

Mesoporous silica anchored Ru catalysts for highly enantioselective hydrogenation of β -ketoesters†

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Recyclable and reusable mesoporous silica anchored Ru catalysts based on 4,4'-substituted BINAPs were synthesized and used for the hydrogenation of β -alkyl β -ketoesters with up to 98.6% e.e. and β -aryl β -ketoesters with up to 95.2% e.e.

New routes are being explored to achieve the economical synthesis of optically pure feedstocks through asymmetric catalysis.¹ Heterogenization of well-established soluble transition metal-based asymmetric catalysts on inorganic oxide or polymer supports allows easy separation and hence recycling and reuse of expensive asymmetric catalysts.² Appropriate covalent attachment of soluble transition metal-based asymmetric catalysts onto the supports can also prevent the leaching of toxic metals into the organic products which can present a formidable challenge if the organic products are to be used as pharmaceutical ingredients. We have recently developed a molecular building block approach toward the heterogenization of homogeneous asymmetric catalysts in zirconium phosphonate hybrid solids.³ Herein we wish to report the immobilization of Ru complexes of 4,4'-substituted BINAPs on well-ordered mesoporous silica SBA-15, and the applications of these heterogeneous asymmetric catalysts in highly enantioselective hydrogenation of β -ketoesters.

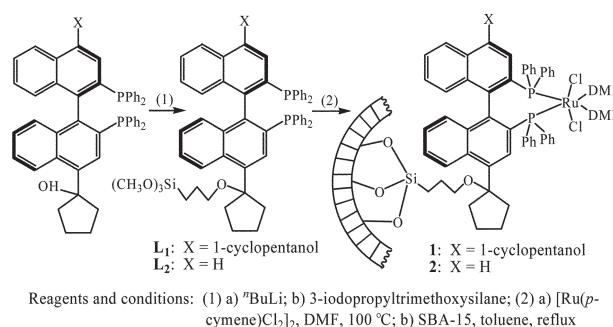
Since their discovery in the early 1990's, well-ordered mesoporous materials have been examined for a number of applications.⁴ Immobilization of homogeneous asymmetric catalysts on the inner walls of such mesoporous solids offers several advantages (including higher surface areas and larger open channels) over other less defined supports such as organic polymers. Mesoporous siliceous materials such as MCM-41 and SBA-15 have indeed been used as supports for the immobilization of several asymmetric catalysts.⁵ We have chosen SBA-15 as the supports for this work because of their ease of synthesis and very large pore sizes (so that diffusion of substrates and products would be more facile).⁶

Lithiation of 4,4'-bis(cyclopentanol)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 4-(cyclopentanol)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl⁷ followed by treatment with 3-iodopropyltrimethoxysilane afforded the modified BINAPs **L**₁ and **L**₂ (Scheme 1). Ligands **L**₁ and **L**₂ have been characterized by ¹H{³¹P} and ³¹P{¹H} NMR spectroscopy. RuL₁(DMF)₂Cl₂ and RuL₂(DMF)₂Cl₂ were synthesized by heating [RuCl₂(*p*-cymene)]₂ and **L**₁ and **L**₂ in DMF at 100 °C, respectively. A suspension of SBA-15 and RuL₁(DMF)₂Cl₂ or RuL₂(DMF)₂Cl₂ in toluene was refluxed overnight to give the heterogenized precatalysts **1** and **2**.⁸ The Ru precatalyst loadings were determined by direct current plasma (DCP) analysis of the Ru content in the modified SBA-15.⁹ The pristine SBA-15 has a BJH surface area of 724 m²/g and a BJH average pore size of 113 Å. Upon the immobilization of the Ru complexes, the solid catalysts **1** and **2** exhibited expected diminished surface areas and pore sizes (Table 1). **2** has slightly larger surface area, pore volume, and pore size than **1**, consistent with the presence of the bulky 1-cyclopentanol group in **1**.

