Impressive Enhancement of the Enantioselectivity for a Hydroxy-Containing Rhodium(I) Bisphosphine Catalyst in Aqueous Solution by Micelle-Forming Amphiphiles

Rüdiger Selke,* Jens Holz, Andreas Riepe, and Armin Börner*

Abstract: The enantioselectivity of the asymmetric hydrogenation of some chelating olefinic substrates with hydroxy-DIOP rhodium(I) chelate **1** as catalyst can be influenced by amphiphiles in water to an unprecedented degree. The differences in enantiomeric excesses compared with blanks (without amphiphile) are in excess of 70 Δ% *ee*. Long alkyl chains in the amphiphile are essential for high Δ% *ee*. The enantioselectivity distinctly exceeds that in pure methanol. The analogous DIOP chelate **4** shows a lower enantiomeric enhancement; this indicates the importance of the hydroxy group of the catayst in this phenomenon. The effect decreases for both catalysts when the proportion of methanol in the solvent mixture is increased and the micelles thereby destroyed. This gives evidence for the importance of micelle formation. Nevertheless, we think that an additive anionic effect may also be taken into account when anionic amphiphiles such as sodium dodecylsulfate (SDS) are used.

Keywords: asymmetric catalysis · hydrogenations · rhodium · solvent effects · surfactants

Introduction

Five years ago Oehme et al.[1] discovered that the enantioselectivity of chiral rhodium catalysts in asymmetric hydrogenation could be enhanced by the action of amphiphilic modifiers; since then, this fact has attracted increasing attention.[2] Dehydroamino acid derivatives in aqueous solution have been the preferred substrates. Buriak and Osborn[2d] achieved selectivity enhancement with imine substrates in apolar solvents such as benzene. However, they have evidence that a sulfonate anion effect caused the observed increase of the enantiomeric excess for the product amine, and not the formation of reversed micelles from the applied amphiphile sodium bis(2-ethylhexyl)sulfosuccinate (AOT). Nozaki et al. published details of a rate enhancement by SDS, with only a minor change of selectivity for a new hydrogen transfer reaction of 1,2-*cis*-cyclohexanedimethanol, giving a cyclic chiral lactone catalyzed by a ruthenium complex.[3]

In the following exposition we give some new evidence for the importance of micelle formation in increasing hydrogenation enantioselectivity in water to an unprecedented degree under the influence of amphiphiles.

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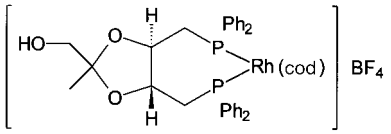
Results and Discussion

From Table 1 it can be seen that the hydrogenation of derivatives of unsaturated prochiral acids by means of the recently introduced[4] rhodium(I) precatalyst [Rh{(*R*,*R*)-HO-diop}(cod)]BF_4 (**1**) containing a bisphosphine carrying a



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hydroxy group yielded high enantiomeric excesses under the action of micelle-forming amphiphiles in water. For the substrate methyl (*Z*)-2-acetamidocinnamate (**2a**) Δ% *ee* reaches nearly 75%. In the case of substrate dimethyl itaconate (**2c**) an inversion to the enantiomeric *S* product results. The question arises as to the reason for this large change in enantioselectivity. Micelles including the catalyst and the substrate may form a less polar environment for the catalyst compared with pure water. In view of the better solubility and the higher enantioselectivity of the catalyst in organic solvents it seems plausible that the association of the catalyst with the micellar aggregation also causes a respectable enantiomeric enhancement. Long alkyl chains of the amphiphiles are essential for high % *ee* (Figure 1). However, an additional anionic effect in the case of anionic surfactants

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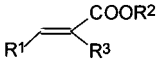
Table 1. Influence of SDS on hydrogenations with [Rh{(*R*,*R*)-HO-diop}(cod)]BF_4 (**1**) in water.[a]



	Substrate			$t_{1/2}$ (min)		% *ee* (*R*)		$Q_{a/b}$[b]
2	R^1	R^2	R^3	blank	+SDS	blank	+SDS	
a	Ph	Me	$NHCOCH_3$	7	5	1.5	76.6	7.3
b	Ph	H	$NHCOCH_3$	9	3	34.4	72.8	3.1
c	H	Me	CH_2COOMe	6	5	26.4	40.3 (*S*)	4.1
d	H	H	CH_2COOH	5	3	11.7 (*S*)	69.7 (*S*)	4.4

[a] 1 mmol substrate; 0.01 mmol **1**; 15 mL H_2O; 25 °C; 0.1 MPa. [b] $Q_{a/b}$ = relative enantioselectivity (refs. [1g, 12]) = $\frac{er_a}{er_b}$; er_a = enantiomeric ratio in the presence of 0.1 mmol amphiphile; er_b = enantiomeric ratio without amphiphile (blank).

