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Ruthenium (II)-Sulfonated BINAP : A Novel Water-Soluble Asymmetric Hydrogenation Catalyst.

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Abstract: Ruthenium (II)-sulfonated-BINAP has been synthesized and this novel water-soluble complex is shown to be an excellent asymmetric hydrogenation catalyst for 2-acylamino acid precursors and methylenesuccinic acid in both methanolic as well as in neat water solvent systems. Enantiomeric excesses approaching 90% have been obtained in aqueous and methanolic solvents. Effects of solvent, pressure and the addition of organic base on enantioselectivity are described.

Introduction: One of the most recent advances in asymmetric synthesis is the use of water-soluble organometallic catalysts.[1,2] Numerous water-soluble, chiral phosphines have been used as ligands for transition-metal-catalyzed asymmetric syntheses in aqueous-organic two-phase solvent systems.[3-6] For asymmetric hydrogenation, chiral, sulfonated di-tert-phosphines have been the most widely used in preparing water-soluble catalysts.[7,8] Thus far, highly stereoselective two-phase hydrogenations have been achieved almost exclusively with Rh (I)-based complexes.[3-5,9-11] Although, most of these water-soluble rhodium (I) complexes are very active catalysts, they are in general less robust than the ruthenium catalysts. Also the variety of Rh (I)-catalyzed reactions is not wide. Several studies have led to the conclusion that the double-bond geometry and, with some exceptions, the presence of the a-acyl amino group is obligatorily important for chiral efficiency.[2] In view of the general synthetic significance of asymmetric hydrogenation, development of water-soluble chiral catalytic systems that are able to reduce a wider range of substrates has long been desired.

Catalytic, asymmetric hydrogenation by means of a large variety of rhodium complexes with chiral ligands such as DIOP,[12] BPPM,[13] CHIRAPHOS,[14] etc. has been extensively used to achieve high enantioselectivity. In contrast, there are relatively few reports on corresponding ruthenium complexes.[15] With the advent of the outstanding performance of various ruthenium-BINAP complexes,[16] several preparation methods for mononuclear ruthenium catalysts in non-aqueous media have been devised.[17-24] However, to our knowledge, no such methods have been developed for water-soluble ruthenium complexes, and in fact, no water-soluble ruthenium chiral diphosphine catalysts have ever been reported in the literature. We have described earlier preliminary results concerning the use of a Rh (I)-sulfonated BINAP complex as an asymmetric hydrogenation catalyst in water.[25] We

now report the synthesis of a novel Ru (II)-sulfonated BINAP complex and its use in asymmetric hydrogenation with aqueous solvent. This ruthenium catalyst reveals superior enantioselectivity and stability when compared to the corresponding rhodium analogue.

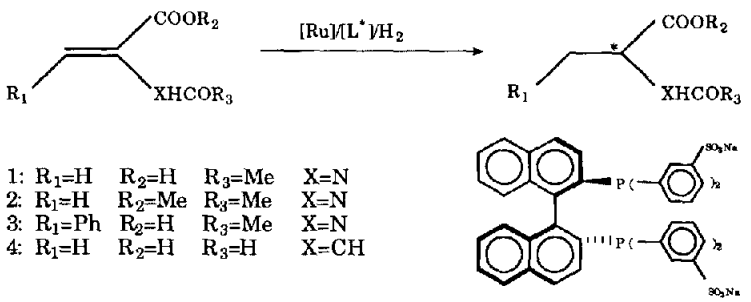
Results and discussion:

Catalyst Preparation: From a practical standpoint, it is of interest to devise a one-step synthesis with water. When [Ru(benzene)Cl_2]$_2$ (0.0037g) is reacted with BINAP-4SO_3Na (0.0182g) [details concerning the preparation and characterization of this ligand can be found elsewhere[25]] in 5 ml water at 55-60°C for 2 hours, a complex revealing a ^{31}P NMR spectrum with two peaks in strictly 1:1 ratio [^{31}P NMR (D_2O): d = 57.5 and 63.7 ppm] is formed. From the difference in line shape, the two resonances appear to be originating from two different phosphorus atoms. A $^2J_{PP}$ coupling could not be observed in water. This complex is not very active for hydrogenation. Because P-C bond cleavage on Rh-phosphine complexes is well-known,[26] we speculate that a similar oxidative addition of the phosphorus-naphthyl bond to the Ru center is occurring. P-C bond cleavage has been observed during the synthesis of Ru-BINAP complexes in organic solvents.[27] Since the oxidative addition of a P-C bond from a phosphine to a transition metal center is promoted by the presence of a vacant coordination site, an aromatic co-solvent (a weakly coordinating agent) can be used to suppress the formation of the above mentioned "unsaturated species" which is proposed to be the responsible "intermediate" for the P-C bond cleavage.[27] P-C bond cleavage has also occurred when combining BINAP-4SO_3Na with [Ru(cod)Cl_2]$_n$ in water. A species with 19% abundance [^{31}P NMR (D_2O): d = 76.0 and 85.0 ppm in 1:1 ratio] is detected and is likely to be a complex with a coordinated 1,5-cyclooctadiene.