Catalytic asymmetric hydrogenation of both β -alkyl and β -aryl β -ketoesters was carried out under a hydrogen pressure of 1400 psi in the presence of **1** or **2** in methanol at r.t. for 20 h. As shown in

Table 2 (entries 1–4), β -alkyl β -ketoesters were hydrogenated with complete conversions and e.e. values in the 96.3 to 98.6% range in the presence of 1 mol% of **1**. These β -alkyl β -ketoesters were hydrogenated over solid catalyst **2** (2 mol%) with similar e.e. values to **1** and complete conversions.¹⁰ The e.e. values exhibited by **1** and **2** are comparable to those of the parent Ru(BINAP) homogeneous catalyst¹¹ and are 4–5% higher than those of zirconium phosphonate-derived heterogeneous catalysts.^{3a} The level of e.e.'s exhibited by **1** and **2** is also comparable to the best polymer-anchored Ru catalysts for the hydrogenation of β -alkyl β -ketoesters.¹²

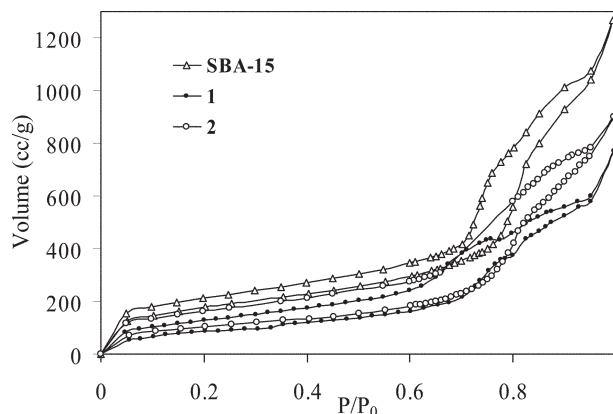
The hydrogenation of β -aryl β -ketoesters was carried out in the presence of 2 mol% of solid catalyst **1** or 4 mol% of solid catalyst **2**. E.e. values in the range of 81.7–95.2% were obtained for **1**, while e.e. values in the range of 71.9–93.5% were obtained for **2** (Table 2,



Scheme 1

Table 1 Surface area, pore volume, and pore size of SBA-15, **1**, and **2**

	SBA-15	1	2
BJH surface area (m ² /g)	724	487	529
BJH pore volume (mL/g)	1.98	1.38	1.52
BJH pore size (Å)	113	96	101

Fig. 1 N₂ adsorption isotherms for SBA-15, **1**, and **2** at 77 K.

† Electronic supplementary information (ESI) available: experimental section. See <http://www.rsc.org/suppdata/cc/b4/b406697a/>

Table 2 Catalytic asymmetric hydrogenation of β -ketoesters by **1** and **2**¹³

(R₃=H except for entry 4)

Entry	R ₁	R ₂	1 ^a	2 ^b
1	Me	Me	98.6	97.6
2	Me	^t Pr	98.4	98.6
3	Me	^t Bu	97.3	97.1
4 ^c	Me	Me	96.3	96.3
5	2'-CF ₃ -Ph	Me	95.2	93.5
6	2'-Cl-Ph	Me	94.2	90.0
7	3'-CF ₃ -Ph	Me	92.7	90.4
8	4'-OMe-Ph	Et	91.5	82.3
9	Ph	Et	91.0	79.9
10	4'-CF ₃ -Ph	Me	87.4	71.9
11	4'-F-Ph	Me	86.3	81.4
12	4'-Cl-Ph	Me	81.7	81.4

^a 1 mol% catalyst loading for entries 1–4 and 2 mol% catalyst loading for entries 5–12. ^b 2 mol% catalyst loading for entries 1–4 and 4 mol% catalyst loading for entries 5–12. ^c R₃ = Me.

entries 5–12). These e.e. values are much higher than those afforded by the homogeneous Ru(BINAP)(DMF)₂Cl₂ catalyst, but a few percent lower than those afforded by the parent Ru[4,4'-(1-cyclopentanol)₂BINAP](DMF)₂Cl₂ catalyst reported by us recently.⁷ Consistent with our earlier discovery of the 4,4'-substituted effects of BINAP in the hydrogenation of β -aryl β -ketoesters,⁷ **2** gave lower e.e.'s than **1** for all the substrates tested because of the lack of a bulky substituent in the 4'-position of the modified BINAP **L**₂.

