Amphiphilic Polymer Supports for the Asymmetric Hydrogenation of Amino Acid Precursors in Water

M. Tobias Zarka, Oskar Nuyken, and Ralf Weberskirch*[a]

Abstract: This paper describes the synthesis and characterization of a new class of amphiphilic, water-soluble diblock copolymers based on 2-oxazoline derivatives with pendent (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine (PPM) units in the hydrophobic block. The synthetic strategy involves the preparation of a diblock copolymer precursor with ester functionalities in the side chain; which were converted into carboxylic acids in a polymer-analogous step and finally reacted with the PPM ligand. The structures of the copolymers were characterized by ^{1}H and ^{31}P NMR spectroscopy and GPC measurements. Subsequently, these polymers were successfully utilized as a polymeric support for the asymmetric hydrogenation of 1) (*Z*)-α-acetamido cinnamic acid and 2) methyl (*Z*)-α-acetamido cinnamate in water, showing 90% substrate conversion at 25 °C within 20 minutes at atmospheric H_2 pressure (1 bar) for methyl (*Z*)-α-acetamido cinnamate.

Keywords: amphiphiles · block copolymers · hydrogenation · supported catalysts

Introduction

Homogeneous catalysts have many advantages over their heterogeneous counterparts owing to the possibility to correlate catalytic activity and selectivity with a molecularly defined structure of the catalyst and its ligand sphere.[1] Nevertheless, industrial large scale applications of homogeneous catalysts encounter some serious drawbacks due to difficulties of catalyst recovery and catalyst recycling on the one hand and isolation of a metal-free product on the other.[2] Although this problem can be easily solved by immobilization of the catalyst on inorganic materials or cross-linked organic polymers, with the use of insoluble polymers and heterogeneous reaction conditions many problems emerge; besides lowered reactivity, extended reaction times, and diffusion problems, many heterogeneous catalysts do not show the selectivity that is desirable for many important catalytic transformations. In the past decade, numerous attempts have been made to combine the advantages of homo- and heterogeneous catalysis. Approaches that have been intensively studied are biphasic catalysis,[3] soluble polymeric supports,[4] such as linear polystyrene[5] and poly(ethylene glycol),[6] and, more recently, dendritic and hyperbranched polymers.[7] In particular poly(styrene) and poly(ethylene glycol) are available in a wide range of different molecular weights with a variety of functional end groups and solubility in both organic solvents and water. Moreover, due to the fact that reagents and catalysts can be immobilized on such polymers, they can be used in liquid-phase synthesis, and reagents can be used in excess to drive the reaction to completion. Polymer-bound catalysts can likewise easily be removed from the reaction mixture and recycled.[8] This methodology avoids the difficulties of solid-phase synthesis, while preserving many of its advantages. A serious drawback of using these linear polymer supports is based on the fact that they are not suitable to transform hydrophobic substrates efficiently in pure aqueous solution, because of the limited solubility of such compounds in water. Even linear, hydrophilic polymer supports, such as phosphine-functionalized poly(*N*-isopropyl)acrylamide[9] or PPM-modified poly(acrylic acid)[10] (PPM = (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine) have been only successfully applied in pure aqueous solution with water-soluble substrates, whereas the transformation of hydrophobic ones was only demonstrated in biphasic solvent mixtures. Beside catalyst/product separation and catalyst recycling, the use of water as the preferred solvent becomes more and more important due to many attractive economical, physiological, and safety-related process engineering reasons.[11] An interesting approach to increase solubility of hydrophobic compounds in aqueous solution is based on the use of amphiphilic polymers. To date, only few papers dealt with the use of amphiphilic polymers as support material for catalysis in aqueous solution, either as amphiphilic PS-PEG resin-sup-

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ported triphenylphosphine (PS-PEG = polystyrene–polyethylene glycol)[12] or as insoluble catalyst network through self-assembly of triphenylphosphine-functionalized amphiphilic polymers and $(NH_4)_2PdCl_4$.[13] An extension of the utility of amphiphilic polymers is based on their unique self-assembly behavior in a selective solvent, that is, a thermodynamically good solvent for one block and a bad solvent for the second one. Dependent on polymer architecture and composition, such as AB, ABA, or ABC block or graft copolymers, these polymers form different types of micellar aggregates in solution.[14] Whereas micellar catalysis in aqueous solution have been known for long time,[15] there are only few reports in literature in which the use of amphiphilic, water-soluble block copolymers for the immobilization of transition-metal catalysts has been studied, although polymers exhibit many advantages over their low-molecular-weight counterparts with respect to structural variability, different solubility, and functionality. G. Oehme et al. used block copolymers based on PEO-PPO (poly(ethylene oxide)–poly(propylene oxide)) to solubilize different catalysts and proved the efficiency of such micellar supported systems in asymmetric hydrogenation.[16] In this case, the catalyst is only solubilized in the micellar core and may be washed out after product/catalyst separation. Clearly, a covalent linkage of the catalyst to the polymer would offer advantages in terms of catalyst recycling. Recently, we reported the successful synthesis of amphiphilic block copolymers bearing triphenylphosphine[17] and bipyridine units[18] in the hydrophobic block and their application for hydroformylation of oct-1-ene[19] or atomic transfer radical polymerisation (ATRP) of methyl methacrylate[18] in pure aqueous solution. With the intention to expand the scope of transition-metal-catalyzed reactions in polymer micelles, we report in this paper the synthesis of new amphiphilic block copolymers with (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine (PPM) units in the side chain and their application in the asymmetric hydrogenation of two prochiral enamides, α-acetamido cinnamic acid and its methyl ester. Additionally, catalyst recovery and reuse is possible by simple extraction of the substrate/product from the aqueous polymer phase after each cycle.

