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Asymmetric Synthesis of Naproxen by Supported Aqueous-Phase Catalysis

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A supported aqueous-phase, asymmetric, hydrogenation catalyst, SAP–Ru–BINAP–$4SO_3Na$, is synthesized. Impregnation of water from an organic phase, ethyl acetate, is used to hydrate the SAP catalyst. Both the activity and enantioselectivity for the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid to naproxen are found to be dependent on the water content. Maximum activity and e.e. are observed when water-saturated ethyl acetate is used to hydrate the SAP catalyst, an initial turnover frequency of 18.2 hr^{-1} and a 70.0% e.e. at room temperature under ~1350 psig of hydrogen pressure. At similar conditions, initial turnover frequencies of 131 and 0.34 hr^{-1} are observed from Ru–BINAP–$4SO_3Na$ in homogeneous (methanol as solvent) and two-phase (water–ethyl acetate) reaction systems, respectively. Although an excellent 96.1% e.e. (at 4°C and 1230 psig of H_2) is found in neat methanol (homogeneous), the enantioselectivity of the SAP catalyst (up to 70% e.e.) is bounded by the intrinsic enantioselectivity limit of the ruthenium complex in water. Recycling of the SAP catalyst is easily achieved without any leaching of ruthenium into the organic phase.

INTRODUCTION

Homogeneous catalysts are known to exhibit high activities and selectivities at relatively mild reactions conditions giving few by-products (1). These characteristics are especially true in the synthesis of chiral compounds (2–4). Among the numerous types of chiral transformations, asymmetric, catalytic hydrogenation of prochiral alkenes is one of the most impressive achievements in catalytic selectivity (5). However, it has long been recognized that a shortcoming of homogeneous catalysis is the obvious need for separating the catalytic species from the reaction mixture. Depending on the system: (i) the catalytic species can be very expensive (6, 7), e.g., rhodium phosphine complexes; (ii) the catalytic species may not be robust enough for a particular separation and/or the separation may not be as complete or cost-effective as desired; and (iii) catalyst contamination in pharmaceutical products must be minimized. Therefore, there continues to be a need for the immobilization of the catalytically active organometallic species in order to enhance the economic viability of the reaction system by eliminating separation and/or catalyst recovery steps and to minimize the possible toxicity hazards by contamination of trace transition metal complexes. Techniques used to immobilize homogeneous catalysts have centered on the retention of the structure and properties of the homogeneous counterpart. Comprehensive reviews on immobilization techniques are available (8–11). Also, there are several informative reviews concerning numerous aspects of heterogeneous, enantioselective catalysis (12–22).

Hydrogenation is arguably the most important synthetic application of asymmetric catalysis because of its potential to produce a wide variety of chiral functional groups. It is therefore not surprising that the largest number of catalytic systems has been described for this reaction type. However, a closer inspection of this literature reveals that there are really only two families of synthetically useful heterogeneous, asymmetric catalytic systems: (i) a Ni catalyst modified with tartate/NaBr (12) and (ii) Pt(Pd) catalysts modified with cinchona alkaloids (23, 24). Though many functionalized olefins can now be hydrogenated with optical yields >95% using homogeneous catalysts (25), the performances of many heterogeneous systems are not that impressive. In fact, at this time there is no heterogeneous system for the enantioselective reduction of C=C bonds that is preparatively useful. One way to create a heterogeneous catalyst is via the immobilization of a homogeneous catalyst onto a support. In this way, the catalyst can in principle acquire the property of insolubility and at the same time retain the same reactivity and selectivity exhibited by its homogeneous analogue. In attempts to do this, homogeneous catalysts have been attached to a variety of supports, including cross-linked polymers (9, 26–30). Cross-linked polystyrenes are one of the most widely used polymer supports for the attachment of phosphine ligands through chemical modifications. In some cases, in highly polar solvents, enhanced rates (31, 32) and greater selectivity for nonpolar olefins (vs polar ones) (32, 33) have been reported in hydrogena-

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tions mediated by polymer-attached achiral phosphine systems. However, results with polystyrenes containing optically active phosphine ligands aimed at effecting asymmetric syntheses have been disappointing (34). In polar solutions of the substrates, the polystyrene beads collapse, preventing entry of the substrate to the catalytic site. Problems of polymer shrinking in polar solvents (34) and leaching of catalytic species from the support have always been the main obstacles.

Recently, a new generation of asymmetric hydrogenation catalysts have been synthesized and consist of Rh(I), Ru(II), Ni(II), or Co(II) complexes anchored in modified USY zeolites (35–37). These catalysts reveal a remarkable support effect on the enantioselectivity for the catalytic hydrogenation of prochiral alkenes. However, this system suffers from a constraint that limits its potential applications; i.e., the small pore size (~8 Å) only allows small substrate molecules to be reacted. Hence, a new type of support as well as the active catalytic species has to be found in order to achieve a practical heterogeneous, asymmetric hydrogenation catalyst for general use.

