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Asymmetric Synthesis of Naproxen by a New Heterogeneous Catalyst

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A new heterogeneous, asymmetric catalyst is described. The catalyst is a modified version of the supported aqueous-phase catalyst reported previously (Wan and Davis, *J. Catal.* 148, 1 (1994)); ethylene glycol is used in place of water as the hydrophilic phase. Both the enantioselectivity and the activity of this new heterogeneous catalyst are comparable to the homogeneous analogue in neat methanol (or ethylene glycol); e.e.'s are 95.7% vs 96.1% and t.o.f.'s are 40.7 hr^{-1} vs 131.0 hr^{-1}, respectively. Recycling of the catalyst is possible without leaching of ruthenium at a detection limit of 32 ppb.

INTRODUCTION

Recently, we reported on the development of an asymmetric version of supported aqueous-phase (SAP) catalysis (1). SAP catalysis enables the efficient use of a water-soluble organometallic complex to promote the reaction of substrates soluble in organic solvents (2). In our previously reported SAP system (1), the water-soluble ruthenium complex, [Ru(BINAP-4SO_3Na)(benzene)Cl]Cl (BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), was impregnated onto a controlled-pore-glass (CPG) support by the incipient wetness technique and the bulk water vacuum evaporated away. Both the activity and the enantioselectivity of the SAP catalyst were found to be sensitive to the amount of water on the catalyst. An *in situ* organic-phase impregnation of water onto the "as-made" SAP catalyst was developed to activate the catalyst. We speculated that the increase in mobility of the ruthenium complex on the support with increasing water loading led to increases in both the activity and the enantioselectivity of the hydrated SAP catalyst. It was shown also that the enantioselectivity limit of the hydrated SAP catalyst could approach that of its two-phase (ethyl acetate–water) analogue. This indicates that the ruthenium complex on the CPG support is more or less as mobile as in homogeneous medium. This is an important point in the immobilization of homogeneous catalysts onto solid supports. Usually, the homogeneous catalysts are covalently bonded to the support and reveal limited mobility (3). This type of immobilization normally leads to an undesirable loss in activity and/or selectivity. For the SAP system, it is the aqueous catalyst solution that is immobilized on the support, not the individual organometallic complexes. This feature of the SAP catalyst may allow for the development of the first genuine hybrid of an active/selective homogeneous catalyst with all the features of a heterogeneous catalyst.

The organometallic ruthenium catalyst used in the asymmetric SAP catalyst was found to exhibit a solvent dependent enantioselectivity when operated homogeneously (1, 4). Although the homogeneous organometallic ruthenium catalyst was effective in promoting the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)-acrylic acid with 96% enantiomeric excess (e.e.) in neat methanol, the enantioselectivity dropped to about 80% e.e. in water (1). As a result, the enantioselectivity of the hydrated SAP catalyst (up to 77% e.e.) was bounded by the intrinsic enantioselectivity limit of the organometallic ruthenium complex in neat water. Hence, further refinements on the SAP catalyst have to be made before a practical, heterogeneous, chiral catalyst can be developed for general use.

Recently, we have reported our new development of a heterogeneous asymmetric catalyst (5). We now describe the detailed design and synthesis of this new heterogeneous catalyst and its use in the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid to naproxen. Here, we describe the new catalyst composition, a new method for the activation of the "as-made" catalyst and reaction conditions that prevent leaching.

EXPERIMENTAL

Materials

Controlled pore glass 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

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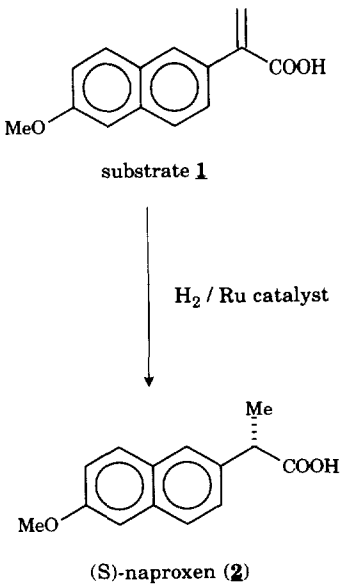
size = 120/200), benzeneruthenium (II) chloride dimer, ethyl acetate, cyclohexane, chloroform, ethylene glycol, and triethylamine were purchased in their highest purity available and used as received. 2-(6′-Methoxy-2′-naphthyl)acrylic acid was received as a gift from Monsanto Company. The sodium salt of tetra-sulfonated BINAP was prepared as reported previously (6). 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 and Activation Procedure