Experimental Section

Materials: All chemicals were purchased from Aldrich and Merck Eurolab and were used as received, unless otherwise noted. 2-Methyl-2-oxazoline, 2-nonyl-2-oxazoline, acetonitrile, and chlorobenzene were refluxed over CaH_2 and stored under dry nitrogen atmosphere and mole sieve 4 Å.

Instrumentation: ^{1}H NMR (300,13 MHz), ^{13}C NMR (75,5 MHz), and ^{31}P NMR (121,5 MHz) spectra were recorded on a Bruker ARX300 spectrometer. FTIR spectroscopy was carried out on a Bruker IFS55 spectrometer. Elemental analyses were measured by the Microanalytical Laboratory of the Inorganic Institute of the TU München. Gel-permeation chromatography (GPC) was carried out on a Waters (GPC) 510 equipped with a UV and refractive index (RI) detector; poly(styrene) was used for the calibration of the poly(2-oxazoline) samples in chloroform as solvent. The rhodium content was determined by inductively coupled plasma atomic emission (ICP-AES, Jobin Yvon JY 38 plus) at the Institute of Analytical Chemistry and Radiochemistry (Prof. M. R. Buchmeiser), University Innsbruck (Austria). Samples were mixed with 3 mL aqua regia, heated in a microwave for several minutes and finally diluted with 10 mL water. HPLC analyses were performed with chiral columns (Chiracel OD; Daicel Chemical Industries) employing *n*-hexane/propan-2-ol as eluents (flow rate: 1.0 mL min^{-1}) and UV detection (Prof. Dr. Bach, Organic Chemistry I, TU München). The fluorescence analysis for the determination of the critical micelle concentration (cmc) was performed on a Spex FLUORLog spectrometer. Polymer solutions were prepared in a concentration range from 10^{-3} to 10^{-10} mol L^{-1} and 0.2 μM solutions of the fluorescence dye 6-*p*-toluidine-2-naphthylsulfonic acid in doubly distilled water.

Methyl 7-chloro-4-oxo-5-azaheptanoate (1a): Methyl succinyl chloride (20.0 g, 0.13 mol) and 2-chloroethylammonium chloride (15.4 g, 0.13 mol) were suspended in dry dichloromethane (150 mL). At 0 °C triethylamine (30.0 g, 0.30 mol) was added dropwise over a period of 1 h. The reaction mixture was allowed to warm up to room temperature and was stirred overnight before water (40 mL) was added. The organic phase was washed twice with water and once with brine, and dried over anhydrous sodium sulfate. After removal of the solvent, a yellow oil remained. Yield: 19.82 g (77 %) of a yellow oil; ^{1}H NMR ($CDCl_3$): $\delta = 2.52$ (t, $J = 6.49$ Hz, 2H), 2.69 (t, $J = 6.49$ Hz, 2H), 3.62 (m, 4H), 3.70 (s, 3H), 6.17 ppm (s, 1H; NH); ^{13}C NMR ($CDCl_3$): $\delta = 29.3$, 30.9, 41.3, 43.9, 51.9, 171.7, 173.4 ppm.

Methyl 3-(oxazol-2-yl)propionate (1): Compound **1a** (19.0 g, 0.098 mol) and anhydrous sodium carbonate (7.6 g, 0.072 mol) were reacted under stirring at a pressure of 0.1 mbar. A clear colorless liquid was obtained after fractionated distillation Yield: 10.2 g (66 %) of a colorless liquid; ^{1}H NMR ($CDCl_3$): $\delta = 2.58$ (t, $J = 7.44$ Hz, 2H), 2.68 (t, $J = 7.44$ Hz, 2H), 3.70 (s, 3H), 3.82 (t, $J = 9.16$ Hz, 2H), 4.24 ppm (t, $J = 9.73$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 23.1$, 30.1, 51.8, 54.4, 67.5, 167.0, 172.8 ppm; elemental analysis calcd (%) for $C_7H_{11}NO_3$ (157,17): C 53.49, H 7.05, N 8.91; found: C 53.39, H 7.11, N 9.01.

Methyl 9-chloro-6-oxo-7-azanonoate (2a): Methyl adipinoyl chloride (20.6 g, 0.115 mol) and 2-chloroethylammonium chloride (13.35 g, 0.115 mol) were used in a reaction similar to that described for **1a**. Yield: 19.3 g (76 %) of a yellow oil; ^{1}H NMR ($CDCl_3$): $\delta = 1.60$ (m, 4H), 2.18 (t, $J = 6.90$ Hz, 2H), 2.28 (t, $^3J = 6.87$ Hz, 2H), 3.55 (m, 4H), 3.60 (s, 3H), 6.58 ppm (s, 1H; NH); ^{13}C NMR ($CDCl_3$): $\delta = 24.7$, 25.3, 34.0, 36.2, 41.6, 44.0, 51.8, 173.4, 174.2 ppm.

