Supported Catalysts

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Mesoporous Silica Nanosphere Supported Ruthenium Catalysts for Asymmetric Hydrogenation**

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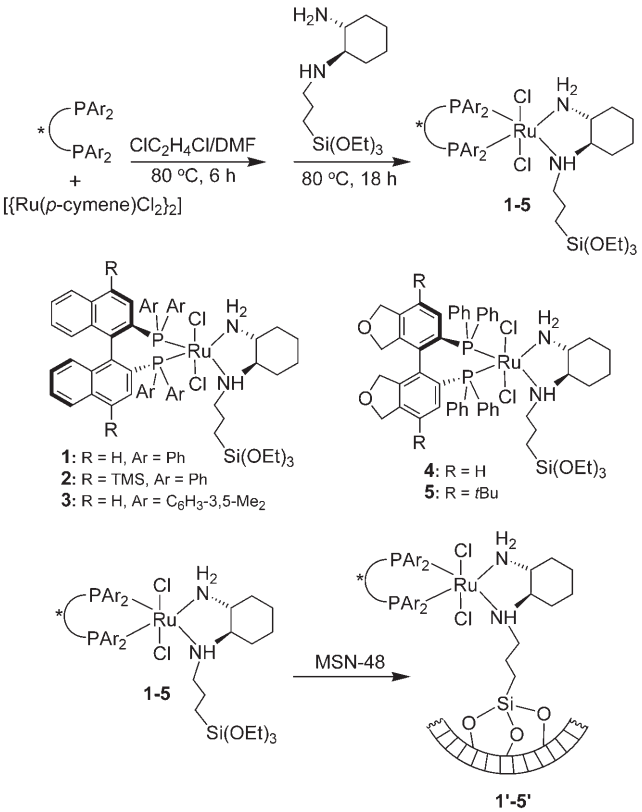
Asymmetric catalysis is a powerful method for the synthesis of pharmaceutically important chiral molecules.[1] Numerous highly selective chiral catalysts have been developed recently, but their practical applications in industrial processes are often hindered by their high costs as well as difficulties in removing trace amounts of toxic metals from the organic products.[2] Many different approaches have been developed to immobilize homogeneous asymmetric catalysts in order to overcome these problems,[3] with the covalent attachment of chiral catalysts to mesoporous silica materials being one of the most promising methods for generating heterogenized asymmetric catalysts.[4] MCM- and SBA-type silicas provide ideal supports for asymmetric catalyst immobilization owing to their ordered structures, very high surface areas, and uniform, large, and tunable pore diameters.[5]

Recent elegant studies by Lin et al. and others have shown that mesoporous silica materials can be obtained as uniform nanospheres under appropriate synthetic conditions.[6] Mesoporous silica nanospheres (MSNs) have further been shown to be excellent supports for bifunctional catalysts that exhibit interesting cooperative catalytic activities.[7] Herein we demonstrate the utility of MSNs as supports for ruthenium catalysts for the asymmetric hydrogenation of aromatic ketones to afford chiral secondary alcohols and racemic arylaldehydes to give chiral primary alcohols. We envisage the generation of highly active heterogeneous catalysts by taking advantage of both the large channel diameters (>2 nm) of MSNs and short diffusion lengths for the organic substrates as a result of small nanoparticle sizes ($<1\,\mu$m). The short diffusion length is of practical importance owing to the typically large size (and hence hindered diffusion) of organic substrates used in asymmetric catalytic processes.

We chose chiral $RuCl_2$–diphosphine–diamine complexes as model precatalysts to be supported on the MSNs because these complexes have been shown to be air- and moisture-stable and can be readily purified by silica-gel chromatography.[8] Most importantly, seminal studies by Noyori and others have shown that base activation of such chiral ruthenium complexes gives highly active and enantioselective catalysts for the asymmetric hydrogenation of prochiral ketones.[9] More recently, chiral $RuCl_2$–diphosphine–diamine complexes have been shown to be highly active catalysts for the asymmetric hydrogenation of racemic aldehydes in the synthesis of chiral primary alcohols via a dynamic kinetic resolution process.[10] Our immobilization strategy relies on tethering the chiral ruthenium complexes to MSNs via a siloxy group installed in the diamine ligand. As shown in Scheme 1, chiral complexes **1**–**5**, which contain pendant siloxy