The active organometallic ruthenium catalyst, [Ru(BINAP-4SO_3Na)(benzene)Cl]Cl, was prepared and impregnated onto the CPG support by the previously described procedures (1). The water content of the "as-made" catalyst was estimated by thermogravimetric analysis to be 1.9 wt%, while the ruthenium content was 1.2–2.5 × 10^{-5} mol/g. Anhydrous ethylene glycol was used to activate the "as-made" catalyst. The impregnation was performed by two different techniques: (A) by the *in situ* activation with ethylene glycol in ethyl acetate (ethylene glycol partitions between the organic solvent and the surface of the CPG), and (B) as follows. The "as-made" catalyst was stirred in ethyl acetate that had been previously premixed with a controlled amount of ethylene glycol. The highly polar ethylene glycol was allowed to partition between the ethyl acetate phase and the CPG surface for about an hour. Because of a small partition coefficient for ethylene glycol between the CPG support and the ethyl acetate, it was found that most of the ethylene glycol remained in the organic phase upon contact with the "as-made" catalyst. This procedure was then repeated. The bulk organic phase was then removed by filtration and the resulting catalyst was washed several times with a 1 : 1 chloroform and cyclohexane mixture that had been premixed with ethylene glycol.

Reaction Conditions and Analytical Methods

Asymmetric hydrogenations of 2-(6′-methoxy-2′-naphthyl)acrylic acid were conducted at various temperatures in a 25-ml stainless steel Parr batch reactor. Special care was taken in order to avoid the presence of oxygen at all times. Catalysts with various amount of ethylene glycol loading were used. Both the neat ethyl acetate and a 1 : 1 mixture of chloroform/cyclohexane were used as the bulk organic phase (5 ml). The conversion was measured by ^{1}H NMR spectroscopy on a G.E. QE-300 spectrometer at 300 MHz and the enantiomeric excess determined by HPLC using a 25-cm × 4.6-cm i.d. Regis (S,S)-Whelk-O 1 column without derivatization. Thermogravimetric analyses (TGA) were obtained in air on a DuPont 951 thermogravimetric analyzer. Ruthenium analyses of the reaction filtrates were performed by Galbraith Laboratories, Inc. (Knoxville, TN).



SCHEME 1. Asymmetric reduction of substrate **1** to naproxen.

RESULTS AND DISCUSSION

With a multi-million-dollar-a-year market, naproxen has been the object of intense study by generic drug manufacturers (7). Hence, the asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid (substrate **1**; a precursor to naproxen) was again chosen to be our model reaction in this study (Scheme 1). The results from this new heterogeneous catalyst are compared to those from the original hydrated SAP catalyst as well as the homogeneous and two-phase analogues (1).

In our earlier study, we have shown that the presence of water tends to lower the enantioselectivity in the homogeneous hydrogenation of substrate **1** in methanolic solvents (1). Aquation of the ruthenium–chloro bond in water was found to be responsible for this solvent dependent enantioselectivity. To prevent the cleavage of the ruthenium–chloro bond, anhydrous ethylene glycol is used here in place of water. The ^{31}P NMR spectrum of the ruthenium complex in 1 : 1 CD_3OD/ethylene glycol reveals the same two doublets (δ = 63.0 and 68.8 ppm; $J \approx 45$ Hz) as are found in neat methanol, indicating that the ruthenium–chloro bond in [Ru(BINAP-4SO_3Na)(benzene)Cl]Cl is still intact. Upon addition of water, only a singlet (δ = 57.5 ppm) is observed in the ^{31}P NMR spectrum. These data suggest that a rapid hydrolysis of the ruthenium–chloro bond has occurred in the presence of

TABLE 1

Homogeneous Reduction of Substrate 1[a]

Solvent	e.e. (%)
MeOH	88.2
1 : 1 MeOH/$HOCH_2CH_2OH$	89.1
$HOCH_2CH_2OH$	88.7
1 : 1 MeOH/H_2O	78.9[b]

[a] Substrate/ruthenium = 100; 1350–1450 psig of hydrogen, at room temperature.
[b] Ref. (1).

water. As a result, hydrogenations of substrate **1** are carried out in the presence of ethylene glycol. Similar enantioselectivities (88–89% e.e.'s as shown in Table 1) are observed for reactions carried out in neat methanol, 1 : 1 methanol/ethylene glycol, and also in neat ethylene glycol. These findings further support the premise that the cleavage of the ruthenium–chloro bond has a detrimental effect on enantioselectivity. Only a 79% e.e. was observed in a 1 : 1 MeOH/H_2O solvent mixture (Table 1) (1). Since the highly polar ethylene glycol is not miscible with most organic solvents, it can be used as a substitute for the aqueous phase in the original SAP system; it replaces the role of water in the immobilization of the ruthenium catalyst onto the CPG support.

