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# Enantioselective hydrogenation in water catalysed by rhodium phosphine complexes bound to polyacrylic acid [1]

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**Abstract**

The coupling of (2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphino-methylpyrrolidine (PPM) to polyacrylic acid demonstrates an easy way to prepare a water-soluble analogue of the parent ligand. The water solubility of the macromolecular ligand is high and this property can be varied by changing the phosphine to carboxylate ratio on the polymer. Reaction of the macromolecular ligand with bis-norbornadienerhodium(I) triflate [$Rh(NBD)_2$]OTf yield a polymer-bound cationic rhodium phosphine complex catalyst which is active in enantioselective hydrogenation in water or under biphasic conditions ($H_2O$:EtOAc). Hydrogenations of different prochiral enamide precursors give the corresponding aminoacid derivative in moderate to good ee:s, the best enantioselectivity is obtained for α-acetamido cinnamic acid (**1a**) giving *N*-acetyl-(*R*)-phenylalanine (**2a**) in 89% ee. The enantioselectivity is dependent on the phosphorus loading on the polymer being high at low loading and low at high loading. The enantioselectivity of the catalysts decreases by increasing $H_2$ pressure up to 22 bar where it remains constant. The aqueous catalysts solutions are easily recovered and recycled by phase separation with no loss in enantioselectivity. 

*Keywords:* Water-soluble phosphines; Rhodium; Polyacrylic acid; Biphasic; Enantioselective hydrogenation

## 1. Introduction

The use of water-soluble phosphine complexes have attained increased interest the last decade [2–4], the main impetus being related to easier recovery and reuse of the catalyst in biphasic or supported aqueous phase catalysis (SAPC) [5,6]. By combining an aqueous phase, containing the catalyst, and a nonmiscible organic phase, containing the substrate and the product, the problem of catalyst recovery and reuse simplifies to a phase separation problem [7,8].

The introduction of polar functional substituents, such as ammonium [9,10], carboxylate [11,12] or sulfonate groups [13–15] to a parent phosphine is the most widely used method to render a phosphine water soluble. The preparation of monosulfonated triphenyl phosphine (TPPMS) marks the starting point in the development [13–15] and application of water-soluble phosphines [16,17]. Trisulfonated triphenylphosphine (TPPTS) is the prototype ligand in the field and concomitant with improvements in the synthesis and purification of TPPTS [18]

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[1] See Ref. [1].

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its coordination chemistry and catalytic chemistry have progressed [19,20]. Complexes of TPPTS have been utilised in rhodium catalysed hydrogenations of olefins [21,22], palladium catalysed telomerisations of dienes [23,24] and platinum catalysed amination of isoprene [25] just to mention a few catalytic applications. The TPPTS ligand is also used industrially in the Ruhrchemie/Rhone-Poulenc process for the hydroformylation of propene [26].

The use of chiral catalysts is one of the most important advances in asymmetric synthesis [27–29] and chiral catalysis is widely applied in laboratory scale enantioselective hydrogenations [30,31], hydrosilylations [32] and hydroformylations of olefins [33]. New chiral phosphine ligands are constantly added to the list of known ones of which BINAP [34], DIPAMP [35], DIOP [36] and Chiraphos [37] are perhaps some of the most well known. These ligands have been used to prepare rhodium and ruthenium complexes which are active in enantioselective hydrogenation of prochiral enamide precursors, with enantioselectivities reaching almost 100% [38]. Monsanto has also developed an industrial process for the manufacturing of L-DOPA using rhodium catalyst based on chiral phosphines [39].

Difficulties to separate the catalyst from the product without concomitant catalyst decomposition are inherent to homogeneous catalysts and for catalysts based on expensive chiral ligands this aspect becomes a serious drawback. Application of water-soluble chiral phosphines [40–43], as ligands in enantioselective hydrogenation catalysts, have demonstrated that the problem of separation and reuse can be solved. Sulfonated BINAP has also been used as a ligand in asymmetric hydrogenations [44] and ee:s in the range of 90% have been reported. However, the general trend is a lower enantioselectivity on going from organic solvents to water. This observation has been explained by the high solvophobicity parameter of water [45].