The supported aqueous-phase catalysis (SAPC), developed by Arhancet *et al.* in 1989 (38), in combination with recent developments in the synthesis of water-soluble, chiral ruthenium–sulfonated-BINAP complexes (39), allows the extension of the SAPC concept to chiral chemistry. We now describe an asymmetric version of supported aqueous-phase catalysis. The catalytic phase that is immiscible with the organic phase containing the reactants/products consists of an aqueous solution of a water-soluble ruthenium(II)–sulfonated-BINAP catalyst (see Fig. 1). Here, we report the preparation of this supported aqueous-phase, ruthenium, asymmetric hydrogenation catalyst and its use in the asymmetric synthesis of naproxen. This immobilized ruthenium catalyst is shown to be an enantioselective hydrogenation catalyst. Furthermore, the SAPC is compared to its homogeneous and aqueous–organic two-phase counterparts.

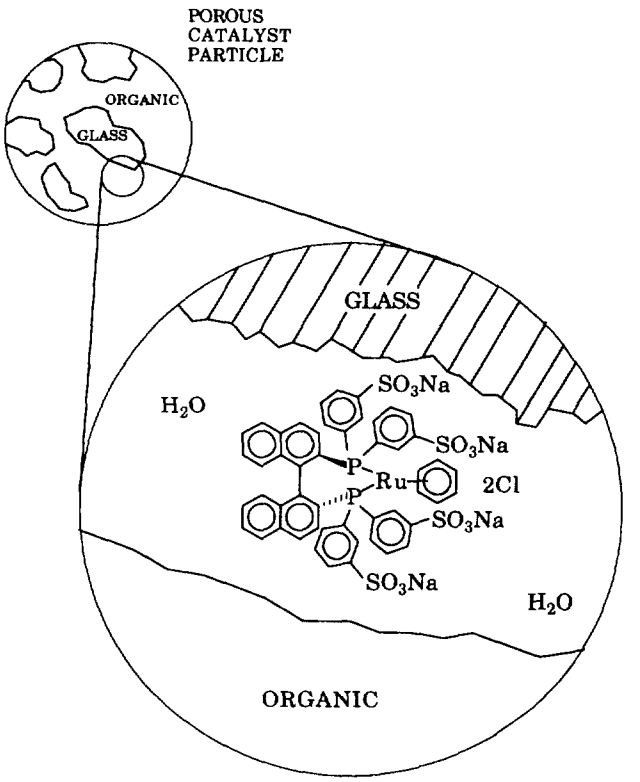

FIG. 1. Schematic diagram of supported aqueous-phase catalysis.

EXPERIMENTAL

Materials

Controlled pore glass CPG-240 (CPG Inc.), benzeneruthenium(II) chloride dimer, ethyl acetate, pyridine, triethylamine, sodium hydroxide, 3-pyridinesulfonic acid, and tetrahydrofuran were purchased in their highest purity available and used as received. 2-(6′-Methoxy-2′-naphthyl)acrylic acid was obtained as a gift from the Monsanto Company. The sodium salt of tetrasulfonated BINAP was prepared as reported previously (40). Sodium 3-pyridinesulfonate was synthesized by neutralizing an aqueous solution of 3-pyridinesulfonic acid with sodium hydroxide, followed by recrystallization in methanol. Unless stated otherwise, all manipulations were performed under argon or nitrogen. Deionized water distilled over potassium permanganate was used in all operations requiring water. All solvents, including water, were degassed by four to five freeze–pump–thaw cycles.

Catalyst Preparation

$[Ru(benzene)Cl_2]_2$ (0.0050 g) was reacted with two equivalents of water-soluble BINAP–$4SO_3Na$ in 4.5 ml of a 1 : 8 benzene/methanol solvent mixture at 55–60°C for 1 hr. The resulting clear, brownish-yellow-colored solution of [Ru(BINAP–$4SO_3Na$)(benzene)Cl]Cl was then vacuum dried at room temperature. The crude solid was redissolved in 2.5 ml water and the solution blended with 0.8–1.0 g of degassed CPG-240 (a narrow pore-size distribution glass: mean pore diameter = 242 Å, pore volume = 0.89 ml/g, surface area = 79 m^2/g, mesh size = 120/200) for 2 hr, followed by vacuum drying at 40–50°C. The final product was a dry, free-flowing yellow powder that was stored under argon at room temperature. The water content of this "dried" catalyst was estimated by thermogravimetric analysis to be 1.9 wt%, while the ruthenium contents were 1.2–2.5 $\times 10^{-5}$ mol/g. Since the ruthenium catalyst is not as hydrophilic as the Rh–TPPTS catalyst used in previous SAPC studies on hydroformylation (38, 41–42), rehydration of the solid catalyst by vapor-phase

impregnation is not feasible in the present system. The dried catalyst was rehydrated from an organic phase that had been previously premixed with a controlled amount of water. It was found that most of the water remains in the organic-phase upon contact with the CPG. The maximum water loading was obtained by using a water-saturated organic phase. Catalysts used in the homogeneous and the two-phase systems were prepared as described in our previous paper (39).

