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Aqueous enantioselective hydrogenations involving silica-heterogenised catalysts

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Abstract

A mesoporous silica (HMS) has been prepared with an average pore size of 26 Å. The pores have been shown to include typical chiral catalysts for enantioselective hydrogenation viz Rh–BPPM and Ru–BINAP. The heterogenised catalysts have been shown to be effective for hydrogenations of water-soluble alkenes, e.g. itaconic acid **3** and the sodium salt of *N*-acetamidocinnamic acid (**1a**). Modest enantioselectivity was achieved for hydrogenation of the cinnamic acid derivative (40–60% ee) but only poor values for the itaconic acid ($0 \leq 16\%$ ee). In some cases, the catalysts could be recovered and reused without significant loss of activity or selectivity. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Rhodium; Ruthenium; Asymmetric hydrogenation; Aqueous solution; Heterogenised catalyst; Silica

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1. Introduction

The need to develop effective catalysts for enantioselective synthesis is becoming even more important as regulatory authorities increasingly insist that a single enantiomer of a racemic bioactive compound be used in pharmaceuticals or agrochemicals [1,2]. Although many effective enantioselective catalyst systems have been developed, most involve expensive chiral ligands and in many cases expensive metals such as Pd, Rh etc. The commercial application of such systems obviously requires an effective method of catalyst recovery and re-use on both economic and environmental grounds.

Several methods for the recycling of chiral catalysts have been described. The attachment of a chiral catalyst to a soluble polymer which can be reprecipitated after use and the immobilisation of chiral catalysts in membranes have been described recently [3]. A modification of this technology involving membrane impregnated carbosilane dendrimers has also been described [4].

Covalent attachment of chiral catalysts to supports such as silica and zeolites [5], layered clays [6] or polymers [7] has been shown to give highly effective enantioselective hydrogenation catalysts. The pore size of the insoluble support has been shown to affect the degree of enantioselectivity of some hydrogenation catalysts [8].

Matrix isolation of chiral catalysts in microporous solids has been limited until recently by the difficulty of obtaining materials with suitable pore characteristics. Davis and his co-workers [9] have described use of a sulfonated-BINAP/Ru catalyst in a porous glass matrix for enantioselective hydrogenations in organic solvents. The concept of supported aqueous phase catalyst (SAPC) [10] in which a water-soluble catalyst is immobilised in a thin water layer adhered within the pores of a high surface area silicate has been extended by van Leeuwen's group to produce a stable and recyclable supported aqueous phase catalyst for highly selective olefin hydroformylation [11].

The aim of this work is to use readily available hexagonal mesoporous silicas (HMS) [12] derived from the original discoveries of the Mobil Oil Company [13] with a pore size such that established chiral hydrogenation catalysts can just be accommodated in the pore. Reactions in aqueous media have been examined with the intention of recovering and reusing the incorporated catalyst. The closeness of fit was designed to maximise catalyst retention. This technique by which

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the catalyst molecule is retained in the host pore by van der Waals interactions is, when successful, simpler than the use of covalent bonding: the latter generally involves fairly complex preparative chemistry and also may lead to undesirable steric constraints.

2. Experimental

2.1. Instrumentation

^{1}H-NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 MHz). The ^{1}H-NMR spectra were run in D_2O solution with TMSP as the internal standard or in CD_3OD with TMS as the internal standard with chemical shifts measured in ppm. The optical yields were determined by polarimetry using a Perkin–Elmer 1600 polarimeter by comparison with the literature values for the optically pure compounds: *N*-acetyl-(*R*)-phenylalanine, $[\alpha]_D^{26} - 51.8°$ ($C = 1$, EtOH) [15]; (*R*)-2-methylsuccinic acid, $[\alpha]_D^{20} + 16.88$ ($C = 2.2$, EtOH) [16]. A Silicon Graphics Indy computer equipped with the Insight II software package [14] was used for molecular modelling. Ru and Rh analyses were carried out using a Varian Liberty 200 Inductively Coupled Plasma Emission Spectrometer with diisobutylketone or water as solvent.

2.2. Materials and reagents

Benzene was dried over phosphorus pentoxide, decanted, distilled from fresh phosphorus pentoxide and stored over sodium wire. Distilled water was used for all aqueous manipulations. All manipulations were carried out under N_2 and solvents degassed before use.

Itaconic acid; α-acetamidocinnamic acid; bis(cycloocta-1,5-diene)dichlorodirhodium (I), [Rh(COD)-Cl]$_2$; (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, (+)-(BINAP); (2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl] pyrrolidine, (BPPM); and [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride (Ru–BINAP) were obtained from commercial sources. Sodium α-acetamidocinnamate (**1a**) was prepared by stirring α-acetamidocinnamic acid (**1b**) (2.03 g, 9.9 mmol) in an aqueous solution of sodium hydroxide (10 ml) containing 9.8 mmol of NaOH. Excess acid was removed by filtration and the sodium salt isolated by the removal of water under vacuum at ambient temperature.

