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Use of rhodium complexes with amphiphilic and nonamphiphilic ligands for the preparation of chiral α-aminophosphonic acid esters by hydrogenation in micellar media

Ingrid Grassert,* Ute Schmidt, Silke Ziegler, Christine Fischer and Günther Oehme *

Institut für Organische Katalyseforschung an der Universität Rostock e.V., 18055 Rostock, Buchbinderstraße 5-6, Germany

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Abstract

Several kinds of micelle forming amphiphiles were tested in the asymmetric hydrogenation of the prochiral dialkyl 1-benzamido-2-phenyl-ethenephosphonates in aqueous media. The chiral catalytic system $[Rh(cod)_2]BF_4$/BPPM or amphiphilized PPM proved to be suitable for the hydrogenation reaction affording enantiomeric excesses up to 99%. A chiral induction is possible to a certain extent (up to 11% *ee*) by selected chiral amphiphiles in the presence of achiral rhodium catalysts.

1. Introduction

Catalytic reactions in aqueous micelles have been an interesting research field in organic chemistry.[1–3] Occuring in a colloid medium, some reactions are influenced in their rate and stereoselectivity.[4,5] We are interested in the asymmetric hydrogenation of amino acid precursors by means of optically active rhodium(I) complexes. Previous experiments showed that this hydrogenation may be carried out in organic solvents, e.g. methanol, and in aqueous surfactant dispersions as well.[6,7] The excellent results of other hydrogenation reactions in water in the presence of surfactants led us to consider the hydrogenation of prochiral esters of 1-benzamido-2-phenyl-ethenephosphonic acid (**1**) to give optically active α-aminophosphonic acid esters (**2**). α-Aminophosphonic acids as analogues of α-amino acids are compounds with potential biological activity. In particular, the aim of investigations in this field is directed to the physiological properties of α-aminophosphonic acids, for instance their peptides as anticancer drugs, as pesticides and bactericides.[8–10]

* Corresponding authors. Tel: 381 4669330; fax: 381 4669324; e-mail: ingrid.grassert@ifok.uni-rostock.de; guenther.oehme@ifok.uni-rostock.de

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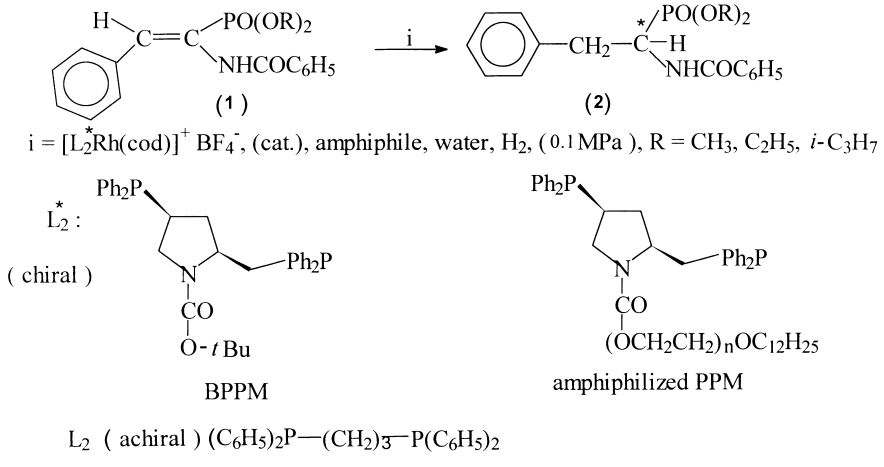
Generally, the utility of α-aminophosphonates and their peptidic derivatives as biological tools strongly depends on the configuration of the carbon centre α to the phosphorus atom.[11,12] As a consequence of the importance of the α-aminophosphonic acids and their derivatives **2**, considerable research has been devoted to the asymmetric synthesis of these compounds over the past decades.[13,14]

2. Results and discussion

Recently it was shown that methanol is a good solvent for the catalytic asymmetric hydrogenation of **1**, providing the best way to **2**.[15,16] We have investigated chiral rhodium complexes as catalysts in the asymmetric hydrogenation of dialkyl 1-benzamido-2-phenyl-ethenephosphonates in aqueous micellar media and demonstrated the influence of different surfactants (anionic, cationic, zwitterionic, nonionic) in water on the enantiomeric excess and the activity of this reaction (Scheme 1, Table 1). The chiral ligand L_2^* was in all cases (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine (BPPM) described by Achiwa[17] and the catalyst was formed in an in situ system of $[Rh(cod)_2]BF_4$ and BPPM.