This new heterogeneous catalyst now consists of a ruthenium organometallic complex dissolved in a film of ethylene glycol which is supported on a high-surface-area hydrophilic CPG support (Fig. 1). Similar to our previous findings with the hydrated SAP catalyst, both the activity and the enantioselectivity of the new catalyst are sensitive to the amount of ethylene glycol in the system. By using the *in situ* organic-phase impregnation of ethylene glycol, controlled amounts of ethylene glycol are introduced into the ethyl acetate and used as the bulk organic phase. Replacement of neat water with ethylene glycol results in at least a 3 times enhancement in the activity. An initial turnover frequency of 54.2 hr^{-1} is observed at an ethylene glycol loading of 400 μl in 5 ml of ethyl acetate (Table 2), whereas only an 18.2 hr^{-1} of initial turnover frequency was observed from the original hydrated SAP catalyst (1). More importantly, this activity is only 2–2.5 times slower than the homogeneous analogue in either neat methanol or neat ethylene glycol (Table 2). We speculate that the higher intrinsic activity of the ruthenium organometallic catalyst in neat ethylene glycol is responsible for the high activity of the new catalyst. This is further shown by the finding of a reasonably high rate in the two-phase system (15.3 hr^{-1}). An almost 50-fold increase in activity is observed when ethylene glycol is used in place of water in the two-phase system (15.3 hr^{-1} vs 0.34 hr^{-1}).

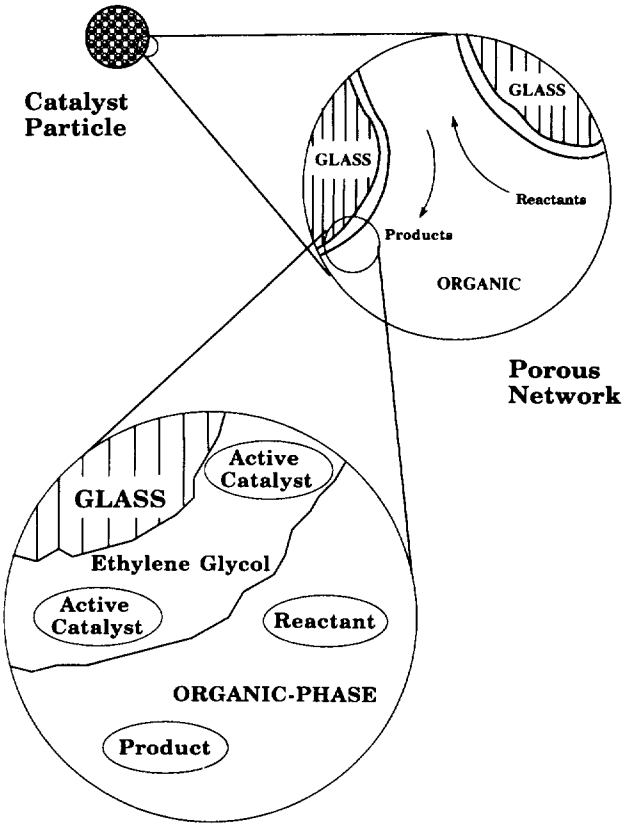


FIG. 1. Schematic diagram of the new heterogeneous catalyst.

With the *in situ* activation (method A) using ethylene glycol, enantioselectivities are found to increase with increasing amount of ethylene glycol in the system. The enantioselectivities as a function of ethylene glycol content are listed in Table 3 (reaction conditions: substrate/

TABLE 2

Activities of Various Catalytic Systems in the Reduction of Substrate 1[a]

Catalyst	Solvent	t.o.f. (hr^{-1})
Homogeneous[b]	MeOH	131.0
Homogeneous	$HOCH_2CH_2OH$	103.4
Two-phase	$HOCH_2CH_2OH$/AcOEt	15.3
Two-phase[b]	H_2O/AcOEt	0.34
Heterogeneous[c]	AcOEt	54.2
Heterogeneous[d]	1 : 1 $CHCl_3$/cyclohexane	40.7
SAP (hydrated)[b]	AcOEt	18.2

[a] Substrate/ruthenium = 30–100; H_2 pressure = 1350–1450 psig; reaction temp. = 24°C; stirring speed = 350 rpm.
[b] Ref. (1).
[c] *In situ* catalyst activation with method A.
[d] Catalyst activation with method B and reaction carried out in 1 : 1 chloroform/cyclohexane.