Ordered mesoporous silica (HMS) of 26 Å average pore size was synthesised in the presence of dodecylamine in water with ethanol as a co-solvent by following procedures similar to those reported previously [12]. Before impregnation, the hexagonal mesoporous silica (HMS) was calcined in air at 550°C for 4 h to remove the structurally incorporated template and fully hydrated by saturation with water vapour at ambient temperature in a desiccator over saturated aqueous NH_4Cl for 48 h. The water content determined by TGA was 21%. The average pore size was confirmed as 26 Å by nitrogen adsorption at −196°C using a standard procedure [17].

2.3. Pretreatment of HMS and impregnation of catalysts

The rhodium catalysts were prepared ‘in situ’ by stirring [Rh(COD)Cl]$_2$ (0.005 mmol) together with the ligand BPPM (0.011 mmol) in dry, deoxygenated benzene (5 ml) for 30 min [18]. The commercial Ru–BINAP (0.005 mmol) was dissolved in dry, deoxygenated benzene (5 ml) by stirring for 30 min.

HMS (100 mg) was dispersed in either 10 ml of 1:1 MeOH–H_2O (v/v) containing 0.1 ml of acetic acid or triethylamine or 10 ml of H_2O containing 0.06 mmol of triethylammonium chloride or benzyltriethylammonium chloride. The mixture was stirred for 1 h at ambient temperature, filtered and washed three times with the same solvent (10 ml each). The pretreated silica was dried under vacuum at ambient temperature for 4 h and then used immediately for the impregnation of catalysts.

A solution of the prepared rhodium or ruthenium catalyst was added, via a syringe, to a Schlenk flask containing the pretreated HMS (100 mg). The mixture was stirred for 16 h at ambient temperature, filtered under dry N_2 and washed three times with degassed benzene (3 × 5 ml). The filtrate and washings were collected and evaporated in vacuo in order to determine the amount of catalyst absorbed. The impregnated support was dried under vacuum at ambient temperature for 4 h and then used immediately.

2.4. Typical hydrogenation procedure

The substrate (200 mg) was dissolved in 10 ml of degassed distilled water or 1:1 MeOH–H_2O (v/v). The solution of the substrate and the impregnated silica (100 mg) were added into a stainless steel autoclave with a glass sleeve. The reactor was evacuated and filled with high-purity hydrogen, and this was repeated three times. Hydrogenation was carried out under the reported hydrogen pressure and with stirring. After the reaction, the autoclave was cooled to ambient temperature and the reaction mixture was filtered.

In the case of itaconic acid (**3**), the silica was washed with distilled water (3 × 5ml) and the combined filtrate and washings evaporated. ^{1}H-NMR spectroscopy was used to determine the extent of reaction by integration

Table 1
Heterogeneous hydrogenation of sodium α-acetamidocinnamate (**1a**) in water

Catalyst	Entry	Run [a]	Time (h)	Temperature (°C)	Pressure (MPa)	Conv. %	ee % (*R*)
Rh-(*S*,*S*)-BPPM [b]	1	0	46	50	0.2	100	49
	2	1	46	50	0.2	73	43
	3	2	46	50	0.2	58	40
Rh-(*S*,*S*)-BPPM [c]	4	0	46	50	0.2	96	48
	5	1	46	50	0.2	76	41
	6	2	46	50	0.2	62	36
Ru-(*R*)-BINAP [b]	7	0	72	60	2.76	81	48
	8	1	92	60	2.76	93	46
	9	2	92	60	2.76	86	43

[a] Number of previous runs with the catalyst (reuse).
[b] HMS–silica dried under vacuum without further treatment.
[c] HMS–silica treated with triethylamine then dried under vacuum.

of the CH_2 signals at δ 2.6 and 2.7 (D_2O) in the product and δ 3.4 (D_2O) in itaconic acid.

In the case of sodium α-acetamidocinnamate (**1a**), the silica was washed with distilled water (3 × 15ml). The combined filtrate and washing were evaporated to ca. 10ml residue and acidified with 1 N HCl. The free acid was extracted with ethyl acetate (3 × 15ml). The extract was dried and evaporated. The conversion was determined by integration of the CH_3CON peaks at δ 1.92 (CD_3OD) for *N*-acetylphenylalanine (**2**) and δ 2.1 (CD_3OD) for α-acetamidocinnamic acid (**1b**).

The product from reactions of the free acid **1b** was isolated by washing the silica with 1:1 MeOH–H_2O (v/v) (3 × 15 ml). The combined washing and filtrate were evaporated and the residue quickly dissolved in 0.5 M NaOH (5 ml) and filtered through a Celite pad. The flask and Celite pad were washed with water (2 × 20 ml). The combined filtrate and washings were reduced to ca. 10 ml under vacuum and extracted with ethyl acetate (2 × 20 ml). The aqueous layer was acidified and the product isolated as above.