Scheme 1. Synthesis of complexes **1**–**5** and their immobilization on MSN-48.

groups, were prepared by heating a mixture of [{$RuCl_2$(*p*-cymene)}$_2$] and a chiral diphosphine in 1,2-dichloroethane/DMF at 80 °C followed by treatment with siloxy-derivatized chiral 1,2-cyclohexanediamine (siloxy-DACH). Five chiral diphosphines, namely 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap), 2,2′-bis(diphenylphosphino)-4,4′-bis(trimethylsilyl)-1,1′binaphthyl (TMS-binap), [2,2′-bis(di-3,5-

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xylylphosphino)-1,1′-binaphthyl (Xyl-binap), (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine) (SegPhos), and (7,7′-*tert*-butyl-4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine) (*t*Bu-SegPhos), were used.[11] All chiral complexes **1**–**5** are diamagnetic and stable to both air and moisture. They are readily purified by silica gel chromatography and were characterized by ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopy as well as ESI mass spectrometry.

Precatalysts **1**–**5** display a characteristic pair of doublets in the range $\delta = 37$–49 ppm in their $^{31}P\{^{1}H\}$ NMR spectra due to the unsymmetrical nature of the monosubstituted diamine. Their ESI mass spectra show the presence of peaks corresponding to the loss of a chloride ligand from the molecular ion, thus confirming the nature of ruthenium(II) precatalysts **1**–**5**.

Mesoporous silica nanospheres with three-dimensional channels (MSN-48) were prepared according to a literature procedure by hydrolysis and condensation of tetraethoxysilane in a water/ethanol solution of cetyltrimethylammonium bromide and ammonia.[12] The particles were isolated by centrifugation and calcined at 600 °C to remove the surfactant template. The spherical morphology of MSN-48 is clearly visible in the SEM image (Figure 1 a). The diameters of MSN-48 particles are tunable from 75 nm to 1 μm, depending on the reagent concentrations used. The TEM image shows striation across the nanosphere, thereby indicating the regularity of the pores (the ordered channels) over the whole particle (Figure 1 b). The ruthenium complexes **1**–**5** were grafted onto MSN-48 by refluxing in toluene for 24 h. Nitrogen adsorption isotherms indicated that the calcined MSN-48 has a Barrett–Joyner–Halenda (BJH) surface area of 1737 $m^2 g^{-1}$ and a pore diameter of 2.2 nm (Figure 1 c). The solid **1′** obtained upon grafting **1** has a BJH surface area of 1131 $m^2 g^{-1}$ and a pore diameter of 1.7 nm. The reduced surface area and pore diameter of **1′** suggests attachment of the ruthenium complex **1** to the surface of MSN-48 via the siloxy linkage. Consistent with this, the pore volume decreases from 1.07 $cm^3 g^{-1}$ for MSN-48 to 0.61 $cm^3 g^{-1}$ for **1′**.

The ruthenium precatalyst loadings on MSN-48 were estimated by thermogravimetric analysis (TGA), which gives the percent weight loss due to the organic moieties, and the ruthenium content was determined by direct current plasma (DCP) spectroscopy. The MSN-supported materials **1′**–**5′** prepared in this fashion have a consistent ruthenium(II) precatalyst loading of 5–7 wt % as determined by TGA and DCP.

Upon activation with base co-catalysts, complexes **1**–**5** were shown to be highly active for the homogeneous asymmetric hydrogenation of aromatic ketones, with enantiomeric excesses of up to 94 % *ee* (Table 1). Control experiments with [Ru(binap)(1,2-cyclohexanediamine)Cl_2] (**6**) indicated that the propyl(triethoxy)silane pendant in **1** enhances the enantioselectivity significantly. It is well known that $RuCl_2$–diphosphine–diamine homogeneous catalysts with two primary amine groups (such as 1,2-diphenylethylenediamine and 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) provide a significant enhancement of enantioselectivity compared with either bulky substituents on the 4,4′-positions of the binaphthyl framework or bulkier 3,5-dimethylphenyl groups on the phosphino moieties.[8,9] Such a beneficial substituent effect is absent in complexes **1**–**5** with an alkylated 1,2-cyclohexanediamine ligand. Thus, the ruthenium(II) complex with a binap ligand (**1**) gives higher *ee* values than those with TMS-binap (**2**) or Xyl-binap (**3**), whereas the *t*Bu groups on the 7,7′-position of SegPhos (in **5**) significantly enhance the enantioselectivity, presumably as a result of the difference in dihedral angles between the binaphthyl system and the SegPhos system.