Treatment of [Ru(benzene)Cl_2]$_2$ (0.0037g) with two equivalents of water-soluble BINAP-4SO_3Na (0.0187g) in 4.5 ml of a 1:8 benzene/methanol solvent mixture at 55-60°C for one hour produces a clear, brownish-yellow colored solution. The ^{31}P NMR spectrum of this solution in CD_3OD reveals a double doublet at d = 63.0 and 68.8 ppm (J = 45Hz). Identical results are obtained with [Ru(cod)Cl_2]$_n$ as precursor. These data indicate that the same species is formed in these syntheses. Thus, the complex contains no 1,5-cyclooctadiene. The splitting is attributed to a loss in symmetry in the molecule; most likely due to a coordinated benzene molecule, [Ru(BINAP-4SO_3Na)(benzene)X]$^{n+}$ (X=Cl or solvent; n=1 or 2). When this species is dissolved in D_2O, only a singlet is found in the ^{31}P NMR spectrum regardless of the ruthenium precursor used [^{31}P NMR (D_2O): d = 57.5 ppm]. Such degenerency indicates that the two P-C bonds are still intact. Vacuum drying of this D_2O solution yields a dark brown solid that when dissolved in CD_3OD regenerates the same ^{31}P NMR spectrum as before [^{31}P NMR (CD_3OD): d = 63.0 and 68.8 ppm]. This reversible process indicates the species in D_2O retains a coordinated benzene molecule. We therefore speculate that the complex is [Ru(BINAP-4SO_3Na)(benzene)]$^{2+}$, obtained through the aquation of the Ru-Cl bonds. These two ruthenium complexes are found to be active asymmetric hydrogenation catalysts (*vide infra*). In addition, polymeric ruthenium complexes can also be the active catalytic components.

Catalytic Studies: The brownish yellow solid isolated from the 1:8 benzene/methanol solvent was used as a catalyst for olefin hydrogenation without further purification. Asymmetric hydrogenations of prochiral 2-acylamino acid precursors and methylenesuccinic acid (Scheme 1) were conducted with a solution of 0.014-0.017M of substrate at either room temperature or 50°C and atmospheric to 100 atmospheres of hydrogen pressure in batch autoclaves.

Scheme 1



1: R_1=H R_2=H R_3=Me X=N
2: R_1=H R_2=Me R_3=Me X=N
3: R_1=Ph R_2=H R_3=Me X=N
4: R_1=H R_2=H R_3=H X=CH

L*=BINAP-4SO_3Na

In a typical run, a conversion of 80-100% was found in 48 hours. The conversion was measured by ^1H NMR spectroscopy and the enantiomeric excess (e.e.) determined by gas chromatography analysis using either a J. & W. Scientific CDX-B chiral capillary column or a Heliflex Chirasil-Val capillary column after derivatization of the reaction products.[28]

In all the reductions catalyzed by the water-soluble, ruthenium sulfonated-BINAP complex, the directions of enantioselection are found to be the same as those obtained from Ru-BINAP in organic solvent (from now on denoted as the parent system).[20b] Representative examples of the asymmetric hydrogenation of prochiral olefins are shown in Table I. Enantiomeric excesses as high as 85-88% have been achieved in both the hydrogenations of methyl-2-acetamidoacrylate and 2-acetamidocinnamic acid. To our knowledge, this is the first example of a water-soluble, ruthenium-based, chiral sulfonated diphosphine catalyst for asymmetric hydrogenation of prochiral alkenes. Similar to its parent system, the chirality induced in the products by the use of this water-soluble ruthenium catalyst is opposite to that obtained from its water-soluble Rh-BINAP-4SO_3Na catalyst in a similar solvent system.[20b,25] Based on these results, we speculate that the rate-determining step for this water-soluble ruthenium system is likely to be very similar to its organic-soluble parent system. In contrast to our previous findings with the water-soluble rhodium analogue, the enantioselectivity from the ruthenium-catalyzed hydrogenation of 2-acetamidoacrylic acids and methylenesuccinic acid shows an opposite trend in solvent dependence; the highest ee (up to 85%) is found in neat methanol (Tables I & II). The drop in ee in neat water is recoverable by an increase in reaction temperature and

an 82% ee in neat water is obtained at a reaction temperature of 50°C (vs. 85% ee in neat MeOH at 50°C). An increase in reaction temperature is not possible with the rhodium-based catalysts because of their lack of thermal stability in either organic or aqueous solvents. For the reduction of 2-acetamidocinnamic acid, the water-soluble ruthenium catalyst appears to give a slightly higher ee in neat water (87.7%) than when using methanolic solvents (81.3% Tables I & II).