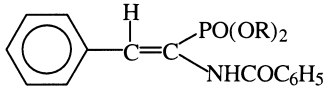


Scheme 1.

In contrast to methanol,[18] water is a poor solvent for both the catalyst and the substrate and leads to low activities and enantioselectivities, but the addition of surfactants increases the activity as well as the enantioselectivity.[7] We found that the rhodium–bppm catalyst gave the best results for the asymmetric hydrogenation of dialkyl 1-benzamido-2-phenyl-ethenephosphonates (**1**) in aqueous micellar media, while the PROPRAPHOS–rhodium catalyst,[15] which is very effective for the hydrogenation in methanol,[16] seems to be unstable in water.

A comparison between the results of the catalytic hydrogenation of dimethyl 1-benzamido-2-phenyl-ethenephosphonate with the rhodium–BPPM catalyst in different systems shows that for instance the (*S*)-enantiomer is formed very selectively (96% *ee*) with an activity of *t*/2=6 min in methanol, whereas the same reaction in water in the presence of the amphiphiles SDS or Tween 40 gives the (*S*)-enantiomer with 98% *ee* (Table 1, entry 3, 5). In the presence of $CTAHSO_4$ the *ee*-value for the (*S*)-enantiomer rises to 99% (entry 4) with a halftime of 7–12 min. In case of sulfobetaines we found a significant dependence on the hydrophobic chain length especially for the activity (entries 6, 7, 8), which may be an effect of different hydrophilic–lipophilic balances (HLBs).

Table 1
Effect of amphiphiles on the hydrogenation of different dialkyl 1-benzamido-2-phenyl-ethenephosphonates (**1**) in water with the catalytic system $[Rh(cod)_2]BF_4$/BPPM. Reaction conditions: 25°C; 0.1 MPa H_2; 7.5 mL H_2O; 0.5 mmol **1**; 0.005 mmol $[Rh(cod)_2]BF_4$+0.005 mmol BPPM; 0.5 mmol amphiphile. *t*/2 is the time necessary to consume half of the theoretical amount of hydrogen

Substrate: 

Entry	R	Amphiphile[a]	*t*/2 min	(*S*), *ee* [%][b]	conversion [%]
1	CH_3	without in H_2O	~ 12 h Rh↓	91	70
2		without in CH_3OH	6	96	100
3		SDS	7	98	100
4		$CTAHSO_4$	11	99	97
5		Tween 40	12	98	100
6		DDAPS	13	98	81
7		HDAPS	17	98	94
8		ODAPS	110	96	96
9	C_2H_5	without in H_2O	~ 10 h Rh↓	93	85
10		without in CH_3OH	12	95	100
11		SDS	4	98	95
12		$CTAHSO_4$	13	98	92
13		Tween 40	22	97	69
14	*i*-C_3H_7	without in H_2O		no hydrogenation	
15		SDS	13	99	65
16		$CTAHSO_4$	80	99	68
17		Tween 40		81	30
18		HDAPS		92	28

a: SDS: sodium dodecyl sulfate, $CTAHSO_4$: cetyltrimethylammonium hydrogen sulfate, Tween 40: polyoxyethylenesorbitane monopalmitateDDAPS: *N*-dodecyl-*N,N*-dimethyl-3-ammonio-1-propanesulfonate, HDAPS: *N*-hexadecyl-*N,N*-dimethyl-3-ammonio-1-propanesulfonate, ODAPS: *N*-octadecyl-*N,N*-dimethyl-3-ammonio-1-propanesulfonate
b: determined by HPLC column: Chiralcel OD-H; R=CH_3: eluent: hexane/2-propanol 90 : 10; R=C_2H_5: eluent: hexane/ ethanol 98:2; R=*i*-C_3H_7: eluent: hexane/2-propanol 99:1.