3. Results and discussion

3.1. Silica preparation and impregnation

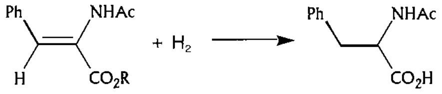
A preparation of 26 Å silica (HMS 26) was carried out using dodecylamine as a template [12]. Treatment of this HMS 26 with a benzene solution of Ru–BINAP led to incorporation of ca. 80% of the Ru-compound. A rhodium complex with the slightly smaller ligand BPPM was also completely incorporated into HMS 26 (96%) but a slightly lower incorporation was achieved with HMS 26 which had been treated with triethylamine (80%).

These complexes were chosen on the basis of molecular modelling experiments using the Insight II program [14]. Calculations for the incorporation of BINAP–Rh–(COD) and BPPM–Rh–(COD) showed that silicas with average pore sizes of at least 20 Å were required. A pore size of 26 Å was chosen so as to allow a reasonably tight fit with significant van der Waals interactions between the catalyst and the silica but with sufficient space to allow access of the substrate to the catalyst. Calculations also showed that it was possible to incorporate the Rh as $(BINAP)_2Rh$ but only with restricted orientation. Calculations for incorporation of [BINAP–Ru–(*p*-cymene)]$^+Cl^-$ showed a similar fit to the mononuclear Rh complexes.

3.2. Hydrogenation of sodium α-acetamidocinnamate (1a)

Hydrogenation of sodium α-acetamidocinnamate using HMS 26 impregnated with the rhodium complex of BPPM and the ruthenium complex of BINAP was carried out in water and results are summarised in Table 1 (Scheme 1). In general the activity of the catalysts was in the order Rh–BPPM (entry 1) > Ru–BINAP (entry 7). More forcing conditions were required to achieve acceptable conversions for Ru–BINAP. A reaction using this catalyst for 46 h at 1 MPa gave only 27% conversion.

The ee values obtained from Rh–BPPM and Ru–BINAP were both ca. 50% (entries 1 and 7). These values compare unfavourably with enantioselective homogeneous reactions of the free acid **1b** in organic solvents [1,2] or of the sodium salt **1a** in aqueous medium using water-soluble Rh-catalysts [19]. Hydro-



1a; R = Na

1b; R = H

2

Scheme 1.

Table 2
Hydrogenation of α-acetamidocinnamic acid (**1b**) using heterogenised Rh-(*S*,*S*)-BPPM in water

Silica treatment	Entry	Time (h)	Temperature (°C)	Pressure (MPa)	Conv. %	ee % (*R*)
[a]	10	46	50	0.2	100	53
	11 [b]	46	50	0.2	9	11
	12 [b]	46	50	0.2	–	–
Et_3N	13	46	50	0.2	100	62
	14 [b]	46	50	0.2	38	49
	15 [b]	46	50	0.2	22	10
$BnN^+Et_3Cl^-$	16	46	60	0.3	100	52
	17	72	35	0.2	59	51
$Et_3N^+HCl^-$	18	72	35	0.2	56	52

[a] HMS–silica dried under vacuum without further treatment.

[b] Catalyst recovered and reused from previous run.

genations of both the free acid **1b** and its methyl ester in water using $[Rh(COD)_2]BF_4$ and BPPM as the catalyst system have also been reported to give high ee's under mild reaction conditions though the ee's have been reported to increase on addition of surfactants [20].

Treatment of the silica with triethylamine as described in the experimental section led to no significant change in either the conversion or the ee (entry 4). The triethylamine treatment was used to remove any possible highly acidic sites on the silica but it should be noted that the addition of triethylamine to Rh–BPPM catalysed homogeneous systems has led to variable but significant effects on resulting enantioselectivities [21]. Addition of triethylamine to a heterogeneous cinchonidine–platinum on alumina catalyst system has been reported to lead to increases in ee under some conditions [22].

Although only modest ee's were achieved with these heterogeneous catalyst systems the validity of our approach, i.e. the recovery and reuse of expensive catalysts of this type, was investigated.

3.3. Recovery and reuse of catalysts

Reactions of the sodium salt of the cinnamic acid **1a** were carried out using the recovered catalysts listed in Table 1. Recovered Rh–BPPM impregnated into either HMS 26 or the triethylamine-treated material showed a significant drop in reactivity but little change in enantioselectivity (see entries 1–3 and 4–6, Table 1). The amount of rhodium lost during the initial reaction with these catalysts (entries 1 and 4) was determined to be less than 4% of the incorporated rhodium. Similar reactions using the recovered Ru–BINAP system showed no loss of reactivity or enantioselectivity (entries 7-9, Table 1). Less than 2% of ruthenium was leached during the first reaction.