Methyl 3-(oxazol-2-yl)pentanoate (2): Compound **2a** (17.6 g, 0.079 mol) and anhydrous sodium carbonate (6.3 g, 0.059 mol) were heated together with stirring at a pressure of 0.1 mbar. A clear colorless liquid with a boiling point of 110 °C (0.1 mbar) was obtained after fractionated distillation. Yield: 9.2 g (63 %) of a colorless liquid; ^{1}H NMR ($CDCl_3$): $\delta = 1.61$ (m, 4H), 2.24 (m, 4H), 3.59 (s, 3H), 3.74 (t, $J = 9.16$ Hz, 2H), 4.15 ppm (t, $J = 9.35$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 25.7/24.7$, 27.8, 33.9, 51.7, 54.6, 67.4, 168.3, 174.0 ppm; elemental analysis calcd (%) for $C_9H_{15}NO_3$ (185.22): C 58.36, H 8.16, N 7.56, O 25.91; found: C 57.15, H 8.00, N 7.66.

Block copolymer synthesis: All polymerizations were carried out in a Schlenk tube under inert atmosphere (N_2) using freshly distilled and dried solvents.

Polymer 3a: A typical procedure for 3a was as follows: 2-Methyl-2-oxazoline (5.11 g, 60 mmol) was added to a solution of methyltriflate (328 mg, 2.0 mmol) in acetonitrile (30 mL) and chlorobenzene (15 mL) at 0 °C. The mixture was heated up to 80 °C and stirred for 12 h. At 0 °C, 2-nonyl-2-oxazoline (1.58 g, 8.0 mmol) and **1** (1.48 g, 8.0 mmol) were added. The solution was stirred at 90 °C for additional 24 h. The polymerization was terminated with piperidine (0.5 g, 6 mmol) at room temperature for 4 h. After removal of the solvent, the residue was dissolved in chloroform (40 mL) and stirred with potassium carbonate (2 g) overnight. After filtration, the polymer was purified by precipitation in ice cold diethyl ether and dried in a vacuum oven at 50 °C. Yield: 6.0 g (73 %) of a white solid; ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, $J = 6.58$ Hz, 3H), 1.26 (m, 12H), 1.58 (m, 2H), 2.11 (m, 3H), 2.33 (m, 4H), 2.64 (m, 4H), 3.05/2.96 (3H), 3.46 (s, 4H), 3.65 ppm (s, 3H); FT-IR (film in $CHCl_3$): $\tilde{\nu} = 1636$ ($C{=}O_{amide}$), 1729 cm^{-1} ($C{=}O_{ester}$).

Polymer 4a: Polymer **4a** was prepared in a similar fashion to **3a** by using methyl triflate (0.164 g, 1 mmol), 2-methyl-2-oxazoline (2.55 g, 30.0 mmol), 2-nonyl-2-oxazoline (0.79 g, 4.0 mmol), **2** (0.74 g, 4.0 mmol), and piperidine (0.22 g, 2.6 mmol). Yield: 2.6 g (62 %); ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (t, $J = 6.49$ Hz, 3H), 1.24 (m, 12H), 1.62 (m, 6H), 2.10 (m, 5H), 2.33 (m, 4H), 3.03/2.94 (3H), 3.45 (s, 4H), 3.63 ppm (s, 3H); FT-IR (film in $CHCl_3$): $\tilde{\nu} = 1636$ ($C{=}O_{amide}$), 1729 cm^{-1} ($C{=}O_{ester}$).

Hydrolysis of the block copolymers

Formation of 3b: Block copolymer **3a** (2.0 g, 0.5 mmol) was dissolved in methanol (20 mL); then 0.1M NaOH (20 mL, 2 mmol hydroxide) was added and the mixture was stirred at room temperature for one hour and for an additional 90 min at 55 °C. Then methanol was removed in vacuum and aq. HCl (20 mL of 0.1M) was added. After removing the water in vacuum, the residue was dissolved in chloroform. The solution was dried over anhydrous sodium sulfate, and the solvent was removed in vacuum. Yield: 1.84 g (92%) of a white solid (**3b**); ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, $J = 6.49$ Hz, 3H), 1.26 (m, 12H), 1.58 (m, 2H), 2.12 (m, 3H), 2.35 (m, 4H), 2.64 (m, 4H), 3.07/2.95 (3H), 3.48 (s, 4H); FT-IR (film in $CHCl_3$): 1636 cm^{-1} (C=O$_{amide}$).

Formation of 4b: Block copolymer **4b** was prepared in a similar fashion to **3b** with 1.0 g of **4a**. Yield: 0.90 g (90%); ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, $J =$ 6.49 Hz, 3H), 1.25 (m, 12H), 1.64 (m, 6H), 2.11 (m, 5H), 3.06/2.95 (3H), 3.47 ppm (s, 4H); FTIR (film in $CHCl_3$): $\tilde{\nu} = 1636$ cm^{-1} (C=O$_{amide}$).