We have previously reported on the preparation of water-soluble phosphine complexes using water-soluble polymers as charge carrying units [46]. The extension of this concept to bidentate chiral phosphines using (2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (PPM) [47] bound to polyacrylic acid has been communicated [1] and in the present study further results concerning the hydrogenation of different enamide precursors are reported. A dramatic effect on enantioselectivity depending on phosphorus loading has been observed. We also demonstrate how the $H_2$ pressure influences the enantioselectivity.

## 2. Experimental

### *2.1. General*

The ligands and the complexes were handled under an inert atmosphere. Organic solvents of p.a. quality were distilled and degassed prior to use and water was doubly distilled and degassed. NMR spectra were recorded on a Varian 300 Unity spectrometer with a transmitter frequency of 121.434 MHz for $^{31}$P NMR and 299.779 MHz for $^{1}$H. $^{31}$P shifts are given with $H_3PO_4$ as external standard, positive values down field, and $^{1}$H shifts are given relative to TMS. IR spectra were recorded on a Nicolette 20 SXC or a Bio-Rad FTS 6000 spectrometer. The enantiomeric excess was determined by polarimetry using a Perkin–Elmer 241 polarimeter. Hydrogenations at elevated pressure were performed in glass tubes fitted into a Roth stainless steel autoclave with magnetic stirring. $[Rh(NBD)_2]OTf$ was prepared according to the literature [48]. The PPM ligand (Merck) and polyacrylic acid (PAA, 63% water solution, Merck) were used as received. α-Acetamido cinnamic acid (**1a**; Acros) was recrystallised from ethanol prior to use. The methyl ester of acetamido cinnamic acid was prepared using trimethylsilylazomethane as methylating agent. High-grade hydrogen (5.7) was supplied by AGA, Sweden. Elemental analysis were performed by AB Mikro Kemi Uppsala, Sweden.

Rhodium analysis were done by Analytica, Solna, Sweden.

### 2.2. Preparation of the PAA–PPM ligands

All ligands **A**–**E** given in Table 1 were synthesised in an analogues way, and the following describes the synthesis of ligand **A**.

A 1.25-g amount of polyacrylic acid (PAA, 63% in $H_2O$) was dissolved in 32 ml THF:water (5:1) mixture. Then, 600 mg of the PPM ligand (1.32 mmol), dissolved in 8 ml THF, was added to the flask. Addition of DCC (340 mg, 1.65 mmol), dissolved in 7 ml THF, was done dropwise over 30 min. The reaction mixture was then left stirring at ambient temperature over night giving a white precipitate of dicyclohexylurea (DHU). The THF was evaporated and 5 ml of water added to the remaining slurry. The pH was adjusted to 8 with $Na_2CO_3$ and the solution stirred for 30 min to ensure complete dissolution of the product. Precipitated DHU was removed by filtration. The precipitate was washed twice with water (5 ml) and the combined water solutions were evaporated till dryness affording 1.59 g of ligand **A** as a white powder.

$^{31}$P NMR ($D_2O$): $-7.5$ (s), $-20.8$ (s) ppm.

IR (KBr) $\nu_{C=O}$: 1610 $cm^{-1}$ amidcarbonyl; 1580 and 1404 $cm^{-1}$ carboxylate anion.

The elemental analysis (N and P) for all the ligands are given in Table 1.

All the catalysts prepared from the different ligands **A–E**, containing different amounts of phosphorus, are in the following text referred to as $\mathbf{Cat_{A-E}}$.

Table 1
Conditions used in the preparation of the ligands and analytical data

| Ligand | g PAA (63% $H_2O$) | mg PPM (mmol) | Elemental analysis |
|---|---|---|---|
| **A** | 1.25 | 600 (1.32) | N: 1.0%, P: 4.0% |
| **B** | 1.35 | 500 (1.10) | N: 0.9%, P: 3.0% |
| **C** | 1.10 | 100 (0.22) | N: 0.4%, P: 1.4% |
| **D** | 4.40 | 100 (0.22) | N: 0.3%, P: 1.0% |
| **E** | 0.55 | 100 (0.22) | N: 0.05%, P: 0.24% |

### 2.3. Isolation of catalyst $Cat_A$ [[(L–L)Rh-(NBD)]$^+OTf^-$ (L–L = ligand A)]

A Schlenk tube containing 5 ml water was charged with 254 mg of ligand **A** (0.33 mmol P). [Rh(NBD)$_2$]OTf (68 mg, 0.16 mmol) was added and the slurry stirred at ambient temperature for 30 min. The resulting homogeneous orange-coloured water solution was washed once with $CH_2Cl_2$. Phase separation and evaporation of the aqueous phase gave 320 mg of $\mathbf{Cat_A}$ as an orange powder.