Reaction Conditions and Analytical Methods

Asymmetric hydrogenations of 2-(6′-methoxy-2′-naphthyl)acrylic acid were conducted at various temperatures and hydrogen pressures in a 25-ml stainless steel Parr batch reactor. Special care was taken in order to avoid the presence of oxygen at all times. The conversion was measured by ^{1}H NMR spectroscopy on a G.E. QE-300 spectrometer at 300 MHz and the enantiomeric excess (e.e.) determined by HPLC using a 25 cm × 4.6 mm i.d. Regis (S,S)-Whelk-O 1 column without derivatization. Thermogravimetric analyses (TGA) were obtained in air on a Du Pont 951 thermogravimetric analyzer. Ruthenium analyses were performed by Galbraith Laboratories Inc. (Knoxville, TN).

RESULTS AND DISCUSSION

Since naproxen and many other chiral 2-arylpropionic acids are high-valued pharmaceutical products, there is great economic incentive for the development of a practical process for the efficient asymmetric hydrogenation of 2-arylacrylic acids. Previous studies have shown that high hydrogen pressure and low reaction temperature elevated the optical yields in the asymmetric hydrogenation of 2-arylacrylic acids (43). Hence, the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid (substrate **1**; a precursor to naproxen) was chosen to be our model reaction in this study. Both the homogeneous and the two-phase reaction systems were examined in order to establish a basis for comparison with the SAPC results.

Homogeneous Catalytic Studies

In contrast to most other sulfonated phosphine systems (44, 45), the ruthenium–sulfonated-BINAP catalyst is quite soluble in neat methanol, and methanol is known to give highest e.e. in many of the asymmetric reactions catalyzed by nonsulfonated complexes. In fact, the asymmetric hydrogenation of substrate **1** by the parent Ru–BINAP system (the term *parent system* will be used here to denote the nonsulfonated analogue) was also carried out in neat methanol (43). Homogeneous, asymmetric hydrogenations of substrate **1** were conducted in methanolic solvents to allow a direct comparison between the sulfonated and parent system. Table 1 summarizes the results obtained from the homogeneous reductions of substrate **1** in methanolic solvents. Reductions were carried out under a hydrogen pressure of 500–1400 psig. It was observed that the enantioselectivity was not very pressure-sensitive in this pressure range (less than a 2% variation in e.e. over this range; entries 1 and 2). It is clear that the presence of water tends to lower the e.e.'s (entry 3). This may be attributed to the compositional change of the ruthenium catalyst in the presence of water. As has been reported in our previous paper (39), the chloro ligand dissociates in the presence of water through the aquation of the Ru–Cl bond. Our present results suggest that a coordinated chloro ligand in [Ru(BINAP–4SO_3Na)(benzene)Cl]Cl found only in neat methanol assists in enhancing the e.e. The retention of the chloro ligand in neat methanol may provide the necessary molecular configuration to facilitate a more enantioselective binding with the substrate. Our speculation is reinforced by a recent report that the cationic complex [(Cp)Ru(BINAP)](PF_6) is completely nonselective in the asym-

TABLE 1

Homogeneous, Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)acrylic Acid by the [Ru(benzene)(BINAP-4SO_3Na)]$^{2+}$ Complex in Methanolic Solvents at Room Temperature

Entry	Solvent	S/C[a]	Hydrogen pressure (psig)	T.O.F. (hr^{-1})[b]	e.e. (%)[c]
1	MeOH	50	1370	—	86.0(R)
2	MeOH	53	500	—	84.7(R)
3	1 : 1 MeOH/H_2O	25	1320	—	78.9(R)
4	1 : 1 MeOH/H_2O	25	1340	—	75.1(R)[d]
5	MeOH	25	1370	—	89.5(R)[d]
6	MeOH	25	1360	—	91.0(R)[d]
7	MeOH	101	1350	131	88.2(R)
8	MeOH	101	1350	927	91.5(R)[d]
9	MeOH	51	1370	—	86.2(R)[e]
10	1 : 1 MeOH/H_2O	51	1320	—	75.7(R)[e]
11	1 : 1 MeOH/H_2O	50	1350	0.77[f]	—
12	1 : 1 MeOH/H_2O	52	1350	—	77.6(R)[g]
13	MeOH	52	500	—	87.5(R)[d]
14	MeOH	—	500	—	93.3(S)[d,h]
15	MeOH	100	1230	—	96.1(R)[d,i]
16	MeOH	—	500	—	96.0(S)[d,h,j]

[a] Substrate-to-ruthenium ratio.
[b] Initial turnover frequency.
[c] e.e. determined at 100% conversion.
[d] With added triethylamine, Et_3N/substrate = 1.
[e] With added sodium 3-pyridinesulfonate, m-SO_3Na-pyridine/substrate = 1.
[f] With added concentrated sulfuric acid in 10 times excess of substrate.
[g] With added tetrahydrofuran in 1.9 times excess of substrate.
[h] Ref. (43).
[i] Reaction temperature = 4°C.
[j] Reaction temperature = 0°C.

metric hydrogenation of methyl acetoacetate, while its neutral chloro complex [(Cp)Ru(BINAP)Cl] gives a 76% e.e. (46).