Macroligand synthesis 3: The hydrolyzed block copolymer **3b** (100 mg, 0.025 mmol), PPM (23 mg, 0.05 mmol), and dicyclohexylcarbodiimide (DCC) (15 mg, 0.07 mmol) were dissolved in degassed dichloromethane (4 mL). The reaction mixture was stirred over night at room temperature. A white precipitate of dicyclohexylurea (DHU) indicates the reaction progress. After one more day the DHU was removed by filtration and the clear filtrate was evaporated till dryness. The residue was dissolved in degassed water (10 mL). The aqueous phase was washed twice with degassed ethyl acetate and finally evaporated till dryness affording macroligand **3** as a white powder. Yield: 110 mg (89%) of a white powder. ^{1}H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J = 6.58$ Hz, 3H), 1.25 (m, 12H), 1.58 (m, 2H), 2.11 (m, 3H), 2.63 (m, 4H), 3.05/2.94 (3H), 3.20 (m, 3H), 3.46 (s, 4H), 7.33 ppm (m, 20H); ^{31}P NMR ($CDCl_3$): $\delta = -7.12, -21.01$ ppm.

Macroligand 4: Ligand **4** was prepared by the procedure described for **3** above with **4b** (100 mg), PPM (22 mg, 0.05 mmol) and DCC (15 mg, 0.07 mmol). Yield: 110 mg (90%); ^{1}H NMR ($CDCl_3$): $\delta = 0.84$ (t, $J =$ 6.49 Hz, 3H), 1.23 (m, 12H), 1.55 (m, 6H), 2.08 (m, 5H), 2.34 (m, 4H), 3.02/2.93 (3H), 3.17 (m, 3H), 3.44 (s, 4H), 7.33 ppm (m, 20H); ^{31}P NMR ($CDCl_3$): $\delta = -8.11, -21.77$ ppm.

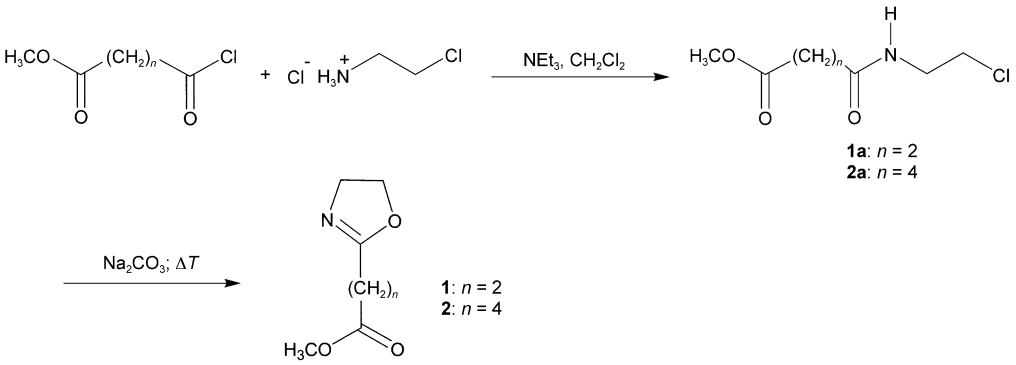
General procedure for the hydrogenation experiments: $[Rh(cod)_2]BF_4$ was added to a Schlenk tube under argon atmosphere and suspended in degassed water (2 mL). Macroligand **3** was dissolved in degassed water (3 mL) and added to the suspension of the rhodium precursor. After stirring for 50 minutes a yellow solution was formed. (*Z*)-methyl α-acetamidocinnamate or its free acid was added, the stirrer speed was increased to 1200 rpm and the inert gas was replaced by a hydrogen atmosphere (1 bar H_2). The hydrogenation was stopped by filling the Schlenk tube with nitrogen. The reaction mixture was extracted twice by stirring with degassed ethyl acetate (10 mL) for 20 min. The combined organic phases were evaporated to dryness and the residue was subjected to ^{1}H NMR and chiral HPLC analysis. The aqueous phase retaining the rhodium catalyst was used in further cycles.

Results and Discussion

The enantioselective hydrogenation of *N*-acyldehydroamino acids and their esters constitutes a standard tool for the synthesis of optically active amino acids.[20] In particular, rhodium–phosphane-based catalysts have been thoroughly investigated, and many efficient chiral ligands have been developed for this purpose.[21] For a successful amphiphilic and functional polymer support, two main features have to be optimized: 1) synthesis of the amphiphilic diblock copolymer and 2) efficient introduction of the chiral ligand in the polymer either directly through suitable monomers or in a polymer-analogous modification step. The cationic ring-opening polymerization of 2-oxazolines provides a versatile monomer system, which allows the synthesis of amphiphilic polymers with different architecture and composition, such as block copolymers, graft copolymers, or dendrimers.[22] In a recent paper we reported on the synthesis of amphiphilic block copolymers with pendent triphenylphosphine groups in the hydrophobic block. The synthetic strategy involved the preparation of an amphiphilic block-copolymer precursor with iodophenyl groups in the hydrophobic block; these were transformed in a Pd catalyzed reaction in the presence of diphenylphosphine to the desired triphenylphosphine ligand.[17] Direct polymerization of a triphenylphosphine-modified 2-oxazoline monomer failed due to the nucleophilic character of the ligand, which interferes with the cationic polymerization mechanism.[19] Based on these results, a similar route was chosen to introduce the asymmetric ligand (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphinomethyl) pyrrolidine (PPM) into an amphiphilic block copolymer. The synthetic scheme can be divided into three steps: 1) the synthesis of an amphiphilic block copolymer precursor with ester groups in the hydrophobic block, 2) polymer analogous ester cleavage and generation of free carboxylic acid groups, and 3) coupling of the amino functionalized PPM ligand with the carboxylic acid groups.