TABLE 3

Enantioselectivities in the Reduction of Substrate 1 as a Function of Ethylene Glycol Content in the Organic Phase[a]

Ethylene glycol content (μl)	e.e. (%)
75	45.0
150	72.1
270	82.1
350	84.2
350	71.3[b]
350	91.1[c]
400	87.7
400	94.8[c]

[a] Catalysts were activated by *in situ* organic-phase impregnation with 5 ml of ethyl acetate; substrate/ruthenium = 30; pressure = 1400 psig, at room temperature.
[b] With addition of triethylamine.
[c] Reaction temperature = 3°C.

ruthenium = 30, [substrate] = 3.6×10^{-3} *M*, solvent volume = 5 ml, pressure = 1400 psig, T = 24°C, stirring speed = 350 rpm). At a maximum ethylene glycol loading of 400 μl (in 5 ml of ethyl acetate), an 87.7% e.e. is observed, while only 45.0% e.e. is found for the system with 75 μl of ethylene glycol. This is in agreement with our previous findings for the hydrated SAP systems where the higher the water content the higher the enantioselectivity (1). We speculate that the increasing rotational mobility of the ruthenium complex with increasing glycol content is responsible for the increase in enantioselectivity. More importantly, the new heterogeneous catalyst with ethylene glycol as substitute for the aqueous phase has already achieved the same high enantioselectivity as its homogeneous analogue in neat methanol (87.7% vs 88.2%). By lowering the reaction temperature to 3°C, the e.e. is increased to 94.8%. However, unlike the homogeneous analogue in neat methanol (1), addition of triethylamine to the heterogeneous catalyst is found to have a detrimental effect on enantioselectivity. An almost 15% drop in e.e. is observed at room temperature upon addition of triethylamine. This is rather unexpected since we believe that the active ruthenium catalyst is nearly the same as the one in neat methanol. Solvation of the ruthenium complex with ethylene glycol may be responsible for the decline in enantioselectivity upon addition of base, but the detailed mechanism is still unclear. A similar drop in e.e. is also reported in our original hydrated SAP system (1).

For long-term stability, the heterogeneous catalyst must remain assembled. To test for this type of stability, a self-assembly test is performed in the following way: 1.1×10^{-6} moles of [Ru(BINAP-4SO_3Na)(benzene)Cl]Cl is dissolved in 400 μl of ethylene glycol and loaded into a 25-ml Parr reactor. 5.7×10^{-5} mol of substrate **1** in 5 ml of ethyl acetate is then added. Finally 0.1 g CPG-240 is added. The reactor is pressurized to 1400 psig with hydrogen and stirred at 350 rpm and at room temperature. The reaction is stopped after 1 hr and analyzed. A control experiment is carried out using exactly the same procedure with the exception that no CPG is added. Complete conversion of **1** is observed when CPG is added, while no detectable conversion is found in the control experiment. After the reaction, the CPG support turns pale yellow and the bulk organic phase is colorless. These results indicate that, under the reaction conditions, the individual components of the heterogeneous catalyst self-assemble into a more thermodynamically stable supported-catalyst configuration. Therefore, the reverse, i.e., the separation of the solution and complex from the support, is unlikely to happen under reaction conditions because it is thermodynamically unfavorable. These results also support the inference that the reaction chemistry is taking place at the liquid–liquid interface. In the control experiment, most of the added ethylene glycol dissolved into the bulk organic phase and left behind small droplets of catalyst solution. The limited interfacial area of the catalyst solution that remains immiscible with the bulk organic phase results in the lack of activity in the control experiment.

Unlike in the original hydrated SAP catalyst, traces of ruthenium are found in the reaction filtrates. The extent of ruthenium leaching was found to be correlated with the enthylene glycol content in the organic phase as shown by the data in Table 4. Since ethylene glycol is less polar than water, it is at least three times more soluble than water in ethyl acetate. The higher solubility of ethylene glycol in ethyl acetate may be responsible for the observed leaching of ruthenium into the bulk organic phase. In order to minimize the leaching of ruthenium into the bulk organic phase, a new method of activation of the "as-

TABLE 4

Ruthenium Leaching as a Function of Ethylene Glycol Content in the Reduction of Substrate 1[a]

Ethylene glycol content[b] (μl)	Ruthenium[c] (ppm)
150	0.17
270	0.27
350	0.23[d]
400	0.37

[a] Substrate/ruthenium = 30; H_2 pressure = 1350–1450 psig; reaction temp. = 24°C; stirring speed = 350 rpm.
[b] *In situ* catalyst activation with method A.
[c] Ruthenium content in the reaction filtrates.
[d] Reaction temperature = 3°C.