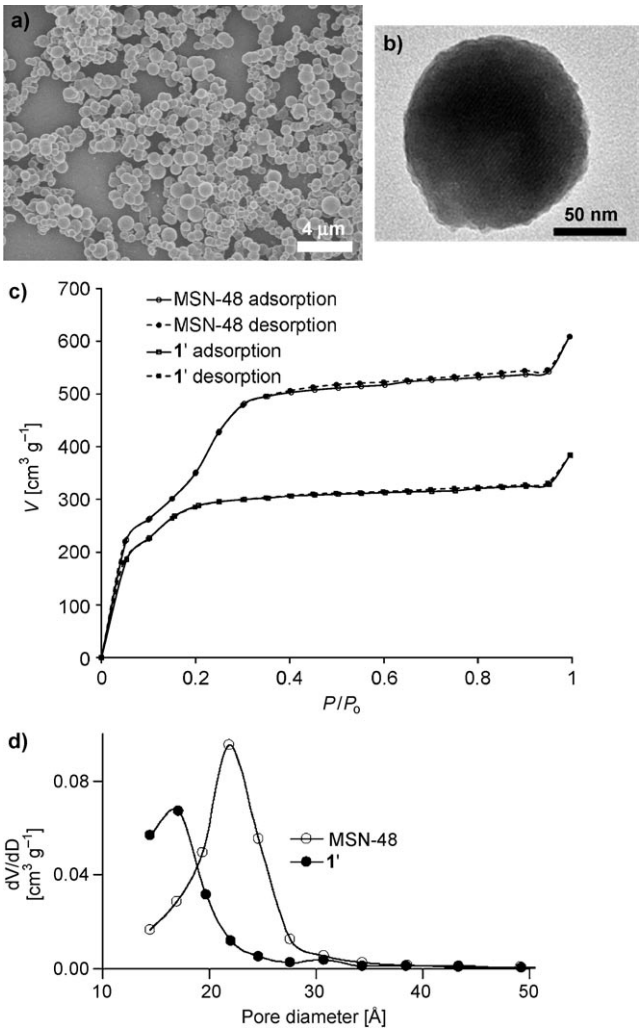
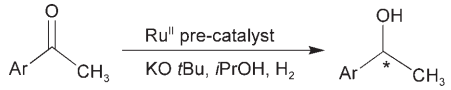


Figure 1. a) Representative SEM image of the MSN-48 showing that the particles range from 300 nm to 1 μm in diameter in this batch. b) TEM image of an MSN-48 particle showing the striations across the nanospheres that correspond to the ordered channels. c) Nitrogen adsorption isotherms for the calcined MSN-48 and the MSN-48 sample (**1′**) grafted with precatalyst **1**. d) Pore-size distribution for the calcined MSN-48 and **1′**.

Upon activation with KO*t*Bu, the MSN-48-immobilized ruthenium complexes **1′**–**5′** are also very active catalysts for the asymmetric hydrogenation of aromatic ketones. As shown in Table 1, no decreases of catalytic activities were observed for the immobilized catalysts, although **1′**–**5′** exhibit lower enantioselectivities than their parent homogeneous catalysts. The highest *ee* value of 82 % was obtained for the hydro-

Table 1: Enantioselectivities [% *ee*] for the asymmetric hydrogenation of aromatic ketones with complexes **1**–**5** and their heterogeneous counterparts supported on MSN-48 (**1′**–**5′**).[a]