We have attempted to recycle and reuse **1** in the hydrogenation of methyl acetoacetate. As shown in Table 3, **1** was successfully used for 5 consecutive runs of asymmetric hydrogenation of methyl acetoacetate. Complete conversions were obtained for the first three runs, and the conversion started to drop in the fourth and fifth run. The e.e. value also deteriorated as the conversion dropped. We believe that the loss of activity and the deterioration of enantioselectivity are probably a result of the air-sensitivity of the catalytically active Ru-hydride species (but not the leaching of Ru-containing complexes). Control experiments showed that the supernatant did not catalyze the hydrogenation of methyl acetoacetate. Consistent with this, DCP spectroscopy showed that less than 0.12% of Ru-containing complexes had leached into the organic phase during each run of asymmetric hydrogenation.

In summary, we have designed recyclable and reusable heterogeneous asymmetric catalysts *via* covalent anchoring to the inner walls of mesoporous SBA-15. These immobilized catalysts have been used for the hydrogenation of β -ketoesters with up to 98.6% e.e.

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Table 3 Recycling and reuse of **1** for the hydrogenation of methyl acetoacetate^a

Run	1	2	3	4	5
e.e. (%)	98.6	98.4	96.2	89.2	82.1
Conversion (%)	> 99	> 99	> 99	91	83

^a All the reactions were carried out with 1 mol% catalyst in MeOH under 1400 psi of H₂ for 20 h.

Notes and references

‡ **Preparation of solid catalysts.** A mixture of [Ru(*p*-cymene)Cl₂]₂ (15.3 mg, 0.025 mmol) and **L**₁ (50 mg, 0.052 mmol) in anhydrous DMF (4 mL) was heated at 100 °C under Ar for 30 min and then cooled to 25 °C. All the volatile components were removed under vacuum to give a dark red solid. This solid was refluxed with 335 mg of SBA-15, that had been dried under vacuum at 135 °C for 3 h, in 10 mL of toluene overnight. The mixture was cooled to r.t. and centrifuged for 30 min, the supernatant was removed. The solid was washed with dry toluene and dried under vacuum. 400 mg of solid catalyst **1** was obtained after this treatment.

§ **A typical procedure for asymmetric hydrogenation of β -ketoester.** 19.2 mg of solid catalyst **1** (2.5 μ mol) was weighed into a Teflon-capped vial inside a drybox, and to this vial was added ethyl benzoylacetate (24 μ L, 0.125 mmol) and anhydrous methanol (0.5 mL) under Ar. The vial was quickly transferred inside a stainless steel autoclave, and sealed. After purging with hydrogen for 6 times, final H₂ pressure was adjusted to 1400 psi; 20 h later, H₂ pressure was released and water (10 mL) was added. The hydrogenated product was extracted with diethyl ether and passed through a mini silica-gel column before chiral GC, HPLC and SFC analyses.

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- Typical loadings are 0.0125 mmol of **1** and 0.0112 mmol of **2** per gram of SBA-15, respectively.
- Although β -alkyl β -ketoesters can be hydrogenated with complete conversions in the presence of 1% of **2**, much inferior e.e. values (10–15% lower) were obtained.
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- All the reactions were judged to have > 99% conversions based on integrations of NMR peaks. E.e.% values were determined by GC using a Supercio γ -Dex 225 column or by HPLC using a Chiralpak AD column and by SFC using a Chiralpak AS column.