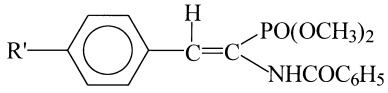
The reactivity of different esters of dehydro-aminophosphonic acids within the micellar system depends on the ester group and decreases from the methyl to the isopropyl ester. We suppose as a conclusion that the embedding of the catalyst–substrate complex within these micelles is more difficult in the case of the isopropyl ester because of a steric effect. A comparison of the stereoselectivity of different amphiphiles shows the best results in the presence of SDS.

To check the limits of the method different 1-benzamido-2-(substituted-phenyl)-ethenephosphonic acid methylesters[16] were hydrogenated in the micellar media with the catalytic system $[Rh(cod_2)]BF_4$/BPPM (Table 2).

In comparison with the results obtained in methanol as solvent[16] the enantioselectivity of the hydrogenation in micellar aqueous media is higher in all cases (7–11%). In a few cases the activities are similar. For instance the hydrogenation of the *p*-F compound in methanol has an activity of *t*/2=7 min and an enantioselectivity of 89% *ee* (*S*),[16] while in water and in the presence of SDS the halftime is *t*/2=6 min with an enantioselectivity of 98% *ee* (*S*) (entry 4). The conversion (H_2-uptake) is quantitative

Table 2
Effect of amphiphiles on the hydrogenation of different dimethyl 1-benzamido-2-(substituted-phenyl)-ethenephosphonates in water with the catalytic system $[Rh(cod)_2]BF_4$/BPPM. For reaction conditions see Table 1

Substrate:



Entry	R	Amphiphile[a]	t/2 min	(*S*), *ee* [%][b]	conversion [%]
1	*p*-Cl	SDS	4	98	100
2		$CTAHSO_4$	7	99	100
3		Tween 40	20	96	65
4	*p*-F	SDS	6	98	100
5		$CTAHSO_4$	12	99	100
6		Tween 40	9	98	100
7	*o*-F	SDS	16	97	93
8		$CTAHSO_4$	13	99	100
9		Tween 40	25	96	95
10	*m*-F	SDS	7	96	100
11		$CTAHSO_4$	20	98	100
12		Tween 40	18	96	96
13	*p*-CF_3	SDS	11	96	98
14		$CTAHSO_4$	14	98	97
15		Tween 40	16	97	90
16	*p*-CH_3	SDS	5	99	100
17		$CTAHSO_4$	8	99	100
18		Tween 40	11	98	100
19	*p*-$CH(CH_3)_2$	SDS	15	98	100
20		$CTAHSO_4$	30	98	100
21		Tween 40	350	80	75
22	*p*-NO_2	SDS	6	98	100
23		$CTAHSO_4$	11	98	91
24		Tween 40		no conversion	

a: Abbreviations see Table 1
b: determined by HPLC column: Chiralcel OD-H; methylesters: eluent: hexane/*2*-propanol 90 : 10; except R'=*m*-F: column: Chiralpak AD, eluent: hexane/ethanol 95:5

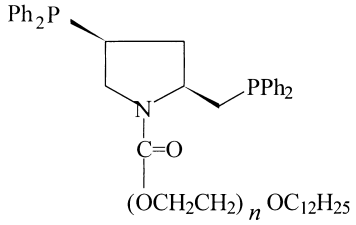
in most cases. A comparison of the different amphiphiles shows that the anionic SDS as a rule gave the best activities and enantioselectivities [up to 99% *ee* (*S*)]. The alternatively used surfactants $CTAHSO_4$ and Tween 40 are less active than SDS but excellent for stereoselectivity, except for Tween 40 for the *p*-isopropyl and the *p*-nitro compounds (entries 21 and 24).