TABLE 5

Enantioselectivities in the Reduction of Substrate 1 with Ruthenium Catalysts in Different Configurations[a]

Catalyst	Solvent	e.e. (%)
Heterogeneous[b]	1 : 1 $CHCl_3$/cyclohexane	88.4
Heterogeneous[b]	1 : 1 $CHCl_3$/cyclohexane	95.7[c]
Heterogeneous[d]	AcOEt	87.7
Heterogeneous[d]	AcOEt	94.8[c]
Homogeneous[e]	MeOH	88.2
Homogeneous[e]	MeOH	96.1[f]

[a] Substrate/ruthenium = 30–100; H_2 pressure = 1350–1450 psig; reaction temp. = 24°C; stirring speed = 350 rpm.
[b] Catalyst activation with method B.
[c] Reaction temperature = 3°C.
[d] *In situ* catalysts activation with method A.
[e] Ref. (1).
[f] Reaction temperature = 4°C in Ref. (1).

made" catalyst with ethylene glycol was devised and is described below.

The "as-made" catalyst was activated by stirring it in an ethylene glycol/ethyl acetate solvent mixture. After equilibration for 1 hr at room temperature, the solid catalyst was filtered and dried at low vacuum (0.2 atm.). The procedure was then repeated. Only a thin film of nonvolatile ethylene glycol was deposited onto the solid catalyst. The amount of ethylene glycol in the film is more or less the same as that found with the original *in situ* activation procedure, and a similar degree of mobility of the ruthenium complex on the support is to be expected. However, now an ethylene glycol-saturated organic phase is used so as to maintain the integrity of this film during the reaction. To minimize the amount of ethylene glycol used in the bulk organic phase, a rather nonpolar 1 : 1 solvent mixture of cyclohexane and chloroform (for solubilization of substrate) is used. As shown in Table 5, the same high enantioselectivity (88.4% e.e. at room temperature) is still obtained with this kind of activation procedure and, more importantly, no ruthenium is found in the reaction filtrate at a detection limit of 32 ppb! By lowering the reaction temperature to 3°C, an 95.7% e.e. is obtained with this new heterogeneous catalyst. As shown in Table 5, the present system is already as enantioselective as its homogeneous analogue (95.7% vs 96.1%). Recycling of the used catalyst is possible without any loss in enantioselectivity.

Using the new formulation, a self-assembly test was again carried out to test the long-term stability of the catalyst. 1×10^{-7} mol of the ruthenium complex in 50 μl of ethylene glycol was mixed with 4×10^{-6} mol of substrate **1** in 5 ml of 1 : 1 chloroform/cyclohexane. 0.2 g of CPG-240 was added, then the reactor was pressurized to 1400 psig with hydrogen and then stirred at room temperature for 2 hr. Complete conversion was observed. However, less than 2% conversion was found from the control experiment where no CPG was added. These results again indicate that, under these new reaction conditions, the individual components of the present catalytic system self-assemble into the more stable supported-catalyst configuration.

As shown by the data in Table 2, the new heterogeneous catalyst activated by method B is slightly less reactive than the *in situ* activated analogue (40.7 hr^{-1} vs 54.2 hr^{-1}). However, it is still only 2.5 times less active than its homogeneous counterpart in neat ethylene glycol. In principle, the catalyst activated by procedure B should be able to attain the same high activity as the *in situ* activated analogue by using an impregnating solvent with higher content of ethylene glycol. As ethylene glycol will form two-phase mixture with ethyl acetate, there exists a certain upper limit for the ethylene glycol content in ethyl acetate. Therefore, it will be more desirable to have an impregnating solvent miscible with ethylene glycol. In this way, higher ethylene glycol content may be impregnated.

With comparable activity and enantioselectivity to the homogeneous catalyst, the present heterogeneous catalyst can be considered as a genuine hybrid of homogeneous and heterogeneous catalysts. As compared to the asymmetric hydrogenation catalysts anchored in modified USY zeolites (8, 9), our system has several distinguishing features. The CPG support possesses large and uniform pore diameters that allow large biosubstrates access to the catalytic sites. Also, CPG supports are commercially available in a wide range of pore diameters (75–3000 Å); for the zeolite-supported catalyst (8), the small pore size (≈8 Å) limits the size of substrates. Furthermore, the active rhodium complex is covalently bonded to the zeolite framework and reasonable activity can be reached only at elevated temperature (60°C). In contrast, the active ruthenium complex in the present system is dissolved in ethylene glycol, which is immobilized as a thin film on the CPG support. At the molecular level, this method of immobilization yields a heterogeneous catalyst that is basically the same as its homogeneous analogue, thus allowing for the high enantioselectivity and activity.

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