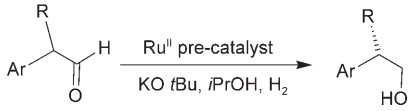


	Homogeneous catalyst					
Ar	**1**	**2**	**3**	**4**	**5**	**6**
Ph	82	77(86)	79	67(95)	80	62(93)
1-naphthyl	**94**	80(83)	78	79(97)	92	73(94)
2-naphthyl	83	80(97)	90	61(96)	82	72(94)
4-MeC_6H_4	83	64(84)	76	67(95)	81(94)	62(94)
4-ClC_6H_4	71	64(86)	86	56(95)	76	61(91)
4-$MeOC_6H_4$	80	47(80)	68	70(96)	85	63(95)
4-*t*BuC_6H_4	89	76	84	74(93)	77	78(94)

	MSN-supported catalyst (mol% loading)				
Ar	**1′**(0.8)	**2′**(0.7)	**3′**(1.0)	**4′**(1.1)	**5′**(0.9)
Ph	61(94)	71	59	58(97)	73
1-naphthyl	67(96)	76(87)	52	76	72
2-naphthyl	68	**82**	66	58(97)	69
4-MeC_6H_4	47	66	60	60	61
4-ClC_6H_4	57	72	62	51	57
4-$MeOC_6H_4$	68	64(48)	49	53	56(97)
4-*t*BuC_6H_4	77	69	53	69(94)	49

[a] All reactions were carried out under a hydrogen pressure of 700 psi in the presence of ruthenium precatalyst and KO*t*Bu in 2-propanol at room temperature for 24 h. All the homogeneous reactions were run with a 1 mol% catalyst loading. Conversions (%) and *ee* values (%) were determined by GC on a Supelco β-Dex 120 column for all of the secondary alcohols. [b] The catalyst loading for **1′**–**5′** was estimated based on the ruthenium content determined by DCP. [c] All the reactions went to completion except those where percent conversions are shown in parentheses.

Table 2: Enantioselectivities [% *ee*] for th asymmetric hydrogenation of aryl aldehydes with complexes **1**–**3** and their heterogeneous counterparts supported on MSN-48 (**1′**–**3′**).[a]



		Homogeneous			*Heterogeneous*		
Ar	R	**1**	**2**	**3**	**1′**	**2′**	**3′**
Ph	Me	42	70	72	52	76	86
Ph	*i*Pr	35	97	**99**	52	**97**	86
Ph	*n*Bu	40	80	92	55	84	49
4-ClC_6H_4	Me	47	69	74	52	78	83
4-$MeOC_6H_4$	Me	53	76	83	63	78	88
2-Naphthyl	Me	44	72	72	68	83	86

[a] All reactions were carried out under a hydrogen pressure of 700 psi in the presence of ruthenium precatalyst and KO*t*Bu in 2-propanol at room temperature for 24 h. All the reactions were run with a 0.1 mol% catalyst loading and were judged to be complete by HPLC and ^{1}H NMR spectroscopy. The *ee* values were determined by HPLC on a Chiralcel AD column.

genation of 2-acetonaphthone using **2′** as catalyst. A similar drop in enantioselectivities has been observed for many asymmetric catalysts immobilized on bulk mesoporous silicas.[13]

These highly active MSN-48-supported catalysts were readily recovered by centrifugation and were shown to be reusable for the asymmetric hydrogenation of aromatic ketones. For example, for the hydrogenation of acetophenone, **1′** was recovered and reused at least five times, with conversions of > 99%, > 99%, 89%, > 99%, and 65% and *ee* values of 61%, 58%, 70%, 68%, and 65% for the five consecutive runs. DCP measurements indicated that less than 4% of the ruthenium species leached from the MSN-supported catalyst during each catalytic cycle.