Table I. Asymmetric hydrogenation of 2-acylamino acid precursors and methylenesuccinic acid by a water-soluble ruthenium (II))sulfonated BINAP complex under one atm. of hydrogen.†

Catalyst	Substrate	Solvent	S/C‡	Temp.(°C)	ee(%)
[Ru(BINAP-4SO_3Na)Cl_2]	1	MeOH	71	RT	84.2(R)
"	1	H_2O	18	RT	68.5(R)
"	2	H_2O	80	RT	75.9(R)
"	2	H_2O	76	50	82.0(R)
"	2	MeOH	75	50	85.0(R)
$Ru_2Cl_4(BINAP)_2(Et_3N)$	*1*	*1:1 EtOH/THF*	—	*35*	*76.0*[a]
[Ru(BINAP-4SO_3Na)Cl_2]	3	MeOH	75	RT	81.3(R)
"	3	EtOH	75	RT	80.1(R)
"	3	H_2O	75	RT	87.7(R)
$Ru_2Cl_4(BINAP)_2(Et_3N)$	*3*	*1:1 EtOH/THF*	—	*35*	*86.0*[a,b]
[Ru(BINAP-4SO_3Na)Cl_2]	4	MeOH	75	RT	81.1
"	4	MeOH	75	RT	90.0[b]
"	4	H_2O	18	RT	50.0
$Ru_2Cl_4(BINAP)_2(Et_3N)$	*4*	*1:1 EtOH/THF*	—	*35*	*88.0*[a,b]

1: -acetamidoacrylic acid
2: ethyl-2-acetamidoacrylate
3: 2-acetamidocinnamic acid
4: methylenesuccinic acid
†: substrate conc. = 0.014-0.017M
‡: S/C = substrate to catalyst ratio
a: from ref. 20b and two atm. of hydrogen
b: with the addition of triethylamine, Et_3N/Substrate = 1

Table II. Reductions of 2-acetamidoacrylic acid and 2-acetamidocinnamic acid by the water-soluble ruthenium sulfonated BINAP catalyst in various water/methanol mixtures at room temperature and 1 atm. of H_2.

Substrate	Solvent	S/C‡	Concentration† (M)	ee (%)
1	H_2O	18	0.017	68.5 (R)
1	7:3 H_2O/MeOH	23	0.017	1.7 (R)
1	3:7 H_2O/MeOH	55	0.017	76.9 (R)
1	MeOH	71	0.017	84.2 (R)
3	MeOH	75	0.015	81.3 (R)
3	1:1 MeOH/H_2O	75	0.015	84.0 (R)
3	H_2O	75	0.017	87.7 (R)
3	EtOH[a]	75	0.016	80.1 (R)

1: 2-acetamidoacrylic acid
3: 2-acetamidocinnamic acid
‡: S/C = substrate to catalyst ratio
†: substrate concentration
a: catalyst prepared from [Ru(p-cymene)Cl_2]2 in neat ethanol

The enantiomeric excess obtained in neat ethanol is almost the same as that from neat methanol. At this stage, it is impossible to explain the origin of the solvent dependent enantioselectivity. It is quite clear that the solvent effect is not only ligand-sensitive but also substrate dependent. Both the size and the polarity of the substrate appear to be important. For example, methylenesuccinic acid is hydrogenated with 81% ee in neat methanol as compared to only 50% ee in neat water. In spite of this, the 50% ee for this substrate is already among the most selective water-soluble enantioselectivities reported in the literature.[9]

Reductions at higher pressure have been examined and the results are summarized in Table III. The data show that the enantioselectivity declines with increasing hydrogen pressure regardless of substrate. In particular, the hydrogenation of methylenesuccinic acid is the most pressure-sensitive. These results are in agreement to those observed from the parent system where high hydrogen pressure and low reaction temperature lowered the enantiomeric excesses in the asymmetric hydrogenation of these types of substrates.[27]

Table III. Pressure effect on the enantioselection for the asymmetric hydrogenation of 2-acylamino acid precursors and methylenesuccinic acid by thewater-soluble ruthenium (II) sulfonated BINAP catalyst at RT.