$^{31}$P NMR ($D_2O$): 48.82 (broad), 16.40 (broad) ppm.

### 2.4. Reaction of $Cat_A$ with $H_2$

Twenty milligrams of $\mathbf{Cat_A}$ (0.012 mmol Rh) was dissolved in 1.5 ml $D_2O$ in a Schlenk tube. The tube was evacuated and filled with nitrogen three times before introducing $H_2$. The solution was stirred for 30 min after which it was transferred to a nitrogen-filled NMR tube via syringe and a septa.$^{31}$P NMR ($D_2O$): 39.38 (broad), 67.64 (broad) ppm.

### 2.5. Biphasic hydrogenation using $Cat_{A-E}$ at atmospheric pressure and ambient temperature

All the catalysts used in the hydrogenations were prepared in situ (vide infra). All reactions were carried out at 1.5 mM rhodium concentration in the reactor with a P:Rh ratio of 2.1. The following exemplifies the procedure for catalysts $\mathbf{Cat_A}$. 7.3 mg of ligand **A** (0.0096 mmol P) was dissolved in 3 ml $H_2O$ in a Schlenk tube. [Rh(NBD)$_2$]OTf (1.95 mg, 0.0045 mmol) was added and the solution was stirred until all the Rh precursor had dissolved. Three milliliters of EtOAc (or EtOAc/bensen 1:1) was added to the solution followed by addition of the substrate (91.9 mg **1a** 0.45 mmol or 48 mg α-acetamido cinnamic methyl ester (**1b**) 0.23

mmol) and by evacuation and refilling of the Schlenk tube with $H_2$ twice. The reaction was started by starting the magnetic stirrer. The pressure of $H_2$ was kept constant by keeping a slow flow of $H_2$ through the reaction mixture. The reaction was stopped (see reactions time in Table 2) and the organic phase separated, the aqueous phase extracted twice with EtOAc and twice with $Et_2O$. The combined organic phases were dried with $Na_2SO_4$, filtered and evaporated until dryness before subjected to NMR and polarimetric analysis.

Recycling of the catalyst solutions were carried out under argon by the following method: The reactant solution from the initial run was phase separated. The aqueous phase, containing the catalyst, was washed twice with EtOAc and twice with $Et_2O$, after which it was transferred back to the reaction vessel and used as above in a second run.

For the hydrogenation in neat water the catalyst solutions were prepared in situ as described above. **1a** (s) was added and pH adjusted to 8 with $Na_2CO_3$ (s) whereby the acid dissolved. After the reaction the pH of the reaction solution was adjusted to 4 by addition of $CH_3SO_3H$ and then extracted as described above. The conversion was determined with $^1H$ NMR (see Table 2).

### *2.6. Slurry hydrogenation at elevated pressure using $Cat_{A-E}$*

All reactions were carried out at 1.5 mM rhodium concentration in the reactor with a