Monomer synthesis: The ester-functionalized 2-oxazoline monomers **1** and **2** were synthesized according to a modified two-step procedure by Levy and Litt.[23] 2-Chloroethylammonium chloride was treated with methyl succinyl chloride to form the intermediate **1a**. Triethyl ammonium chloride precipitates during the reaction and was separated by addition of water and decantation of the aqueous phase. The ring-closing step was performed by heating a neat solution of **1a** with water-free sodium carbonate carefully giving **1** after distillation of the mixture in fine vacuum as a colorless liquid. Monomer **2** was prepared in a similar fashion (see Scheme 1). The structure and purity of the monomers were confirmed by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

Synthesis of the polymeric macroligands: For the synthesis of diblock copolymers based on monomer **1** and 2-methyl-2-oxazoline, it was important to find out, if the weakly nucleophilic ester functionality would interfere with the cationic polymerization mechanism. Thus, a homopolymer of **1** was prepared with a monomer/initiator ratio [**1**]:[initiator] = 10. The polymerization was initiated with methyl triflate at 0 °C; after 12 h the reaction was terminated with piperidine. The polymer was precipitated in diethyl ether and characterized with ^{1}H NMR and IR spectroscopy and size exclusion chromatography (SEC). Proton spectra showed typical signals for the polymer backbone between $\delta = 3.4$ and 3.6 ppm and a sharp peak at $\delta = 3.7$ ppm for the methyl group of the ester functionality (see Figure 1). The degree of polymerization was calculated based on ^{1}H NMR end-group analysis and gave a value of 11 (theoretical 10) and polydispersity M_w/M_n of 1.17, indicating clearly that the ester functions do not interfere with the cationic ring-opening polymerization mechanism. This opens the opportunity to introduce carboxylic acid functionalities into poly(2-oxazoline)s by the ester route and to utilize them for post-analogous coupling of amino- or hydroxy-functionalized ligands to the polymer backbone.



Scheme 1. Synthesis of the 2-oxazoline monomers **1** and **2** with ester functionalities.

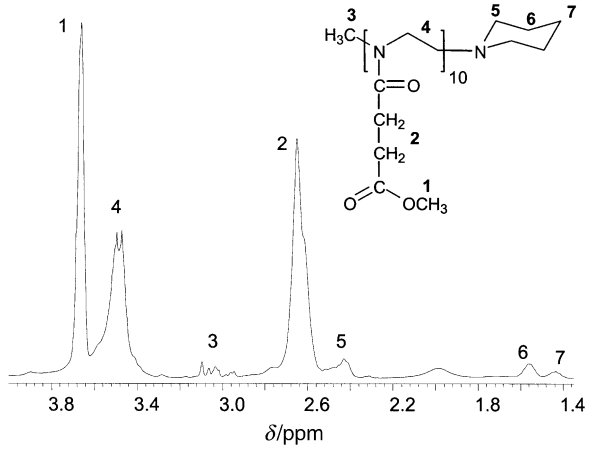


Figure 1. ^{1}H NMR of poly(**1**) in $CDCl_3$, 300 MHz, $T = 20\,^\circ C$.

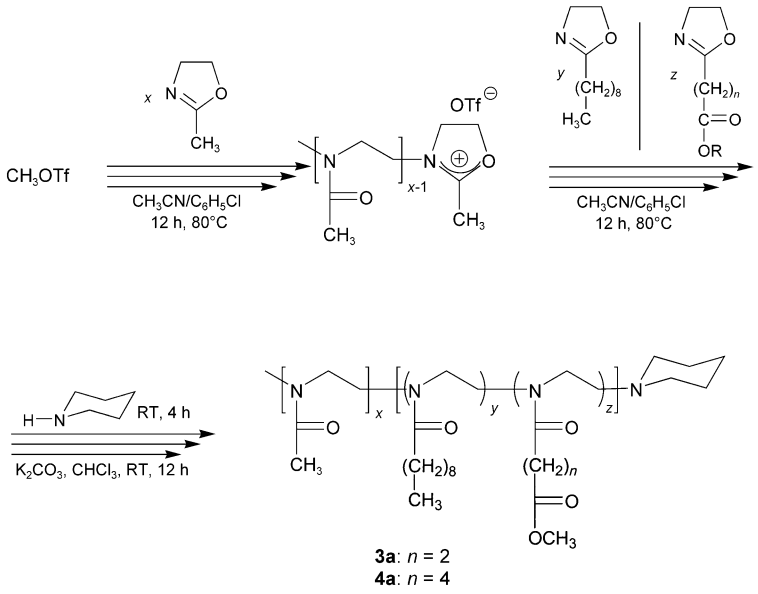
Table 1. Analytical data of the synthesized block copolymers with ester functionality.

