

Mesoporous Silica SBA-15-supported Norephedrine and Ephedrine as Heterogeneous Chiral Ligands

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Successful development of the homogeneous catalysts has been sometimes followed by attempts to attach the catalysts on an insoluble polymeric support. A suitably designed immobilized catalyst can retain the advantages of a heterogeneous catalyst in terms of simplified workup procedure and recyclization while maintaining reactivity and selectivity of a homogeneous catalyst.¹ The immobilization of homogeneous species is of particular interest in the field of asymmetric catalysis since it is desirable to be able to regenerate and reuse expensive chiral catalysts.² Polystyrene resin and silica gel have been most commonly used as insoluble supports for the immobilization of the catalysts.³ Recently, mesoporous silica SBA-15 with large uniform pore diameters and high specific surface areas have become of high interest as inorganic supports.⁴ Our interest in the field led to prepare SBA-15-supported ephedrine **1** and norephedrine **2**. Herein, we report our investigation on the asymmetric addition of diethylzinc reagent to aldehydes⁵ and on the asymmetric transfer hydrogenation of ketones mediated by the supported ligands.⁶

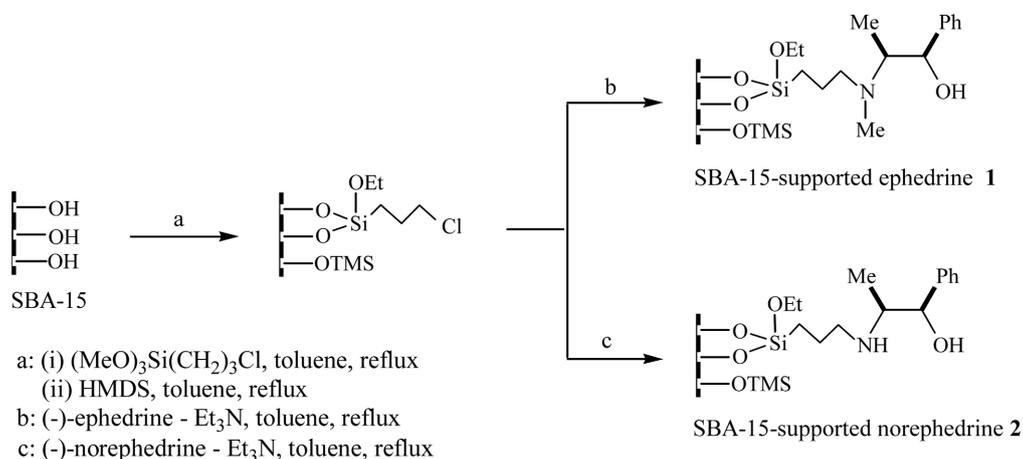
As shown in Scheme 1, (–)-ephedrine was anchored on SBA-15 silica in a similar procedure as for silica gel-supported ephedrine **1**.⁷ Treatment of SBA-15 with an excess of (3-chloropropyl)triethoxysilane in refluxing toluene gave chloropropylated SBA-15. The free silanol group was end-capped by treatment with hexamethyldisilazane (HMDS). Reaction of the samples are summarized in Table 1. The surface area was decreased considerably in the chloro-

Table 1. Characterization of SBA-15-supported chiral ligands

	Surface area (m ² /g)	Pore diameter (nm)	Loading amount (mmol/g)
SBA-15	803	7.9	–
1	452	7.4	0.62
2	471	7.6	0.65

propylation, but the pore diameter was not changed substantially during the modification steps. chloropropylated SBA-15 with 1.5 equiv. excess of (–)-ephedrine in refluxing toluene in the presence of 1 equiv of diisopropylethylamine afforded SBA-15-supported ephedrine **1**. SBA-15-supported norephedrine **2** was also prepared from (–)-norephedrine by the same method. The degrees of functionalization were determined by weight gain or nitrogen elemental analysis for the modified SBA-15. The characteristics of the two samples are summarized in Table 1. The surface area was decreased considerably during the modification, but the pore diameter was not changed substantially.

With the supported ephedrine **1** in hand, we examined its catalytic efficiency in asymmetric addition of diethylzinc to aldehyde in hexane.⁸ Aldehydes were converted to the corresponding (*R*)-secondary alcohols with moderate ee's in high yields. The results were compared to the data previously obtained with amorphous silica gel-supported ephedrine. As can be seen in Table 2, SBA-supported ephedrine **1** gave much higher reaction rate and better



Scheme 1

Table 2. Asymmetric addition of diethylzinc to aldehydes^a

$$\text{ArCHO} + \text{Et}_2\text{Zn} \xrightarrow[\text{hexane}]{\text{ligand (6 mol\%)}} \text{Ar}-\text{CH}(\text{OH})-\text{Et}$$