Table 2
Conditions and results of the hydrogenations

| Entry (substrate) | Rh:olefin[a] | Solvent | Ligand | Conversion[b] % (time h) | ee % (configuration)[c] | Remark[d] |
|---|---|---|---|---|---|---|
| 1 (**1a**) | 1:100 | MeOH | **B** | 100 (4) | 21 (*R*) | |
| 2 (**1a**) | 1:100 | MeOH | **D** | 100 (4) | 24 (*R*) | |
| 3 (**1a**) | 1:100 | $H_2O$ | **B** | 78 (18) | 62 (*R*) | pH > 8 |
| 4 (**1a**) | 1:100 | $H_2O$ | **D** | 70 (18) | 70 (*R*) | pH > 8 |
| 5 (**1a**) | 1:70 | $H_2O$/EtOAc | **A** | 100 (6) | 72 (*R*) | |
| 6 (**1a**) | 1:100 | $H_2O$/EtOAc | **B** | 100 (6.5) | 76 (*R*) | |
| 7 (**1a**) | 1:100 | $H_2O$/EtOAc | **C** | 100 (4.5) | 82 (*R*) | |
| 8 (**1a**) | 1:100 | $H_2O$/EtOAc | **D** | 100 (5) | 89 (*R*) | |
| 9 (**1a**) | 1:100 | $H_2O$/EtOAc | **E** | 90 (5) | 54 (*R*) | |
| 10 (**1a**) | 1:100 | $H_2O$/EtOAc | **B** | 100 (5) | 81 (*R*) | 50 mM $NaClO_4$ |
| 11 (**1a**) | 1:100 | $H_2O$/EtOAc | **B** | 100 (8) | 71 (*R*) | 100 mM $NaClO_4$ |
| 12 (**1a**) | 1:100 | $H_2O$/EtOAc | **B** | 100 (8) | 54 (*R*) | 1.0 M $NaClO_4$ |
| 13 (**1a**) | 1:100 | $H_2O$/EtOAc | **D** | 100 (8) | 72 (*R*) | 50 mM $NaClO_4$ |
| 14 (**1a**) | 1:100 | $H_2O$/EtOAc | **D** | 100 (7.5) | 58 (*R*) | 200 mM $NaClO_4$ |
| 17 (**1a**) | 1:100 | $H_2O$ | **A** | 100 (15) | 61 (*R*) | slurry 14 bar, 60°C |
| 18 (**1a**) | 1:100 | $H_2O$ | **D** | 100 (15) | 74 (*R*) | slurry 14 bar, 60°C |
| 19 (**1b**) | 1:50 | $H_2O$/EtOAc | **B** | 100 (18) | 53 (*R*) | |
| 20 (**1b**) | 1:50 | $H_2O$/$C_6H_6$/EtOAc | **B** | 50 (18) | 58 (*R*) | |
| 21a (**1b**) | 1:50 | $H_2O$/EtOAc | **D** | 100 (18) | 66 (*R*) | |
| 21b (**1b**)[e] | 1:50 | $H_2O$/EtOAc | **D** | 100 (18) | 67 (*R*) | |
| 22a (**1b**) | 1:50 | $H_2O$ | **B** | 100 (13) | 24 (*R*) | slurry 14 bar, 60°C |
| 22b (**1b**)[e] | 1:50 | $H_2O$ | **B** | 100 (16) | 27 (*R*) | slurry 14 bar, 60°C |
| 23a (**1b**) | 1:50 | $H_2O$/$C_6H_6$/EtOAc | **B** | 100 (8) | 27 (*R*) | 14 bar, 60°C |
| 23b (**1b**)[e] | 1:50 | $H_2O$/$C_6H_6$/EtOAc | **B** | 100 (8) | 30 (*R*) | 14 bar, 60°C |

[a] [Rh] = 1.5 mM.
[b] Determined by $^1H$ NMR.
[c] Determined by polarimetry.
[d] If nothing else stated ambient temperature and pressure.
[e] Recycled catalyst.

P:Rh ratio of 2.1. The following procedure exemplifies a typical reaction.

Ligand **C** (21 mg, 0.0095 mmol P) was dissolved in 3 ml $H_2O$ in a Schlenk tube. $[Rh(NBD)_2]OTf$ (1.95 mg, 0.0045 mmol) was added and the solution was stirred until all the Rh precursor had dissolved after which **1a** (46 mg, 0.23 mmol) was added. The resulting slurry was then transferred under argon from the Schlenk tube to the glass tube in the autoclave and the autoclave closed. The autoclave was heated to the selected temperature (ambient or 60°C see Table 2 and Fig. 5) pressurised with $H_2$ and vented three times before the selected pressure (10–50 bar) was set and the reaction commenced by starting the stirring. After reaction the autoclave was vented slowly to bring the pressure down to atmospheric. The reaction mixture was extracted twice with EtOAc and twice with $Et_2O$. The combined organic phases were dried with $Na_2SO_4$, filtered and finally evaporated till dryness.

The yield was determined with $^1$H NMR (see Table 2).

*N*-acetyl-(*S*)-phenylalanine (**2a**): ($CD_3OD$); s, 1.89, C**H**$_3$C(O); dd 2.95 C**H**(H)–CH; dd, 3.10, CH(**H**)–CH; dd, 4.63, C**H**–CH$_2$; m, 7.20, C$_6$**H**$_5$ –. polarimetry $[\alpha]_D^{20} = +46.0$ (c = 1, EtOH) [41] *N*-acetyl-(*S*)-phenylalanine methyl ester (**2b**): ($CDCl_3$); s, 1.89, C**H**$_3$C(O)N; sep, 3.11, C**H**$_2$–CH; s, 3.71, C**H**$_3$C(O); dd, 4.85, C**H**–CH$_2$. polarimetry $[\alpha]_D^{20} = +101.3°$ ($c = 1$, $CHCl_3$) [41].

