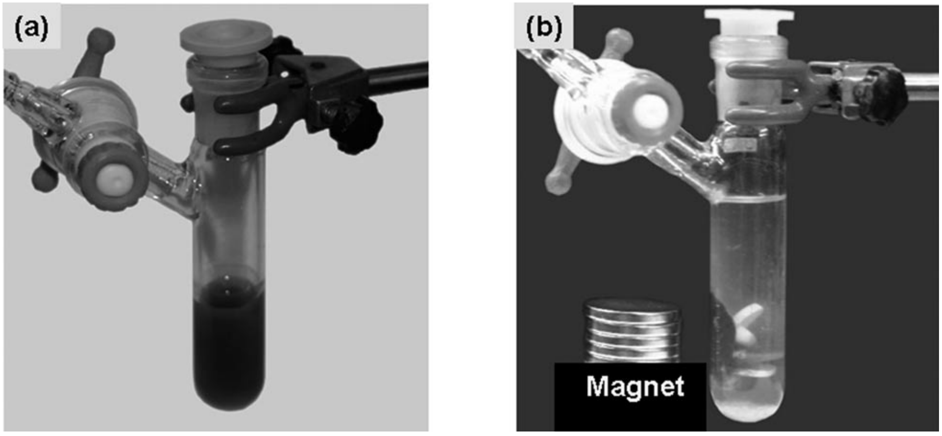


Figure 3. (**a**) AD reaction mixture containing M-HMMS-L6, and (**b**) M-HMMS-L6 collected using an external magnet after the reaction.

a 1% margin of the initial run (>99.5 to 98.5%) with >95% yields even at the eighth recycle (entry 1). These results are comparable to the best results obtained with other immobilized ligands on silica materials.[1,9,10] The same alkaloid ligand L6 anchored on SBA-15 has shown a considerable decrease of ees (>99.5 to 94%) even at the 2nd recycle in the reaction of *trans*-stilbene.[10a] The highly conserved reactivity and enantioselectivity observed with M-HMMS-L6 may be due to the efficient, filtration-free magnetic separation of the ligand system.

In summary, we have developed a new type of magnetically separable ligand system using magnetic mesocellular mesoporous silica (M-HMMS) as a ligand support, which has easily accessible 3D open pores allowing for favorable reaction kinetics over other mesoporous materials. The immobilized ligand for asymmetric dihydroxylation exhibited almost the same activity and enantioselectivity for ADs of several olefins as those obtained in the homogeneous reaction. The magnetically recovered ligand could be recycled eight times with good to excellent conservation of reaction rates and enantioselectivities in most cases. This filtration-free heterogeneous ligand system may pave the way to the development of other magnetically separable heterogeneous ligand/catalyst systems free from filtration problems, thus providing a practical means to highly recyclable and efficient catalyst systems.

Experimental Section

Magnetically Separable Hierarchically Mesocellular Mesoporous silica (M-HMMS)

$Fe(NO_3)_3 \cdot 9\,H_2O$ (1.34 g, 3.3 mmol) dissolved in methanol was impregnated onto 0.5 g HMMS[13] silica and dried in a drying oven at 85 °C until the material was free from methanol. The $Fe(NO_3)_3$-impregnated silica was allowed to react with propionic acid at 85 °C for 3 h to form the iron propionate complex. The composite was heated to 300 °C under air (1 °C/min) for decomposition of the iron propionate complex and allowed to remain at that temperature for 30 min. The obtained silica was denoted as M-HMMS (magnetic HMMS). BET surface area: 253 m^2/g. Mean pore diameter: 27 and 12 nm.

M-HMMS Functionalized with Chlorobenzyl Linker (M-HMMS-F)

M-HMMS (500 mg) was suspended in dry toluene and 2-(4-chloromethylphenyl)ethyltrimethoxysilane (Gelest, Inc., 300 μL, 1 mmol) was added. This mixture was heated to reflux under nitrogen. After 24 h, this solution was filtered and washed with toluene, MeOH, ether, and hexanes. The filtered brown solid was dried under vacuum. Grafted amount (1.06 mmol/g) was calculated from the mass% of carbon. Elemental analysis (%): N (–), C (12.87), H (1.57).

Immobilization of *Cinchona* Alkaloid Ligand on M-HMMS (M-HMMS-L6)

M-HMMS-F (400 mg, 1.06 mmol/g) was suspended in dry toluene, and the modified *Cinchona* alkaloid ligand (L6, 455 mg, 0.5 mmol)[10a] was added. The resulting mixture was heated to reflux and stirred under nitrogen. After 24 h, the mixture was filtered and washed with toluene, MeOH, ether, and hexanes. The filtered brown solid was dried under vacuum. Grafted amount (0.27 mmol/g) was calculated from the mass % of nitrogen. Elemental analysis (%): N (2.34), C (28.96), H (3.01), S (1.11). BET surface area: 85 m^2/g. Mean pore diameter: 21 and 7 nm.

General Procedure for Asymmetric Dihydroxylation using M-HMMS-L6

Immobilized ligand M-HMMS-L6 (30 mg, 0.008 mmol), $K_3Fe(CN)_6$ (494 mg, 1.5 mmol), K_2CO_3 (207 mg, 1.5 mmol) and $MeSO_2NH_2$ (47 mg, 0.5 mmol) (not necessary for terminal olefins) were dissolved in *t*-BuOH-H_2O (v/v = 1 : 1, 3 mL). This mixture was cooled to 0 °C. Within 15 min olefin (0.5 mmol) and OsO_4 (4 wt % aqueous solution, 0.005 mmol) were added to the solution. After completion of the reaction, the reaction mixture was diluted with EtOAc (4 mL). The magnetically separable ligand (M-HMMS-L6) was indirectly collected through placing a strong magnet for 30 min from outside of the reaction vessel. The reaction mixture was carefully decanted and the remaining M-HMMS-L6 was subsequently washed with EtOAc. The combined organic solution was treated with saturated aqueous sodium sulfite solution. The layers were separated and the organic layer was dried with anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified through chromatography on silica gel with EtOAc/hexanes affording the desired *cis*-diol. The enantiomeric excesses of the diols were determined through HPLC analysis using chiral columns. The magnetically separated ligand (M-HMMS-L6) was reused for successive reactions.

Acknowledgements

T. H. would like to express thanks for the financial support from the Korean Ministry of Science and Technology through the National Creative Research Initiative Program. B. M. K. thanks the Ministry of Science and Technology of Korea through the Research Center for Nanocatalysis, one of the National Science Programs for Key Nanotechnology.

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