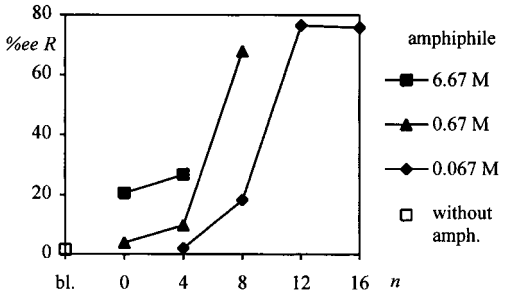


Figure 1. Effect of the alkyl chain length *n* of modifying *n*-alkyl sulfates on the enantioselectivity of **1** as precatalyst for the hydrogenation of substrate **2a** in water (bl. = blank, □ = without amphiphile, *n* = 0 means Na_2SO_4). For conditions see Table 1.

cannot be excluded. Sulfate ions alone have a small effect: the presence of 10 mmols sodium sulfate per 0.01 mmol catalyst increases the enantioselectivity of hydrogenation of **2a** from 1.5 (in the absence of sulfate) to 20.6% *ee* methyl (*R*)-*N*-acetylphenylalaninate (Figure 1). Furthermore, it should be mentioned that the action of SDS is already visible distinctly below the critical micelle concentration (cmc) for SDS in pure water (Figure 2). It may be misleading to use this as an argument to exclude micelle formation as a reason for the enhancement of enantioselectivity by added amphiphiles. The presence of substrate excess must be taken into account; it is well-known that the cmc decreases in the presence of additives.[5] Moreover, it has been found that the cmc of amphiphilic ligands may decrease by several orders of magnitude on the complexation of transition metals.[6] Even the oxidation state of the metal may have a distinct influence on the surface-active properties.[7] With the change of rhodium valency in our catalytically active system we therefore have little chance of proving the real aggregation state under hydrogenating conditions. We can see that addition of even small amounts of SDS to the system starts an agglomeration, giving an orange grease having the constitution [Rh{(*R*,*R*)-HO-diop}(cod)]$C_{12}H_{25}OSO_3$ (**3**). Using **3** as precatalyst for the hydrogenation of **2a** in toluene, we obtained methyl (*R*)-*N*-acetylphenylalaninate in 60% *ee* within five minutes.

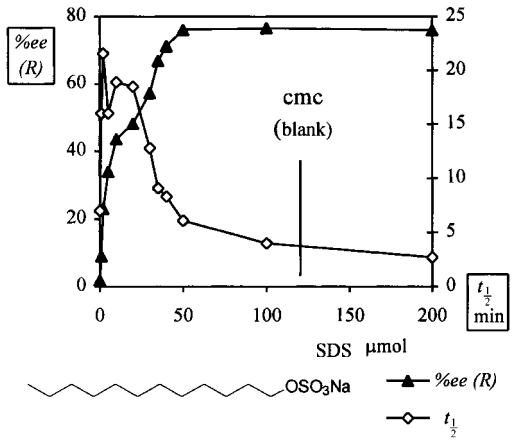


Figure 2. Influence of SDS on half-life ($t_{1/2}$) and %*ee* (*R*) of **1** as precatalyst for the hydrogenation of substrate **2a** in water. For conditions see Table 1, footnote [a].

The partial precipitation of rhodium as **3** explains the decrease of activity visible as an increase of the half-life in the starting period of the curve in Figure 2. The amount of **3** is decreased by addition of increasing amounts of SDS and fully disappears when a 5/1 ratio of SDS/**1** is reached, but the liquid phase remains opaque. Just at this point the maximum enantioselectivity for the system is obtained and the curve for the half-life shows a break, indicating that the activity has nearly reached its final value. We think that the dispersion of **3** is rendered possible by formation of mixed micelles between SDS and **3**.

Using Triton X-100 as a nonionic amphiphile we found a very similar increase in enantioselectivity, which was likewise observable distinctly below the cmc of the pure surfactant but without any intermediate complex precipitation (Figure 3).

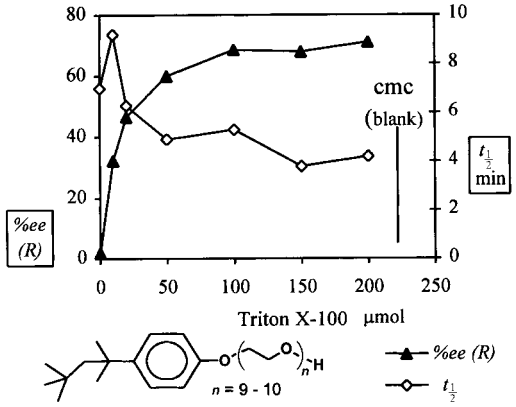


Figure 3. Influence of Triton X-100 on half-life and %*ee* (*R*) of **1** as precatalyst for the hydrogenation of substrate **2a** in water. For conditions see Table 1, footnote [a].