The next aim was the investigation of the influence of rhodium(I) complex catalysts with amphiphilized ligands on the hydrogenation of dehydro-aminophosphonic acid esters. The synthesis of amphiphilic ligands like this has been described elsewhere.[19]

These in situ formed amphiphilic complexes are capable of forming catalytic metallomicelles in water themselves or can act together with other amphiphiles to form mixed micelles (Table 3 and Fig. 1).

The results in Table 3 show satisfying activities with the amphiphilic rhodium complexes for the asymmetric hydrogenation of **1** in water with high enantioselectivities without the addition of other amphiphiles (entries 1–4). In comparison to these results the hydrogenation with the rhodium–BPPM complex without amphiphiles in water would be very slow (*t*/2=12 h, see Table 1, entry 1) due to

Table 3
Effect of rhodium(I) complexes with amphiphilized ligands on the hydrogenation of dimethyl 1-benzamido-2-phenyl-ethenephosphonate (**1**) in water with the catalytic system $[Rh(cod)_2]BF_4$/amphiphilized phosphine A or B (with or without the presence of SDS). For reaction conditions see Table 1: 0.5 mmol **1**; Rh:phosphine:substrate=1:1:100, 1:1:50, 1:1:400



A : $n = 10$

B : $n = 23$

Ligand: amphiphilized phosphine

Entry	Rh : ligand : substrate : amphiphile	*t*/2 min	(*S*), *ee* [%][a]	conversion [%]
1	1 : 1 A : 100 : 0	33	93	100
2	1 : 1 B : 100 : 0	63	94	80
3	1 : 1 A : 50 : 0	29	95	92
4	1 : 1 B : 50 : 0	30	95	80
5	1 : 1 A : 100 : 20 SDS	4	98	100
6	1 : 1 B : 100 : 20 SDS	5	98	98
7	1 : 1 A : 400 : 80 SDS	11	98	95
8	1 : 1 B : 400 : 80 SDS	20	98	100

a: HPLC see Table 1 and Experimental

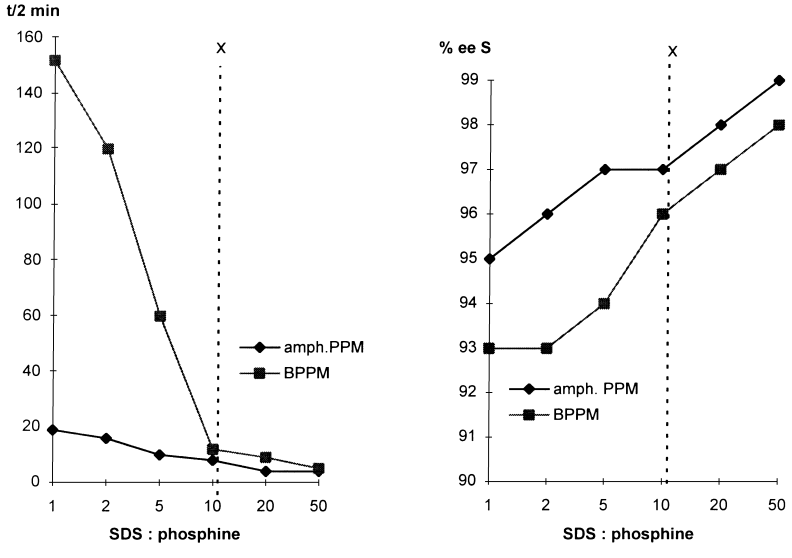


Figure 1. Rh–amphiphilic PPM catalyst in comparison with Rh–BPPM catalyst in the presence of different SDS concentrations. Enantioselectivity and activity of the hydrogenation of dimethyl 1-benzamido-2-phenyl-ethenephosphonate (**1**) in water. The dotted vertical line (×) marks the cmc of SDS in water

destruction of the catalyst. The addition of nonfunctional amphiphiles like SDS increases the activity and the enantioselectivity in both systems because micelles or mixed micelles are formed. The concentration of the catalytic system could be decreased significantly with the use of mixed micelles without loss of enantioselectivity (entries 7 and 8).