Polymer	$x:y:z_{exp}$[a]	$x:y:z_{NMR}$[a]	M_n (NMR)[b]	Yield [%]	M_w/M_n[c]
3a	30:4:4	32:4.1:4.3	4320 (4070)	62	1.28
4a	30:4:4	29:3.7:3.6	3960 (4180)	71	1.29

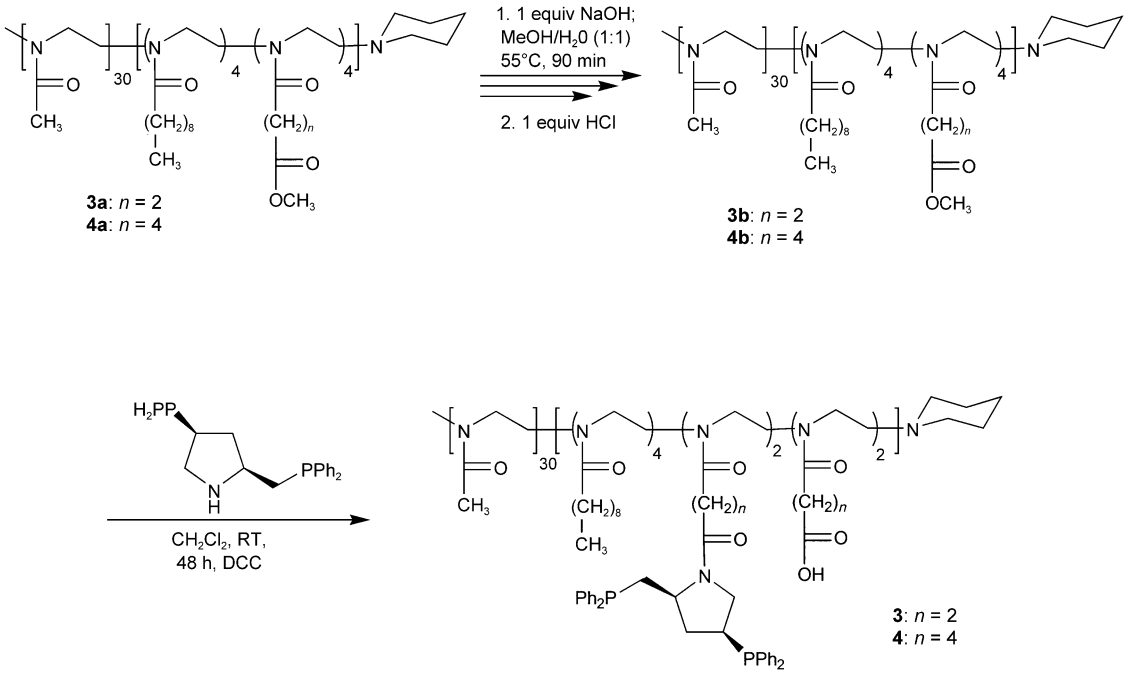
[a] x,y,z = number of repeating units according to polymer structure in Scheme 2. [b] Calculated by ^{1}H NMR end group analysis; brackets: theoretical expected value. [c] Based on calibration with PS standards in chloroform.

In the next step, diblock copolymers **3a** and **4a** were prepared by sequential polymerization of 2-methyl-2-oxazoline to form the hydrophilic block that provides water-solubility, and subsequently a mixture of **1** or **2** and 2-nonyl-2-oxazoline was used to form the second block. 2-Nonyl-2-oxazoline was hereby added to increase the hydrophobicity of the second polymer block. The synthesis is depicted in Scheme 2.

As solvent, a mixture of acetonitrile and chlorobenzene ($v/v = 2{:}1$) was used to guarantee homogeneous reaction conditions. Table 1 summarizes the analytical results obtained by ^{1}H NMR spectroscopy; these data confirm the structure of the resulting polymers. Size-exclusion chromatography gave monomodal curves with polydispersity indices ranging from 1.28 to 1.29. In the next step (Scheme 3), the ester functionality was hydrolyzed. Conditions had to be chosen carefully to allow for quantitative ester hydrolysis on the one hand and to avoid cleavage of the amide function on the other, which would result in linear polyethyleneimine. Methanol was chosen as co-solvent to reduce micelle formation and thus increase hydrolysis efficiency.[24] Quenching with one equivalent of HCl gave the desired free carboxylic acid groups (**3b** and **4b**). ^{1}H NMR analysis indicated successful carboxylic acid formation as can be visualized by the disappearance of the peak at 3.7 ppm (see Figure 2). Coupling of the chiral diphosphane ligand PPM to the polymer was accomplished using dicyclohexylcarbodiimide (DCC) as activation agent. We used a 100 % excess of the carboxylic acid function versus the amine group of PPM in



Scheme 2. Synthesis of the polymer precursors **3a** and **4a**.



Scheme 3. Preparation of polymeric macroligand **3** and **4**.