Ar	ligand	time (h)	yield ^b (%)	ee ^c (%)
Ph	silica-eph ^d	48	75	25
Ph	1	24	80	56
<i>o</i> -MeOC ₆ H ₄	silica-eph	48	71	34
<i>o</i> -MeOC ₆ H ₄	1	18	85	71
<i>p</i> -MeC ₆ H ₄	1	24	82	56
<i>p</i> -ClC ₆ H ₄	1	18	84	61

^aReactions were carried out in hexane at RT using 2 equiv. of Et₂Zn. Absolute configuration was assigned by the sign of the optical rotation. ^bMeasured as %-conversion into the product by GC. ^cDetermined by HPLC analysis using chiralcel OD-H column. ^dSilica-eph = silica gel-supported ephedrine.

asymmetric induction than silica gel-supported ephedrine. The improved outcome of the reaction seems to be attributed to crystalline structure of SBA-15. The SBA framework allows regular array of chiral catalytic sites on the pore surface. This leads to elegant site-isolation, which may result in enhanced enantioselectivity. In the case of *o*-methoxybenzaldehyde, enantioselectivity was greatly increased from 34% to 71%. The significant increase is presumably due to the interaction between the methoxy group and the SBA surface and the resulting accessibility to chiral environment of the chiral catalytic sites on the SBA surface. These results are comparable to those of the homogeneous system using *N*-alkyl ephedrine.^{5a}

Next, the efficiency of SBA-15-supported norephedrine **2** was assessed in ruthenium-catalyzed asymmetric transfer hydrogenation of ketones.⁹ The chiral ruthenium catalyst was generated *in-situ* by mixing [Ru(η^6 -arene)Cl₂]₂ and supported ligand **2** (Ru : ligand = 1 : 2) in 2-propanol at 80 °C for 1 h. The catalyst afforded (*S*)-secondary alcohols with

Table 3. Asymmetric transfer hydrogenation of ketones^a

$$\text{Ar}-\text{C}(=\text{O})-\text{R} \xrightarrow[\text{iPrOH, KOH}]{\text{2} + [\text{Ru}(\text{HMB})\text{Cl}_2]_2} \text{Ar}-\text{CH}(\text{OH})-\text{R}$$

entry	ketone	time (h)	yield ^b (%)	% ee ^c
1	α -tetralone	24	71	84
2 ^d	α -tetralone	24	82	82
3	acetophenone	18	85	81
4	2'-acetonaphthone	18	83	76
5	propiophenone	15	80	75

^aThe reaction was carried out at RT; ketone : Ru : ligand **2** = 100 : 1 : 2. ^bMeasured as %-conversion into the product by GC. ^cDetermined by HPLC analysis using Chiralcel OB-H column. ^d[Ru(*p*-cymene)Cl₂]₂ instead of [Ru(HMB)Cl₂]₂ was used.

high ee's of up to 90% in reasonable conversions. The reaction conditions and results are summarized in Table 3. The enantioselectivity seems to depend on the structure of the substrate. As the bulkiness of the alkyl substituent increases, the degree of ee was lowered. [Ru(hexamethylbenzene)Cl₂]₂ as a Ru(II) source gave somewhat higher ee than [Ru(*p*-cymene)Cl₂]₂. It should be noted that SBA-15-supported ligand **2** is as effective as comparable free (–)-ephedrine ligand^{6a} in terms of enantioselectivity.

In conclusion, we have shown that the SBA-15 can be served as a potential support for the heterogeneous chiral ligand. Our studies partially support the possibility of achieving high reactivity and enantioselectivity in heterogeneous systems. Further synthesis of SBA-supported chiral ligands and their use to asymmetric catalysis are underway in our laboratory.

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- General procedure: To a solution of ligand **1** (160 mg, 0.62 mmol/g) in hexane (1.6 mL) was dropwise added diethylzinc (2 mL, 1.0 M in hexane) at 0 °C. The mixture was allowed to warm to RT. Aldehyde (1.0 mmol) was then added and the reaction mixture was stirred at room temperature, observing the progress of the reaction by GC. After work up, the residue was purified by column chromatography and the e.e. was measured by HPLC on a Chiralcel OD-H column.
- General procedure: A mixture of [Ru(HMB)Cl₂]₂ (3.4 mg, 0.005 mmol) and supported ligand **2** (30 mg, 0.65 mmol/g) was heated in dry 2-propanol (1 mL) at 80 °C for 50 min. After the solution was cooled to room temperature, a solution of aromatic ketone (1.0 mmol) in dry 2-propanol solution (10 mL) was added, followed by KOH (0.5 mL, 0.1 M in 2-propanol). The reduction was conducted at room temperature under nitrogen. The reaction was monitored by GC and the e.e. was measured by HPLC on a Chiralcel OB-H column.