Fig. 1 shows the effect of the amphiphilized catalyst in comparison with the rhodium–BPPM catalyst in the presence of different SDS concentrations. Here a clear discrepancy is observed in the activity and in the enantioselectivity between the amphiphilized and nonamphiphilic rhodium complexes. Whereas the hydrogenation of **1** with the rhodium–BPPM catalyst is very slow in the presence of small concentrations of the anionic SDS, the amphiphilic rhodium complex increases in activity as well as enantioselectivity when low SDS concentrations are used.

The causes of this effect seem to be different. Nonamphiphilic rhodium–substrate complexes are solubilized by embedding within the micelles and the dependence of the activity and enantioselectivity on the SDS concentration shows, for the BPPM complex, a common increase near the cmc of SDS (8.1×10^{-3} mol/L). In the case of the amphiphilic ligands a mixed micelle should result and the activity begins much earlier because of the lower cmc of the polyether containing ligand. It was not possible to measure the cmc of the highly air sensitive phosphines or phosphine complexes, but it is known that similar surfactants derived from pyrrolidine, (*S*)-2-hydroxymethyl-pyrrolidine and (2*S*,4*R*)-4-hydroxymethyl-pyrrolidine have cmcs in all cases between 3×10^{-5} and 7×10^{-5} mol/L. A comparison with these values shows that the cmcs of the amphiphilic ligands are much lower than that of SDS. Therefore, the metallomicelles can themselves have a similar effect to polymerized micelles.[20]

Pure metallomicelles have an extreme high concentration of catalytically active groups in the polar layer of the micelles which probably limits the accessibility. This should be overcome by mixing with 'nonfunctional' surfactants like SDS, and the experiments with mixed micelles display as a 'mixing effect' an enhancement of activity and enantioselectivity.

Besides the asymmetric hydrogenation in water in the presence of nonchiral amphiphiles and chiral catalysts we were also interested in testing the chiral induction in hydrogenations using achiral catalysts and chiral amphiphiles. The possibility of chiral induction by chiral micelles is known for several reactions, e.g. ester saponification,[21] hydrogenation of ketones,[22] oximercuration,[23] etc.

The influence of different carbohydrate amphiphiles such as tetradecyl α- and β-D-maltoside, dodecyl α- and β-D-maltoside and decyl β-D-maltoside were investigated in the presence of the achiral catalyst [Rh(cod)(bdpp)]BF_4 for the hydrogenation of different dialkyl 1-benzamido-2-phenyl-ethenephosphonates (**1**).

Carbohydrate amphiphiles could not only activate the hydrogenation but could also induce chirality on a low level as can be seen in Fig. 2. There are differences in the chiral induction between the maltoside amphiphiles with different chain lengths and between the α- and β-maltosides. The influence seems to be connected with the ability to form micelles and to solubilize substrate and complex. A similar effect was observed in the hydrogenation of methyl α-acetamido-cinnamate.[24] Besides the chiral induction is influenced by different alkyls in the ester groups of the 1-benzamido-2-phenyl-ethenephosphonates (**1**).

α-Maltosides gave no chiral induction within the hydrogenation product in all cases. In contrast the β-maltosides led to a chiral induction between 6 and 11% *ee* (*S*). The effects of the decyl-, dodecyl- and tetradecyl β-D-maltosides are different. The reason could be the different hydrophilic–lipophilic balance (HLB)[25] in these three carbohydrate amphiphiles.