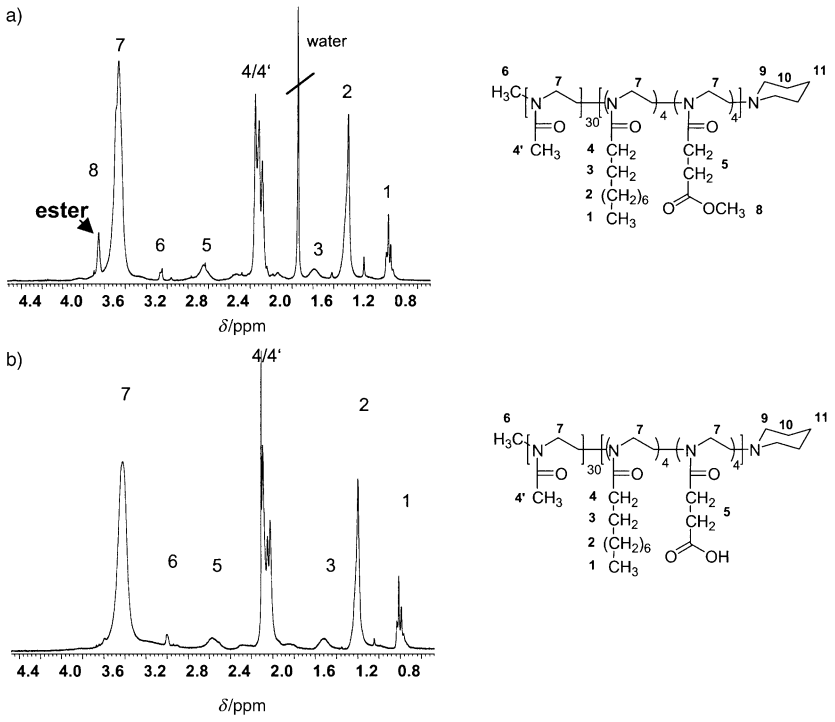


Figure 2. ^{1}H NMR spectra ($CDCl_3$, 300 MHz, $T = 20\,^\circ C$) of a) before (**3a**) and b) after (**3b**) hydrolysis of the ester functionalities.

the coupling reaction to allow for quantitative coupling of the expensive ligand to the polymer (**3** and **4**). Successful coupling can be followed by ^{31}P NMR spectroscopy. Whereas the free PPM ligand displays two signals at $\delta = -3.77$ and -19.93 ppm, we observed a shift of these two signals to $\delta = -7.10$ and $-20{,}94$ ppm (see Figure 3), which is in good agreement with the commercially available boc-PPM derivative, which has two signals at $\delta = -6.92$ and -20.45 ppm.

Hydrogenation: The rhodium-complex-catalyzed asymmetric hydrogenation of unsaturated amino acid derivatives in water in the presence of low molecular weight surfactants and polymeric amphiphiles has already been intensively investigated.[25] The addition of amphiphiles increased the solubility of the hydrophobic substrates and enhances in most cases both the activity and enantioselectivity of the catalytic process.[26] The rhodium(I)-complex-catalyzed asymmetric hydrogenation of (*Z*)-α-acetamido cinnamic acid (**A**) and methyl (*Z*)-α-acetamido cinnamate (**B**) was chosen to study the influence of the polymer-bound catalyst system (Scheme 4).

In order to make sure, that micelles are formed during the catalytic experiments, the critical micelle concentration (cmc) of **4a**, **4b**, and **4** was determined by fluorescence spectroscopy. This method gave values for the cmc of **4a** of 0.8 μM, which increased for **4b** with free carboxylic acids groups to 12.6 μM, and decreased again to 1.0 μM for macroligand **4**. The concentration of the polymeric macroligand **3** or **4** in the catalytic experiments was 0.9 mmol, which was about 1000-fold well above the critical micelle concentration (cmc). The active catalyst can be directly formed in aqueous solution; the polymer–metal

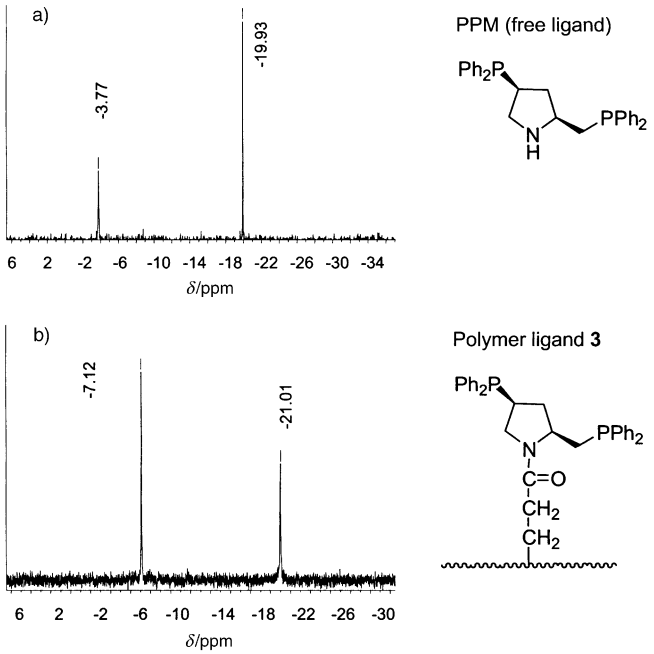
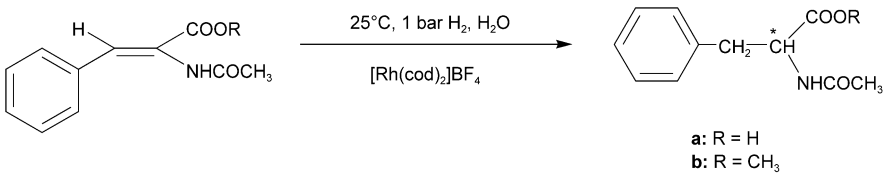


Figure 3. ^{31}P NMR (121.5 MHz, $CDCl_3$, $T = 20\,^{\circ}C$) spectra of a) free PPM, b) polymer-bound PPM in **3**.