The addition of triethylamine in neat methanol not only improves the e.e. to 91.5% at a reaction temperature of 23°C (entry 8) and 96.1% at 4°C (entry 15) but also enhances the activity by a factor of seven. Initial turnover frequencies of 927 and 131 hr^{-1} are observed in the presence and absence of triethylamine, respectively (entries 7 and 8). As the substrate chelation to the metal center is unlikely to be the rate-determining step, the base-induced deprotonation of the substrate carboxylic group for facile metal chelation cannot be responsible for this rate enhancement. In addition, no such rate-enhancement effect is found in the [Ru(BINAP)$(O_2CR)_2$] catalyzed hydrogenation of α,β-unsaturated carboxylic acids with the addition of tetrabutylammonium hydroxide (47). However, a slow initial turnover frequency of 0.77 hr^{-1} (entry 11) under acidic conditions is found with the addition of excessive amounts of concentrated sulfuric acid. Consistent with this, addition of trifluoromethanesulfonic acid to the [Ru(BINAP)$(O_2CR)_2$] system results in complete loss in activity (47).

An opposite effect on enantioselectivity of added triethylamine is found in aqueous methanolic solvent. An almost 4% drop in e.e. (entry 4) is found in 1 : 1 methanol/water solvent system although the same rate enhancement is again observed with the addition of triethylamine. These results are in agreement with our previous findings of the solvent-dependent effects of added triethylamine on enantioselectivity with other substrates (39). Other bases were also tested in these initial screening experiments. Water-soluble sodium 3-pyridinesulfonate is found to have little effect on enantioselectivity either in neat methanol or in aqueous methanolic solvents (entries 9 and 10). These findings lead us to investigate further the origin of the enantioselectivity enhancement through the addition of triethylamine. It is apparent that the chiral modification is a direct consequence of the ligand effect and probably involves the coordination of triethylamine to the ruthenium center (thus allowing a fine tuning of the enantioselectivity through steric and electronic effects). Because of the presence of an electron-withdrawing sulfonate group, sodium 3-pyridinesulfonate is expected not to coordinate with the metal, resulting in no change in enantioselectivity. In contrast, unsubstituted pyridine is known to be a good ligand for d^6 ruthenium(II) complexes and it generally gives species that are even more stable than those formed from aliphatic amines, e.g., triethylamine. No conversion is observed with the addition of pyridine in 1 : 1 methanol/water solvent under 1350 psig of hydrogen pressure. In addition, the effects of added tetrahydrofuran were also examined. Tetrahydrofuran, being a moderately σ-donating ligand, gives an almost unchanged 77.6% e.e. in 1 : 1 methanol/water solvent system at 1350 psig of hydrogen pressure (entry 12). Further experiments are currently being conducted in search for an aqueous counterpart of triethylamine for applications in two-phase and SAP systems. Nevertheless, in neat methanol, the present system (96.1% at 4°C and 1230 psig of H_2 in entry 15) is as enantioselective as its parent system (96.0% at 0°C and 500 psig of H_2 in entry 16) (43).

Two-Phase Catalytic Studies

We examined a simple two-phase reaction system (results listed in Table 2) for comparison with the homogeneous catalytic results (Table 1) as well as the SAP catalysis discussed below. Anhydrous ethyl acetate was chosen as the organic solvent. When substrate **1** was charged into

TABLE 2

Two-phase, Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)acrylic Acid by the [Ru(benzene)(BINAP–4SO_3Na)]$^{2+}$ Complex in 1 : 1 Ethyl Acetate/Water Solvent Mixture at Room Temperature

Entry	S/C[a]	Hydrogen pressure (psig)	Stirring speed (rpm)	Reaction time (days)	Conv. (%)	T.O.F. (hr^{-1})[b]	e.e. (%)
1	50	1380	250	3.5	53.6	0.34	78.4
2	25	1360	250	1.5	56.7	—	81.1
3	25	1360	250	1.5	56.4	—	78.0[c]
4	25	1370	250	1.5	57.0	—	82.7[d]
5	15	1365	450	2.8	90.0	0.20	77.2[e]
6	14	1320	400	2.5	100.0	—	73.0[f]

[a] Substrate-to-ruthenium ratio.
[b] Initial turnover frequency.
[c] Aqueous solution recycled once.
[d] Aqueous solution recycled twice.
[e] Reaction temperature = 5°C.
[f] With added triethylamine, Et_3N/substrate = 1.

the hydrogenation reactor along with an aqueous solution of the ruthenium catalyst (10 ml of 1 : 1 ethyl acetate/water and S/C = 50), a 53.6% conversion was observed in 3.5 days with an initial turnover frequency of 0.34 hr^{-1} (entry 1). The two-phase reaction is therefore at least 350 times slower than the homogeneous reaction system. Because of the limited solubility of this substrate in water, most of the reaction is taking place at the interface of the aqueous–organic phase, and the rate is therefore limited by the interfacial surface area between the catalyst containing aqueous phase and the substrate containing organic phase. As will be mentioned in the next section, the present two-phase system is at least 50 times less active than the SAP system, where a much larger interfacial surface area is provided from the high-surface-area CPG support. Because of a limited solubility of the substrate in water, we cannot rule out the possibility that a small portion of the conversion is by reaction in the bulk aqueous phase. A 78.4% e.e. is obtained from the two-phase reaction. Recycling of the catalyst containing aqueous phase after phase separation is possible without any loss in enantioselectivity (entries 2, 3, and 4), the e.e.'s range from 78.0–82.7% over several recycles of the catalytic solution. Similar e.e.'s but lower activities (0.20 hr^{-1}) were found at a reaction temperature of 5–6°C (entry 5). Addition of triethylamine increased the reaction rate at a slight expense of enantioselectivity (entry 6). Similar results on the effects of added triethylamine have been reported in our previous work on other substrates (39).