*3.4. Hydrogenations of α-acetamidocinnamic acid (**1b**)*

Hydrogenations of the free acid **1b** were carried out in water using Rh–BPPM incorporated into HMS 26 which had been treated with Et_3N, its hydrochloride salt $Et_3N^+HCl^-$ and the quaternary ammonium salt $Et_3N^+BnCl^-$ and the results are summarised in Table 2. The free acid had only limited solubility in water but reactions at 50 or 60°C led to complete conversion and ee's that, though modest (50–62%, entries 10, 13 and 16), were slightly greater than those obtained from hydrogenations of the sodium salt (ca. 50%, see entries 1 and 4, Table 1). Treatment of the silica with the base Et_3N or the surface active agent $Et_3N^+BnCl^-$ had little effect (see entries 10, 13 and 16). Reactions of $Et_3N^+BnCl^-$ or $Et_3N^+HCl^-$ treated silicas at 35°C had lower conversions but with no improvement in ee (entries 17 and 18).

Attempts to recover and reuse the catalysts were unsuccessful as the recovered catalysts showed dramatically reduced activity (entries 10–12). It was shown that the initial recovered material had lost nearly 90% of the

Table 3
Hydrogenation of α-acetamidocinnamic acid (**1b**) using heterogenised Rh-(*S*,*S*)-BPPM in MeOH–water [a]

Silica treatment	Entry	Conv. %	ee % (*R*)
Et_3N	19	100	80
	20 [b]	98	44
	21 [b]	98	18
AcOH	22	100	59
	23 [b]	100	43
	24 [b]	100	35

[a] Reactions carried out in 1:1 $MeOH–H_2O$ (v/v) at 50°C for 20 h under 0.2 MPa H_2 pressure.

[b] Catalyst recovered and reused from previous run.

Table 4
Heterogeneous hydrogenation of itaconic acid (**3**) in water [a]

Catalyst	Entry	Temperature (°C)	Pressure (MPa)	Conv. %	ee % (*S*)
Rh-(*S*,*S*)-BPPM	25	50	0.3	100	23
	26 [b]	50	0.3	100	19
	27 [b]	50	0.3	86	17
Ru-(*R*)-BINAP	28	60	1	100	15
	29 [b]	60	1	95	14
	30 [b]	60	1	93	14
	31	50	1	79	16

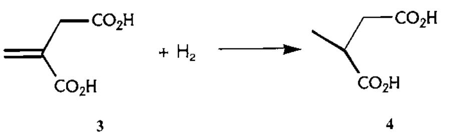
[a] Reaction time 46 h using HMS–silica dried under vacuum without further treatment.

[b] Catalyst recovered and reused from previous run.

incorporated rhodium. This was ascribed to the use of a methanol wash of the silica in order to isolate the substrate. A loss of recovered catalyst activity was also observed with the Et_3N-treated silica (entries 13–15) and again it was found that ca. 60% of the Rh had been lost after the first reaction.

Attempts to use 1:1 methanol–water as solvent in which the free acid has improved solubility led to good conversions with shorter reaction times even for recovered catalysts (entries 19–21 and 22–24, Table 3). Treatment of the silica with Et_3N or acetic acid again had no major effect (cf. entries 19 and 22) but the recovered catalysts were shown to have lost ca. 60% Rh even though the conversions for subsequent runs was almost complete (entries 19–21, and 22–24). It was suspected that the aqueous methanol may be leaching out sufficient Rh–BPPM such that a homogeneous reaction was taking place. Evidence in support of this proposal came from homogeneous reactions using Rh–BPPM in aqueous methanol in which the same amounts of Et_3N and AcOH as for the heterogeneous reactions had been added. Complete conversion and ee's of 74% (Et_3N) and 68% (AcOH) were obtained (cf. entries 19 and 22).

*3.5. Hydrogenations of itaconic acid (**3**)*



3 **4**

A limited number of hydrogenations of itaconic acid in water using heterogenised Rh–BPPM and Ru–BINAP catalysts were carried out (Table 4). Although only low ee's were obtained (< 20% entries 25–31), the recovered catalysts showed no loss of activity and the ee values though low were maintained (compare entries 25–27 and 28–30). This maintenance of catalyst activity during recovery and reuse is identical to that observed using these catalysts for hydrogenations of sodium α-acetamidocinnamate (see Table 1).

4. Conclusions

The use of a good match of catalyst dimension and silica pore size allows for the preparation of heterogenised chiral Rh and Ru catalysts which can, at least in favourable cases, be used, recovered, and reused without loss of activity or enantioselectivity for hydrogenations in water. Although only modest ee's have so far been obtained the heterogeneous catalysts can be readily prepared from commercially available starting materials.

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