Scheme 4. Asymmetric hydrogenation of different substrates a) (*Z*)-α-acetamido cinnamic acid and b) methyl (*Z*)-α-acetamido cinnamate.

complex dissolves in water to give a deep yellow solution, the ^{31}P NMR spectrum of which has two signal groups at 17 ppm and 44 ppm; these values are in good agreement with the results reported by Malmström and Anderson.[27] Unreacted substrate and product can be extracted with ethyl acetate by more than 98% and conversion was determined by ^{1}H NMR spectroscopy. Enantioselective hydrogenation of substrate A proceeded under atmospheric hydrogen pressure in water to give (*R*)-*N*-acetylphenylalanine in moderate yield (Table 2, 45–48%, entries 1, 2). The low reactivity of the substrate can be attributed to the high polarity, which most likely prevents efficient solubilization in the micellar core. The activity of hydrogenation was notably enhanced when the more hydrophobic substrate methyl (*Z*)-α-acetamido cinnamate was used (Table 2, entries 3–5). Conversion of 90 to 95% was observed after 20 min reaction time and enantioselectivities of 85% were obtained, compared to the results of Andersson et al., who reported on 100% conversion after 13–16 h with an enantiomeric excess of 24 and 27 (*R*) in neat water and 100% conversion after 18 h reaction time with an enantiomeric excess of 67% (*R*) in a water/ethyl acetate mixture.[27] Our results demonstrate clearly, that the amphiphilic block-copolymer supports are superior over the water-soluble homopolymer counterparts and give even better results than biphasic reaction conditions in transforming the more hydrophobic methyl (*Z*)-α-acetamido cinnamate in aqueous solution. A kinetic investigation indicated a zero-order reaction rate (see Figure 4); this is in excellent agreement with the results found by J. Halpern et al.[28] A slightly higher activity of 15% was observed macroligand **3** than for **4**, whereby the PMM ligand is bound to the polymer backbone via a C2 versus a C4 linker and turn over frequencies (TOF) of 142 and 122 h^{-1}, respectively, were obtained (see Figure 4). However, more experiments with longer alkyl spacer are necessary to elucidate the correlation of spacer length, micellar characteristics, and finally catalytic result in more detail. In addition, after the reaction was complete, the product was easily separated by extraction with ethyl acetate. The recovered aqueous phase containing the catalyst was reused in the second hydrogenation cycle to give the same enantiomeric excess (Table 2, entry 5, 86% *ee*) with a slightly reduced activity in the second cycle of 90%. Rhodium content of the isolated products as determined by ICP-AES indicated 3–4% loss of the metal after each cycle; this is probably due to residual water with solubilized macroligand in the organic phase and incomplete

Table 2. Analytical data of the hydrogenation experiments.[a]

	Substrate	Macro-ligand	Conversion [%][b]	Reaction time [h]	*ee* [%][c]	Rh [%][d]	TOF [h^{-1}][f]
1	A	**3**	46	24	n.d.	n.d.	0.96
2	A	**4**	48	24	n.d.	n.d.	1.00
3	B	**4**	90	0.37	85 (*R*)	0.03–0.04	122
4	B	**3**	94	0.33	85 (*R*)	0.03–0.04	142
5[e]	B	**4**	81	0.37	85 (*R*)	0.03–0.04	110

[a] Rh:olefin = 1:50; $T = 25\,^{\circ}C$, 1 bar H_2 pressure. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC. [d] Rhodium content of the isolated product as determined by ICP-AES. [e] Recycled catalyst from entry 4, second cycle. [f] TOF = n(product)/n(cat) × conversion × 1/h).

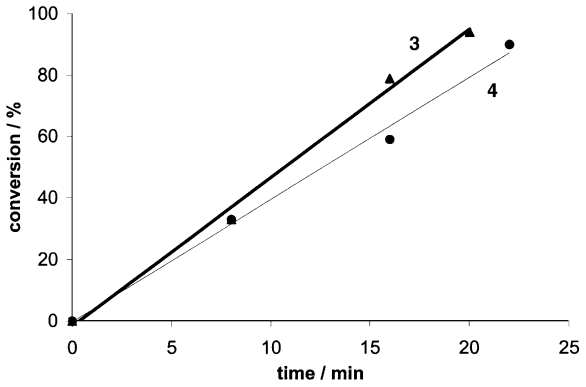


Figure 4. Kinetic study of the hydrogenation of methyl (*Z*)-α-acetamido cinnamate in the presence of macroligands **4** and **3** (see Table 2, entries 3 and 4).

phase separation. Moreover, we assume, that after the extraction with ethyl acetate a considerable amount of the solvent stays solubilized in the micellar core; this prevents efficient solubilization of the substrate again and, in addition, is responsible for the reduced activity in the second cycle. New developments in catalyst separation, such as nanofiltration are particularly interesting for such soluble support systems, owing to the higher molecular weight of the polymer-bound ligand, and have already been proven to be very useful in catalyst recycling without any loss of activity in a second or third cycle and will help to overcome this problem in future experiments.[29]

Conclusion

In conclusion, we have developed a novel amphiphilic, water-soluble polymer support with chiral (2*S*,4*S*)-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine ligands covalently linked to the hydrophobic block. These polymers were found to be effective catalysts for the enantioselective hydrogenation of methyl (*Z*)-α-acetamido cinnamate in aqueous media with enantioselectivities of 86% and 90–95% yield after 20 minutes reaction time. The results described in this paper clearly illustrate the advantages of amphiphilic block copolymers for the efficient transformation of hydrophobic substrates in water. We anticipate that the accessibility and structural versatility of this amphiphilic polymer support system will render very promising catalysts and will be of general use for other transition-metal-catalyzed reactions of hydrophobic substrates in aqueous solution.

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