Even the cationic amphiphile hexadecyltrimethylammonium hydrogensulfate enables the aqueous system to form methyl (*R*)-*N*-acetylphenylalaninate in 70% *ee*. This unexpectedly strong influence on the degree of Δ% *ee* enhancement for non- and cationic tensides corresponds to a relative enantioselectivity $Q_{a/b} = 5.5$ (compared with the blank experiment[2g]) and is a strong indication of the importance of micelle formation in the changes in selectivity.

There is a further argument for the importance of micelle formation: it is well-known that the ability of SDS to form

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micelles decreases as the percentage of methanol in the water/alcohol mixture increases.[8] Indeed, we can show that a large decrease in enantioselectivity is connected with an increase above 20% methanol in the solvent mixture. This selectivity decrease stops at 50% methanol content, when it reaches the normal blank curve of %*ee* dependence of methanol content in water/methanol (Figure 4). In the concentration region

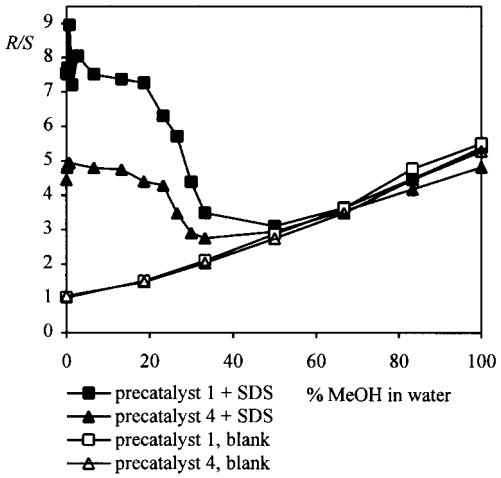
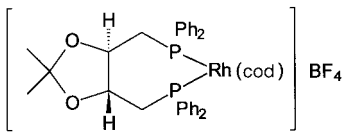


Figure 4. Influence of varying amounts of methanol in water on the enantiomeric ratio ($er = R/S$) in the hydrogenation of substrate **2a** with 0.1 mmol SDS. For conditions see Table 1, footnote [a].

beneath 5% methanol the reproducibility is poor and may be connected with a decrease in the cmc in presence of a very small proportion of alcohol.[9, 10]

In addition in Figure 4 we show the behaviour of the analogous precatalyst complex [Rh{(*R,R*)-diop}(cod)]BF_4 (**4**), which contains Kagan's ligand (*R,R*)-DIOP[11] without the



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hydroxy group of **1**. Impressive differences in selectivity result for the complexes which are completely absent in experiments without SDS. Note that the enantioselectivity is given in *enantiomeric ratio* ($er = R/S$), a better measure for comparison of similar catalysts than %*ee*.[12] Furthermore, Figure 4 demonstrates the improvement of the water/SDS system about pure methanol solvent for the hydroxy group containing precatalyst **1**. Such an effect, however, is absent for the precatalyst **4**.

The reason for the change in enantioselectivity is under discussion.[13] In principle four intermediate catalyst substrate chelates are possible for the C_1-symmetric **1**.[13e,f] Induced by changes of conformation and the electronic state around the rhodium, their ratio and relative hydrogenation reactivity will be influenced by the surrounding medium: solvent, associated amphiphiles or counterions. Evidence for the participation of catalyst–olefin-dihydride intermediates in the asymmetric hydrogenation has been given recently.[14]

Experimental Section

Equipment and general methods: Gas chromatography was performed with a Hewlett Packard (5890 series II) gas chromatograph. Elemental analyses were carried out on a LECO CHNS-932. The experimental procedures for the hydrogenation, the synthesis of substrates, the derivatization of the hydrogenated products and the determination of the enantioselectivity have been described earlier.[1b, 2g, 12a] Water as solvent was distilled and stored under argon. For the estimation of enantioselectivity the hydrogenation suspension was evaporated to dryness and the residue dissolved in methanol and analyzed by gas chromatography. Acid products were analysed after esterification with diazomethane. The volatile dimethyl 2-methylsuccinate hydrogenation product of **2c** had to be obtained by extraction with methylene chloride rather than by evaporation of the suspension.

[Rh{(*R,R*)-HO-diop}(cod)]$C_{12}H_{25}OSO_3$ (3): Precatalyst **1**[4] (405 mg, 0.5 mmol) and SDS (144 mg, 0.5 mmol) were dissolved in methanol (5 mL) at 50 °C under argon. Water (100 mL) was added slowly while the mixture was stirred and the heating switched off. The orange-yellow precipitate of **3** was separated from the mother liquor and washed with water (2 × 2 mL). The residue was dried at 30 °C under vacuum and afforded the product **3** in 41.2% yield. Elem. anal. $C_{51}H_{69}O_7P_2RhS$: calcd C 61.81, H 7.02, P 6.25, Rh 10.38, S 3.24; found C 61.24, H 6.87, P 6.31, Rh 10.08, S 3.09.

A second crop of 40–50% yield may be obtained by addition of further 100 mL of water to the mother liquor.

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