Supported Aqueous-Phase Catalytic Studies

In supported aqueous-phase configuration, anhydrous ethyl acetate is used as the organic phase (the catalytic data obtained from this system are listed in Tables 3 and 4). The activities of the SAP catalysts are improved over the two-phase system due to the much higher interfacial area of SAP catalyst. When substrate **1** (S/C = 25) is hydrogenated with a dried sample of the SAP catalyst (1.9 wt% water), no detectable conversion is observed even after 70 hr at room temperature under 1300 psig of hydrogen pressure (T.O.F. < 0.008 hr^{-1}; entry 1 in Table 4). Significantly, when water-saturated ethyl acetate is used as solvent, a 100% conversion (S/C = 31.5) is achieved in ~3 hr under the same reaction conditions with an initial turnover frequency of 18.2 hr^{-1} and a 70%

TABLE 3

Heterogeneous, Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)acrylic Acid by SAP–Ru–BINAP–4SO_3Na Catalyst in Ethyl Acetate

Entry	Cycle[a]	Solvent	S/C[b]	Hydrogen pressure (psig)	Stirring speed (rpm)	e.e (%)
1	0	AcOEt (40 μl H_2O)	25	1300	350	28.7(R)
2	0	AcOEt (H_2O sat.)	33	1300	350	69.0(R)[c]
3	1	AcOEt (H_2O sat.)	30	500	350	68.3(R)
4	1	AcOEt (H_2O sat.)	25	1330	350	68.6(R)[c]
5	2	AcOEt (H_2O sat.)	25	1330	350	70.0(R)[c]
6	0	AcOEt (H_2O sat.)	30	1360	300	67.0(R)
7	1	AcOEt (H_2O sat.)	30	1360	300	67.0(R)
8	2	AcOEt(H_2O sat.)	31	1360	300	66.0(R)
9	0	AcOEt (H_2O sat.)	30	1330	500	69.0(R)
10	1	AcOEt (H_2O sat.)	30	1250	500	65.0(R)
11	2	AcOEt (H_2O sat.)	30	1050	550	66.0(R)
12	3	AcOEt (H_2O sat.)	30	1260	350	77.0(R)[d]
13	5	AcOEt (H_2O sat.)	31	1360	350	62.8(R)[e]
14	6	AcOEt (H_2O sat.)	30	1350	350	63.6(R)
15	7	AcOEt (H_2O sat.)	30	1370	350	64.6(R)[c,e]
16	0	AcOEt (200 μl NaOH)	30	1380	350	62.8(R)[f]
17	1	AcOEt (NaOH sat.)	30	1380	350	59.9(R)[f]
18	2	AcOEt(NaOH sat.)	30	1000	350	59.8(R)[f]
19	3	AcOEt (NaOH sat.)	30	500	350	58.6(R)[f]
20	4	AcOEt (H_2O sat.)	30	1350	350	62.7(R)

[a] Number of catalyst recycles.
[b] Substrate-to-ruthenium ratio.
[c] *No ruthenium found in the filtrate with a detection limit of 1 ppm.*
[d] Reaction temperature = 8°C.
[e] With added triethylamine, Et_3N/substrate = 1.
[f] With 0.22 *M* sodium hydroxide solution.

TABLE 4

Catalytic Activity as a Function of Water Content in the Heterogeneous, Asymmetric Hydrogenation of 2-(6′-Methoxy-2′-naphthyl)acrylic Acid by SAP–Ru–BINAP–4SO_3Na Catalyst in Ethyl Acetate

Entry	S/C[a]	Hydrogen pressure (psig)	Water content (μl)[b]	T.O.F. (hr^{-1})[c]
1	33	1330	0	<0.008
2	25	1330	40	0.22
3	30	1350	125	0.25[d]
4	30	1360	145	1.06[d]
5	31	1370	160	2.35[d]
6	30	1400	195	2.84[d]
7	30	1370	215	5.12[d]
8	32	1370	270 (sat.)	18.21[d]

[a] Substrate-to-ruthenium ratio.

[b] Hydrogenations were carried out in 10 ml of ethyl acetate at room temperature and with 350 rpm stirring speed, [substrate] = 4.6–4.8 × 10^{-3} M.

[c] Initial turnover frequency.