The stability of the carbohydrate micelles is indicated by the cmc, representing the ability to form micelles, the HLB as a measure of the dispersibility in water and hydrogen bonds in the headgroup, which are responsible for a stabilization of the micelles on the interface to water. It seems that the combination of these three facts is optimal in the β-maltosides and results in their chiral induction ability. The influence

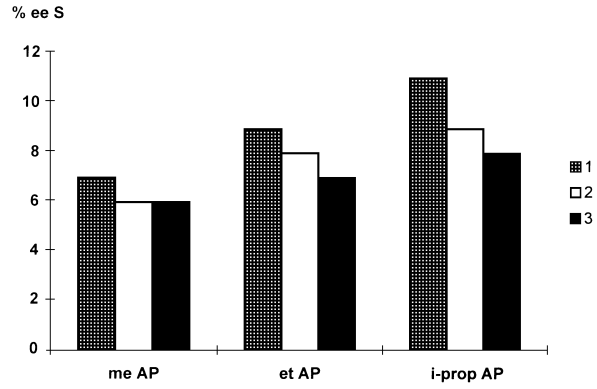


Figure 2. Asymmetric hydrogenation of different esters (methyl-, ethyl-, *i*-propyl) of 1-benzamido-2-phenylethenephosphonic acid AP in water. Chiral induction in the presence of achiral Rh-catalysts and chiral amphiphiles. 1=Decyl β-D-maltoside; 2=dodecyl β-D-maltoside; 3=tetradecyl β-D-maltoside

of the hydrogen bond on the micelle formation in water has been discussed by Kano and Ishimura.[26] In addition the size of the substrate influences the inclusion in the chiral part of the micelle. As described by Shinitzky and Haimowitz,[27] for serine amphiphiles the requirements for a transfer of chirality may be a chiral suprastructure due to hydrogen bonds within the headgroup of the amphiphiles on the surface of the micelle and the location of the catalytic system near the stereogenic centres. We suppose that due to the highest chiral induction of 11% *ee* (*S*) in the case of the *i*-propylester group that the catalyst substrate system of this compound is better situated between the chiral head group and the hydrophobic tail than the catalyst–substrate complex of the smaller ethyl- and methylesters.

Chiral induction of several dimethyl 1-benzamido-2-(substituted-phenyl)-ethenephosphonates is shown in Table 4. There are only small differences between the different kinds of substituted compounds.

3. Conclusions

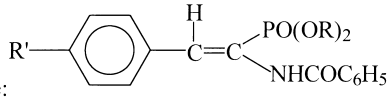
Different types of micelle-forming amphiphiles promote activity and enantioselectivity in asymmetric hydrogenation of several esters of 1-benzamido-2-(substituted-phenyl)-ethenephosphonic acids (**1**) in aqueous media. With a rhodium(I)–BPPM complex as the optically active in situ catalyic system halftimes of 4 min and enantioselectivities up to 99% *ee* could be observed. There are differences in the reactivity of the tested substrates. The best results were obtained with dimethyl 1-benzamido-2-phenyl-ethenephosphonate.

Hydrogenations with metallomicelles which were formed by rhodium(I) complex and new amphiphilized PPM ligands led to enantioselectivities of 95% *ee* (*S*) and by addition of SDS even to 98% *ee* (*S*) at relatively high substrate concentration (rhodium:substrate=1:400). The rhodium(I) complex forms with amphiphilized PPM in the presence of small SDS concentrations mixed micelles and a clear advantage is observed in activity and enantioselectivity of the hydrogenation in comparison to the system of rhodium(I)–BPPM complex and varying concentrations of SDS.

Chiral induction up to 11% *ee* (*S*) was obtained with nonchiral rhodium–phosphine complexes and carbohydrate amphiphiles. The chiral induction increased by changing from dimethyl 1-benzamido-2-phenyl-ethenephosphonate to the di-*i*-propylester when similar carbohydrate amphiphiles were used.

Table 4
Experiments for chiral induction within chiral micelles. Hydrogenation of dimethyl 1-benzamido-2-(substituted-phenyl)-ethenephosphonates (**1**) in water with the achiral catalytic system $[Rh(bdpp)(cod)]BF_4$. Effect of carbohydrate amphiphiles. For reaction conditions see Table 1. BDPP: $(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2$

Substrate:



Entry	R	R'	Amphiphile[a]	*t*/2 min	(*S*), *ee* [%] [b]	conversion [%]
1	CH_3	H	$TD_ßM$	24	5	100
2			$DD_ßM$	41	6	98
3			$D_ßM$	55	7	96
4	C_2H_5	H	$TD_ßM$	38	7	100
5			$DD_ßM$	50	8	100
6			$D_ßM$	35	9	95
7	$CH(CH_3)_2$	H	$TD_ßM$	95	9	100
8			$DD_ßM$	90	9	100
9			$D_ßM$	130	11	90
10	CH_3	*p*-Cl	$DD_ßM$	16	5	89
11			$D_ßM$	50	6	85
12	CH_3	*p*-F	$DD_ßM$	97	4	96
13			$D_ßM$	15	6	100
14	CH_3	*o*-F	$DD_ßM$	28	6	97
15			$D_ßM$	33	9	100
16	CH_3	*m*-F	$DD_ßM$	11	5	100
17			$D_ßM$	44	6	98
18	CH_3	*p*-CH_3	$DD_ßM$	40	7	95
19			$D_ßM$	165	8	100
20	CH_3	*p*-$CH(CH_3)_2$	$DD_ßM$	100	7	92
21			$D_ßM$	20 h	8	50

a: Abbreviations see Fig. 2
b: HPLC see Table 1 and Experimental

4. Experimental

The enantiomeric excess (% *ee*) was determined by HPLC using a Liquid Chromatograph 1090 series II equipped with DAD (Hewlett Packard) and Chiralyzer (IBZ Messtechnik GmbH, Hannover). Separations were carried out on Chiralcel OD-H or Chiralpak AD analytical columns, 4.6×250 mm I.D. (Daicel, Mallinckrodt Baker, Germany). The esters were determined as follow: all methylesters (except R=*m*-F): Chiralcel OD-H column, eluent: hexane:isopropylalcohol 90:10; R=*m*-F: Chiralpak AD column, eluent: hexane:ethanol 95:5; all ethylesters: Chiralcel OD-H column, eluent: hexane:ethanol 98:2; all isopropylesters: Chiralcel OD-H column, eluent: hexane:isopropylalcohol 99:1.

All detergents and BPPM were purchased from commercial sources and used as obtained. Tween and sulfobetaines were from Sigma GmbH, BPPM from Merck, $CTAHSO_4$ and SDS and the phosphine bis(diphenylphosphino)propane from Fluka. The starting complex $[Rh(cod)_2]BF_4$ was prepared in accordance with the literature,[28] as were the phosphine complexes $[Rh(cod)(bdpp)]BF_4$ and $[Rh(cod)(bppm)]BF_4$.[18,29] The synthesis of the dehydro-benzamidophosphonates has been described.[16]

4.1. Synthesis of the amphiphilized ligands A and B

A solution of 1.1 mmol of the pyrrolidine and 1.32 mmol of triethylamine was cooled to 0°C under stirring. Then 1.1 mmol alkylpolyoxyethylene oxycarbonyl chloride in 3 mL CH_2Cl_2 was added dropwise. The mixture was stirred for 3 h at room temperature, the solvents were removed under vacuum and the residue dissolved in 10 mL ether. After storing overnight the crystallized triethylamine hydrochloride was filtered over Celite 545 and glass wool, the filtrate was concentrated in a vacuum and the residue dried in a vacuum.[19]

4.2. Hydrogenation

Hydrogenation was performed under normal pressure at 25°C. A suspension of 1 mmol dimethyl 1-benzamido-2-phenyl-ethenephosphonate, 0.01 mmol $[Rh(cod)_2]BF_4$, 0.01 mmol of the nonamphiphilic or amphiphilic ligand (phosphine) and 1 mmol surfactant in 15 mL deaerated water was stirred for 15 min under argon in a thermostated hydrogenation flask. Then stirring was stopped, the argon was replaced by hydrogen under atmospheric pressure, and the hydrogenation was started by stirring. The reaction was followed volumetrically. The time necessary to consume half of the theoretical amount of hydrogen (halftime, $t/2$) was taken as a measure of the activity. The mixture was extracted with 5 mL chloroform after finishing the experiment. The enantiomeric excess of the product was determined by HPLC on a Liquid Chromatograph 1090 as described above.

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