## 3. Results and discussion

The coupling of the PPM ligand to polyacrylic acid via *N*-acylation, using dicyclohexylcarbodiimide (DCC) [49] as the coupling reagent is an efficient way to convert the PPM ligand to a water-soluble macromolecular ligand (Fig. 1). The coupling step is quantitative, i.e., no unreacted phosphine can be detected in the precipitated DHU (dicyclohexylurea). Work up under slightly alkaline conditions affords the

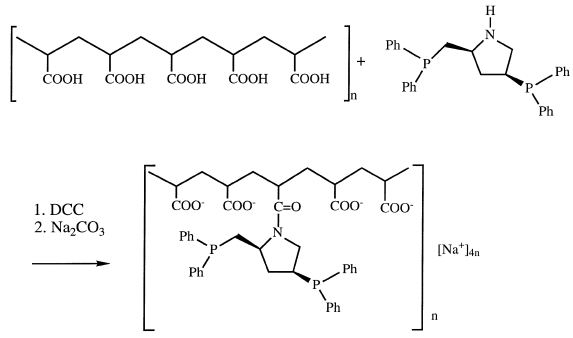


Fig. 1. Preparation of PAA–PPM. The ligands **A**–**E** have different phosphine moiety to carboxylate ratio.

sodium salt of the macromolecular ligand as a white powder. The IR spectrum of the isolated solid shows CO stretching frequencies of the amid at 1610 $cm^{-1}$ and the carboxylate anion at 1580 and 1404 $cm^{-1}$. The $^{31}$P NMR spectrum of the ligand is simple, showing two resonances at −7.5 and −20.8 ppm for the two different phosphines, and these are in good agreement with literature values [49] for the parent PPM ligand displayed at −6.2 and −22.7 ppm. Provided that the synthesis is performed with strict exclusion of oxygen, no phosphine oxide can be detected in the $^{31}$P NMR spectrum of the isolated product. The $^1$H NMR spectrum of the compound is not very informative; besides the phenyl protons it exhibits only broad polymer skeleton resonances which are very difficult to assign unambiguously. The phosphine loading of polyacrylic acid can be varied by changing the amount of phosphine used in the synthesis step and a series of ligands (**A**, **B**, **C**, **D**, and **E**) with 4.0, 3.0, 1.4, 1.0, and 0.24% phosphorus content (Table 1) have been prepared. Ligand **A** containing 4.0 w/w% phosphorus has a maximum solubility of 115 mg/ml water which corresponds to a phosphorus concentration of 0.13 M. The water solubility of the ligands increases as the phosphine loading decreases and ligand **B** has a water solubility of 150 mg/ml (0.14 M P). All the macromolecular ligands **A**–**E** are soluble in methanol in their protonated form.

When a water solution of ligand **A** is reacted with solid $[Rh(NBD)_2]OTf$ (P:Rh = 2.1) the initial slurry slowly turns into an orange homogeneous solution as the complex $[(A)Rh(NBD)]^+$ is formed. This complex can be isolated as an orange solid and its structure verified by the $^{31}P$ NMR spectrum which exhibits two resonances at 16.4 and 48.8 ppm, in good agreement with NMR data previously reported for the corresponding PPM complex in organic solvents [50]. The peaks are very broad (half-line width 800–1000 Hz) thus hampering the determination of the Rh–P coupling constants and this is due to slow tumbling of the large polymeric aggregates which causes fast $T_1$ relaxation [51].