Substrate	Solvent	Conc.† (M)	S/C‡	Pressure (atm)	ee (%)
3	MeOH	0.015	75	1	81.3(R)
3	MeOH	0.012	75	50	64.0(R)
3	1:1 MeOH/H_2O	0.045	75	1	84.0(R)
3	1:1 MeOH/H_2O	0.045	75	50	61.0(R)
3	1:1 MeOH/H_2O	0.012	75	55	64.0(R)
3	H_2O	0.017	75	1	87.7(R)
3	H_2O	0.017	76	75	82.5(R)
3	H_2O	0.017	75	50	68.3(R)
2	MeOH	0.015	75	1	84.7(R)
2	MeOH	0.015	76	10	72.0(R)
2	H_2O	0.017	75	1	75.9(R)
2	H_2O	0.017	77	10	50.6(R)
4	MeOH	0.015	75	1	81.1
4	MeOH	0.017	75	50	18.2
4	MeOH	0.017	75	100	10.1

2: methyl-2-acetamidoacrylate
3: 2-acetamidocinnamic acid
4: methylenesuccinic acid
†: substrate concentration
‡: S/C = substrate to catalyst ratio

For the reduction of methylenesuccinic acid, the addition of triethylamine to the reaction system gave interesting results (Table IV). A 9% increase in ee is found in neat methanol when triethylamine is added, giving up to 90% ee with 1:1 molar ratio between the base and the substrate. However, an almost 16% drop in ee is observed in neat water when triethylamine is added.

Table IV. Effect of added triethylamine on the enantioselectivities for the asymmetric hydrogenation of methylenesuccinic acid and methyl-2-acetamidoacrylate by the water-soluble ruthenium (II) sulfonated-BINAP catalyst at RT and one atmospheric pressure of hydrogen.

Substrate	Solvent	Conc.† (M)	S/C‡	Et_3N/Substrate (M/M)	ee (%)
4	MeOH	0.015	75	0	81.1
4	MeOH	0.015	75	1	90.0
4	H_2O	0.014	18	0	49.6
4	H_2O	0.015	75	1	34.0
4	*EtOH/THF*	*0.050*	*50*	*0*	*86.0*[a]
4	*EtOH/THF*	*0.050*	*50*	*1.2*	*88.0*[b]
2	MeOH	0.017	85	0	84.7(R)
2	MeOH	0.015	76	1	62.7(R)

2: methyl-2-acetamidoacrylate **4**: methylenesuccinic acid
†: substrate concentration ‡: S/C = substrate to catalyst ratio
a: $RuHCl(BINAP)_2$ [Et_3N being added during the catalyst synthesis] as catalyst at 35°C and 2 atm. of hydrogen (ref. 20b)
b: $Ru_2Cl_4(BINAP)_2(Et_3N)$ as catalyst at 35°C and 2 atm. of hydrogen (ref. 20b)

In the literature, there are no other studies on the effect of the addition of organic base on enantioselectivity for other water-soluble systems and it is therefore impossible for us to make any comparison.

Further experiments are currently being conducted on: (i) improved catalyst preparation, (ii) catalyst characterization, (iii) hydrogenations of other substrates with pharmaceutical applications, (iv) activity studies, (v) the effects of additions of inorganic bases and weakly coordinating co-solvents on enantioselectivity and (vi) catalysis in the supported aqueous-phase configuration.[29] Promising results from the SAPC system have been obtained and these data will be published later.

Conclusion: A one-step synthesis of a water-soluble, chiral ruthenium (II) sulfonated BINAP complex in methanolic solvent is accomplished. This is the first literature reported water-soluble ruthenium (II)-sulfonated chiral diphosphine complex. Similar to the synthesis of the non-sulfonated complex, a weakly coordinating co-solvent is required to inhibit the oxidative cleavage of P-C bonds when synthesizing the ruthenium complex with the water-soluble diphosphine ligand. The performance of the water-soluble ruthenium complex as an asymmetric hydrogenation catalyst is found to be as selective as its non-water-soluble analogue in alcoholic solvents. In some circumstances, the present system is superior to the non-sulfonated complexes, e.g., an 85.0% ee is obtained for the hydrogenation of 2-acetamidoacrylic acid by the sulfonated ruthenium complex in methanol at RT, where only an 76% ee is obtained by $Ru_2Cl_4(BINAP)_2(Et_3N)$ even at 35°C and two atmospheres pressure of hydrogen.[20b] Similarly, a 90.0% vs. 88.0% ee is found in the reduction of methylenesuccinic acid.[20b] However, when the hydrogenation is carried out in neat water, there is a drop in enantioselectivity for some of the substrates. Nevertheless, a 75.9% ee is found when this

water-soluble ruthenium catalyst is used to hydrogenate methyl-2-acetamidoacrylate in neat water and this value is comparable to the parent system that gives a 76.0% ee even after the addition of triethylamine.[20b] Additionally, the hydrogenation of 2-acetamidocinnamic acid yields a slightly higher ee (87.7% vs. 86.0%) in neat water than that obtained from the parent system in organic solvent.

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