[d] No ruthenium found in the filtrate with a detection limit of 1 ppm.

e.e. (entry 5 in Table 3 and entry 8 in Table 4). This enantioselectivity is only slightly lower than that found in the water–organic two-phase system. Similar results are also observed from other batches of SAP catalysts (entries 2, 6, and 9 in Table 3). Additionally, when using a SAP catalyst with 40 μl water in 10 ml of ethyl acetate as the organic solvent, the e.e. of the hydrogenated product is found to be only 28.7% (R) (entry 1 in Table 3). It is therefore evident that the water content in the SAP catalyst has dramatic effects on both the activity and the enantioselectivity. Since the present ruthenium–sulfonated-BINAP catalyst is not as hydrophilic as the rhodium–TPPTS catalyst, developed by Arhancet *et al.*, vapor-phase impregnation of water onto the CPG support is not feasible for the present system (38, 41). The revised method of *in situ* rehydration by water-loaded blank CPG also requires higher reaction temperatures (80–100°C) for the redistribution of water over the SAP catalyst (42). Again, this approach for loading water in the present SAP catalyst is not possible. However, another rehydration procedure that is more feasible, especially in terms of scale-up, was devised for this particular system; namely, the organic-phase impregnation. The dried SAP catalyst is rehydrated from an organic phase that has been previously premixed with a controlled amount of water. In order to achieve a reasonable activity, the amount of water added to the organic phase is found to be greater than the void volume of the CPG support (60–70 μl), suggesting a large portion of water is still retained in the organic phase. A maximum water loading of 2.8–3.1 wt% (g H_2O/g AcOEt × 100; i.e., ~275 μl water in 10 ml of ethyl acetate) was accomplished by using a water-saturated organic phase. The initial turnover frequencies as a function of water content are listed in Table 4 (reaction conditions: substrate/ruthenium ~30, [substrate] = 4.6–4.8 × 10^{-3} M, pressure = 1350–1400 psig, T = 25°C, stirring speed = 350 rpm). Water is introduced to the dried SAP catalyst from the ethyl acetate (10 ml) and the content controlled by adding variable amounts of water, e.g., 0, 40, 125, 145, 160, 195, 215, and 270 μl. The maximum activity, as determined by the initial turnover frequency, is observed at the highest water content (~3 wt% water in ethyl acetate) with an initial turnover frequency of 18.2 hr^{-1} (entry 8 in Table 4). The enantioselectivity of the SAP catalyst is also dependent on the water content and shows a similar trend to that observed in the activity; the observed range is 28.7–70.0% R) (entries 1 and 5 in Table 3). Thus, as previously mentioned, the water content affects the activity and enantioselectivity of the SAP catalyst. The present findings are quite different from what have been observed in the hydroformylation of 1-octene by a SAP–rhodium–TPPTS catalyst (41). In the hydroformylation of 1-octene, the activity is much more sensitive to the water content of the SAP catalyst with a bell-shaped curve that describes the activity dependence on water content. Maximum activity is observed at ~8 wt% (g H_2O/g SAPC × 100) water content of the SAP catalyst and complete loss of activity is observed at ~50 wt% (41). Two factors appear to be responsible for the difference in behaviour toward the water content of these two SAP catalysts. First, the [Ru(benzene)(BINAP–4SO_3Na)]$^{2+}$ complex is stable even in neat water while HRh(CO)$(TPPTS)_3$ is not at high synthesis gas pressure. At high water loading, the HRh(CO)$(TPPTS)_3$ complex decomposes, resulting in a drop in activity. Second, the decrease in the interfacial area of the SAP catalyst with increasing water loading also contributes to the rapid decline in the activity of the more hydrophilic SAP–Rh–TPPTS catalyst. Because of the small partition coefficient of water between the CPG support and the ethyl acetate, conditions have not yet been reached in the present SAP–Ru–BINAP–4SO_3Na that approximates the high water loadings obtained with the SAP–TPPTS catalyst. Thus, the actual amount of water being loaded onto the SAP–Ru–BINAP–4SO_3Na catalyst is far below the amount loaded by the vapor-phase impregnation into the much more hydrophilic SAP–Rh–TPPTS catalyst.

In view of the high water content of the ethyl acetate in the present system, the leaching of the catalytic species into the organic phase may be more likely than with anhydrous solvents. Filtration of the reaction mixture to remove the solid catalyst after the hydrogenation reaction yields a colorless solution of product in ethyl acetate. All

filtrates were found not to contain any ruthenium at a detection limit of 1 ppm (entries 2, 4, 5, and 15 in Table 3 and entries 3–8 in Table 4). In addition, for some of the experiments, filtrates were tested indirectly for the presence of ruthenium by attempting the catalytic hydrogenation of methylenesuccinic acid using the filtrate alone as catalyst. In no case was catalytic activity observed from the filtered solutions. For example, filtered solutions gave no conversion of methylenesuccinic acid at room temperature with one day of contact under a pressure of 30 psig of hydrogen. The inactivity of these filtered solutions together with the elemental analyses suggests that no soluble ruthenium species have leached out into the organic phase.