Intrigued by recent elegant work concerning homogeneous asymmetric hydrogenation of racemic α-branched aryl aldehydes by $RuCl_2$–diphosphine–diamine complexes for the synthesis of chiral primary alcohols,[10] we have also examined the utility of MSN-48-immobilized ruthenium complexes in such a dynamic kinetic resolution process (Table 2). At a 0.1 mol% catalyst loading, homogeneous catalysts **1**–**3** all gave complete conversion of aryl aldehydes to their hydrogenated products, with *ee* values as high as 99% (for 3-methyl-2-phenylbutanal, which has an *i*Pr group at the α-position). This level of enantioselectivity is slightly superior to that obtained with the soluble $RuCl_2$–diphosphine–1,2-cyclohexanediamine complexes examined by Zhou et al.,[10] thereby suggesting the positive influence of the propyl(triethoxy)silane pendant on the enantioselectivity of the dynamic kinetic resolution process. It is of interest to note that there is significant enantioselectivity enhancement with either bulky substituents on the 4,4′-positions of the binaphthyl framework (for **2**) or bulkier 3,5-dimethylphenyl groups on the phosphino moieties (for **3**).

The MSN-48-supported ruthenium complexes **1′**–**3′** are also highly active catalysts for the asymmetric hydrogenation of racemic α-branched aryl aldehydes (Table 2). Interestingly, unlike the asymmetric hydrogenation of aromatic ketones, the immobilized catalysts **1′**–**3′** gave higher enantioselectivity for most of the aryl aldehydes examined (with as much as a 24% increase of the *ee* value for the hydrogenation of α-2-naphthylpropionaldehyde using **1** vs. **1′**). The highest *ee* value obtained for the heterogeneously catalyzed reaction is 97% for 3-methyl-2-phenylbutanal with **2′**. The different effects of immobilization on the enantioselectivity of two asymmetric hydrogenation reactions highlight the subtlety of catalyst immobilization and the need to examine other reaction types and immobilization strategies.

In summary, we have prepared chiral $RuCl_2$–diphosphine–diamine complexes with a siloxy functionality which can be readily attached to a silica surface. We have successfully immobilized these ruthenium complexes on mesoporous silica nanospheres with three-dimensional channels, and have demonstrated for the first time the utility of MSNs as supports for ruthenium catalysts in the asymmetric hydrogenation of aromatic ketones to afford chiral secondary alcohols and racemic aryl aldehydes to give chiral primary alcohols. The generality of this catalyst immobilization strategy should allow the design of many highly active and enantioselective heterogeneous asymmetric catalysts.

Experimental Section

Typical procedure: **1**: A solution of (*R*)-binap (25 mg, 40.1 μmol) and [{Ru(*p*-cymene)Cl_2}$_2$] (12.5 mg, 20 μmol) in dichloromethane (2 mL) and DMF (0.5 mL) was heated at 50 °C under argon for 24 h and then cooled to room temperature. (*R*,*R*)-Siloxy-DACH (12.8 μL, 40.1 μmol) was added and the mixture was heated at 50 °C for another 24 h. The solvents were removed under reduced pressure to yield a dark red solid, which was purified by silica gel column chromatography with hexanes/ethyl acetate (2:1, v/v) as eluent.

Typical procedure: **3′**: A mixture of **3** (11 mg, 8.9 μmol) and MSN-48 (110 mg) in toluene (3 mL) was heated to reflux under argon for 24 h. After cooling to room temperature, the mixture was washed with toluene (3 × 10 mL) and dichloromethane (2 × 10 mL). The resulting MSN-48 material was dried under reduced pressure for 18 h. TGA and DCP indicated the ruthenium precatalyst loading to be in the 5–7 wt % range.

Asymmetric Hydrogenation: The precatalyst (0.5 μmol) and KO*t*Bu (5 μmol) were added to a one-dram vial containing 50 μmol of aromatic ketone and a stir bar inside a drybox. 2-Propanol (1 mL) was added under argon and the vial was capped with a septum punched with a needle. The reaction vessel was quickly transferred to a stainless-steel autoclave and sealed. After purging six times with H_2, the final H_2 pressure was adjusted to 700 psi. The autoclave was depressurized after 24 h and the reaction mixture extracted with diethyl ether. The ether layer was collected and passed through a small silica gel column. The resulting solution was concentrated and an aliquot was analyzed by GC to determine conversion and *ee* values. The asymmetric hydrogenation of racemic aryl aldehydes was carried out in a similar manner except the *ee* values were determined by HPLC and the conversions were determined by HPLC and ^{1}H NMR spectroscopy.

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