It is reasonable to suggest that the ruthenium complex becomes increasingly mobile (does not necessarily imply translational mobility but rather rotational mobility) as the water loading increases, as evidenced from the data in Table 4 that the hydrated SAP catalyst is at least 2000 times more active than the dried SAP catalyst. With a higher degree of mobility, the SAP catalyst can approach the same enantioselectivity as its counterpart in the two-phase system. (Increased mobility with higher water contents was shown previously to occur with the SAP–Rh–TPPTS catalyst (41).) Because of the much larger interfacial surface area between the catalyst containing aqueous phase and the substrate containing organic phase, the SAP system is found to be at least 50 times more active than the two-phase system. In the best cases, T.O.F.'s obtained using hydrated SAP catalyst are only a factor of seven times slower than homogeneous catalyst in neat methanol under the same conditions. We have observed a similar drop (6.7 times) in initial turnover frequency in the homogeneous hydrogenation of methyl-2-acetamidoacrylate by $[Rh(BINAP\text{–}4SO_3Na)(H_2O)]^+$ in neat water (40), where both the substrate and the catalyst are mixed together in one single phase, and attributed this to the fact that hydrogen solubility is four to five times higher in alcoholic solvents (oxidative addition of hydrogen to the rhodium catalyst is rate determining).

The effect of added base on the SAP system was examined and the results are listed in Table 3. The addition of either aqueous sodium hydroxide or triethylamine is found to have little effect on the enantioselectivity (entries 13, 15, and 16 in Table 3), although it does promote the activity to some extent. In the presence of sodium hydroxide, the enantioselectivity is found to be rather pressure-insensitive in the pressure range of 500–1400 psig (entries 17–19 in Table 3). The e.e.'s are almost constant from the hydrated SAP catalyst in the pressure range of 500–1400 psig (entries 2 and 3 in Table 3). Similar to the case of the homogeneous analogue, higher e.e.'s (77%) are achieved with a lower reaction temperature of 8°C, but at the expense of activity (T.O.F. = 0.43 hr^{-1}). The possibility of catalyst decomposition during the synthesis of SAP material is ruled out by the fact that a hydrogenation of substrate **1** with an 86% e.e. is accomplished by using a redissolved catalyst solution from a used SAP catalyst in methanol. Thus, the ruthenium complex is still stable in the SAP configuration. It is therefore apparent that the performance of the hydrated SAP catalyst is bounded by the intrinsic enantioselectivity limit of the ruthenium-sulfonated BINAP catalyst in water. Additionally, it is clear that the CPG support plays no important role in the enantioselection.

A series of reactions was carried out to test the possibility of recycling the SAP catalyst. The used SAP catalyst was removed from the hydrogenation mixture by simple filtration. It was then washed several times with fresh ethyl acetate, followed by the addition of fresh substrate and solvent. Similar values of e.e. (65–70%) were found throughout the recycling of the SAP catalyst (entries 2, 4, 5, 6–8, and 9–11 in Table 3).

CONCLUSION

A supported aqueous-phase, asymmetric, hydrogenation catalyst, SAP–Ru–BINAP–$4SO_3Na$, is prepared. Because of the much larger interfacial area due to the CPG support, the SAP catalyst is found to be at least 50 times more active than its two-phase counterpart and only seven times less active than its homogeneous analogue. Both the catalytic activity and the enantioselectivity are dependent on the water content of the SAP catalyst, with the hydrated SAP catalyst being at least 2000 times more active than the dried catalyst. It is suggested that the mobility of the ruthenium–sulfonated-BINAP complex on the surface of the CPG support is very critical to the overall performance of this SAP catalyst. Although the active ruthenium–sulfonated-BINAP catalyst (96.1% e.e.) is as enantioselective as its nonsulfonated analogue (96.0% e.e.) under homogeneous conditions, the performance of its SAP version is only moderate and bounded by the intrinsic enantioselectivity limit of the ruthenium catalyst in water. The loss of the chloro ligand through aquation of the Ru–Cl bond in water is proposed to be responsible for the decline in enantioselectivity. From this work, the concept of supported aqueous-phase catalysis has been demonstrated to be applicable in asymmetric catalysis. The advantage of easy catalyst separation and recycling makes this system attractive in the transition-metal-catalyzed asymmetric synthesis of high-valued specialty chemicals, though further refinements on detailed configurations have to be developed before a genuine practical heterogeneous chiral catalyst can be achieved for general use.

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REFERENCES

1. Parshall, G. W., "Homogeneous Catalysis." Wiley, New York, 1980.
2. Parshall, G. W., and Nugent, W. A., *Chemtech.* **March,** 184 (1988).
3. Parshall, G. W., and Nugent, W. A., *Chemtech.* **May,** 314 (1988).
4. Parshall, G. W., and Nugent, W. A., *Chemtech.* **June,** 376 (1988).
5. Noyori, R., *Chem. Soc. Rev.*, 187 (1989), and references cited therein.
6. Kagan, H. B., *in* "Asymmetric Synthesis" (J. D. Morrison, Ed.), Vol. 5, p. 1. Academic Press, Orlando, 1985, and references cited therein.
7. Karim, A., Mortreaux, A., and Petit, F., *J. Organomet. Chem.* **312,** 375 (1986).
8. Bailey, D. C., and Langer, J. H., *Chem. Rev.* **81,** 109 (1981).
9. Hartley, F. R., *in* "Supported Metal Complexes" (R. Ugo and B. R. James, Eds.), Reidel, New York, 1985.
10. Pittman, C. U., *in* "Comprehensive Organometallic Chemistry" (G. Wilkinson, F. G. A. Stone, and E. W. Abel, Eds.), Chap. 55. Pergamon Press, Oxford, 1982.
11. Lamb, H. H., Gates, B. C. Knözinger, H., *Angew. Chem. Int. Ed. Engl.* **27,** 1127 (1988).
12. Tai, A., and Harada, T., *in* "Taylored Metal Catalysts" (Y. Iwasawa, Ed.), p. 265. Reidel, Dordrecht, 1986.
13. Morrison, J. D., "Asymmetric Synthesis," Vol. 5. Academic Press, Orlando, 1985.
14. Morrison, J. D., and Mosher, H. S., "Asymmetric Organic Reactions." American Chemical Society, Washington, DC, 1976.
15. Izumi, Y., *Adv. Catal.* **32,** 215 (1983).
16. Brunner, H., *Top. Stereochem.* **18,** 129 (1988).
17. Bartok, M., *in* "Stereochemistry of Heterogeneous Metal Catalysts," Chap. XI, p. 511. Wiley, New York, 1985.
18. Pracejus, H., *Fortschr. Chem. Forsch.* **8,** 493 (1967).
19. Inoue, S., *Adv. Polym. Sci.* **21,** 78 (1976).
20. Aglietto, M., Chiellini, E., D'Antone, S., Ruggeri, G., and Solaro, R., *Pure Appl. Chem.* **60,** 415 (1988).
21. Fish, M. J., and Ollis, D. F., *Catal. Rev.-Sci. Eng.* **18,** 259 (1978).
22. Mathieu, J., and Weill-Raynal, J., *Bull. Soc. Chim. Fr.* 1211 (1968).
23. Blaser, H. U., Jalett, H. P., and Wiehl, J., *J. Mol. Catal.* **68,** 215 (1991).
24. Blaser, H. U., Boyer, S. K., and Pittelkow, U., *Tetrahedron: Asymmetry* **2,** 721 (1991).
25. Noyori, R., and Kitamura, M., *in* "Modern Synthetic Methods" (R. Scheffold, Ed.), p. 115. Springer-Verlag, Berlin, 1989.
26. Pittman, C. U., and Evans, G. O., *Chemtech*, 560 (1973).
27. Manassen, J., "Catalysis Progress in Research" (F. Basolo, and R. L. Burwell, Jr., Ed.), p. 117. Plenum Press, New York, 1973.
28. Bailar, J. C., *Catal. Rev.* **10,** 17 (1974).
29. Lezenoff, C., *Chem. Soc. Rev.* **3,** 65 (1974).
30. Manassen, J., *in* "Catalysis, Heterogeneous and Homogeneous" (B. Delmon and G. Jannes, Eds.), p. 293. American Elsevier, New York, 1975.
31. Grubbs, R. H., Gibbons, C., Kroll, L. C., Bonds, W. D. Jr., and Brubaker, C. H., Jr., *J. Am. Chem. Soc.* **95,** 2373 (1973).
32. Bruner, H., and Bailer, J. C., Jr., *Inorg. Chem.* **12,** 1465 (1973).
33. Grubbs, R. H., Kroll, L. C., and Sweet, E. M., *J. Macromol. Sci. Chem.* **7,** 1047 (1973).
34. Dumont, W., Poulin, J. C., Dang, T. P., and Kagan, H. B., *J. Am. Chem. Soc.* **95,** 8295 (1973).
35. Corma, A., Iglesias, M., Pino C. del, and Sanchez, F., *J. Chem. Soc. Chem. Commun.*, 1253 (1991).
36. Sanchez, F., Iglesias, M., Pino C. del, and Corma, A., *J. Mol. Catal.* **70,** 369 (1991).
37. Corma, A., Iglesias, M., Pino C. del., and Sanchez, F., *J. Organomet. Chem.* **431,** 233 (1992).
38. Arhancet, J. P., Davis, M. E., Merola, J. S., and Hanson, B. E., *Nature (London)* **339,** 454 (1989).
39. Wan, K. T., and Davis, M. E., *Tetrahedron: Asymmetry*, **4**(12), 2461, 1993.
40. Wan, K. T., and Davis, M. E., *J. Chem. Soc. Chem. Commun.* 1262 (1993).
41. Arhancet, J. P., Davis, M. E., Merola, J. S., and Hanson, B. E., *J. Catal.* **121,** 327 (1990).
42. Arhancet, J. P., Davis, M. E., and Hanson, B. E., *J. Catal.* **129,** 94 (1991).
43. Chan, A. S. C., Laneman, S. A., and Miller, R. E., *in* "Selectivity in Catalysis" (M. E. Davis and S. L. Suib, Eds.), Chap. 3, p. 27. ACS Symposium Series, Vol. 517, American Chemical Society, Washington, DC, 1993.
44. Amrani, Y., Lecomte, L., Sinou, D., Bakos, J., Toth, I., and Heil, B., *Organometallics* **8,** 542 (1989).
45. Bartik, T., Bartik, B., Hanson, B. E., Guo, I., and Toth, I., *Organometallics* **12,** 164 (1993).
46. Hoke, J. B., Hollis, L. S., and Stern, E. W., *J. Organomet. Chem.* **455,** 193 (1993).
47. Halpern, J., and Ashby, M. T., *J. Am. Chem. Soc.* **113,** 589 (1991).