When a water solution of $\mathbf{Cat_A}$ is reacted with $H_2$ for 10 min, the $^{31}P$ NMR spectrum changes, displaying two new resonances at 67.6 and 39.4 ppm. On the basis of the $^{31}P$ NMR resonances for the corresponding $[(BPPM)Rh(MeOH)_2]^+$ complex (BPPM = *N*-butoxy carbonyl protected PPM), which exhibits two sets of resonances at 69.6 and 42.1 ppm [50] and on the observation that bidentate phosphine ligands tends to give the bis–solvato and not bis–hydrido complexes [52], the observed resonances can be assigned to the bis–aqua complex $[(L–L)Rh(H_2O)_2]^+$ (L–L = ligand **A**). Upon treatment of $\mathbf{Cat_A}$ with $H_2$ some phosphine oxide (< 10%) is inevitable formed although performing the hydrogenation with strict exclusion of oxygen. It has previously been shown [53,54] that $H_2O$ can act as oxidant for phosphine oxidations and this possibility can not be ruled out in the present case.

### *3.1. Catalytic hydrogenation of prochiral substrates*

#### *3.1.1. Stability of the catalysts*

Although cationic complexes of the general formula $[Rh(NBD)(L–L)]OTf$ can be isolated readily in a pure state, we have observed that isolated samples, using PAA–PPM as ligand, undergo slow deterioration even upon storage under an argon atmosphere at −20°C. The deterioration is not accompanied by changes in the $^{31}P$ spectrum but the sample acquires a slightly more reddish colour and the catalytic activity of a stored catalyst is substantially lower than that of a fresh catalyst. All the catalysts used in the reduction of prochiral dehydroamino acid precursors (Fig. 2) were therefore prepared in situ by adding $[Rh(NBD)_2]OTf$ to water solutions of the different ligands.

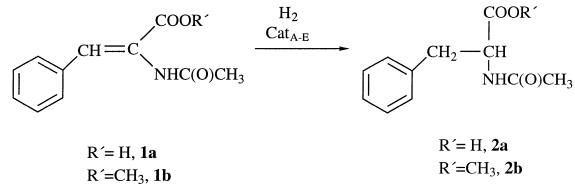


Fig. 2. Hydrogenation of different prochiral olefines.

#### *3.1.2. Hydrogenations at atmospheric pressure*

*3.1.2.1. In methanol.* There are ample previous results regarding the enantioselectivity of cationic rhodium catalysts based on the parent PPM and BPPM ligands in alcohol solvents, e.g., reduction of substrate **1a** gave 6% ee using rhodium complexes of the PPM ligand in ethanol [47] while BPPM ligand based complexes gave 87.1% ee in methanol [50]. This latter enantioselectivity was further improved to 93.5% by addition of triethylamine. The macromolecular ligands we have prepared are also soluble in methanol provided that the carboxylate groups on the polymer are protonated. For the sake of comparison we have therefore investigated two catalysts based on ligands **B** and **D** in the reduction of **1a** in methanol. Although having the pyrrolidine *N*-atom acylated, as in the BPPM ligand, the enantioselectivities obtained 19% and 23%, respectively, (Table 2, entries 1 and 2) are far from those previously obtained with the BPPM ligand. A difference in pH is one factor which differentiate our catalysts from the BPPM based catalyst, but it has previously been shown that there is no conflict between high enantioselectivity and acidic conditions [42]. Having all the carboxylate groups on the polymer proto-

nated, intermolecular hydrogen bonding between the substrate amide group and the carboxylic acid groups on the polymer can interfere with the substrate orienting effect and thus explain the low enantioselectivity.

*3.1.2.2. In water solution*. Substrate **1a** is soluble in water under slightly alkaline (pH > 8) conditions to an extent which enables the hydrogenation to be performed under strict homogeneous conditions. Contrary to the methanol case, the observed enantioselectivities using $\mathbf{Cat_B}$ and $\mathbf{Cat_D}$ in neat water approach those of the BPPM-based catalysts giving 62 and 70% ee, respectively (Table 2, entries 3 and 4).

The catalytic reactions, in water, using $\mathbf{Cat_B}$ and $\mathbf{Cat_D}$ are, however, considerably slower (Table 2) than the corresponding reaction using the BPPM based complexes in methanol [55]. In a homogeneous system there are no phase transfer limitations but despite this the catalytic hydrogenation in neat water at pH 8 is also considerably slower than that observed for the same catalysts under biphasic conditions (vide infra). The low reaction rate is puzzling, but tentatively we suggest that under alkaline conditions, the catalytically active intermediate $[(L–L)Rh(H_2O)_2]^+$ can undergo a protolysis reaction forming a hydroxo-complex or a hydroxo-bridged dimer which exhibits lower catalytic activity. Coordination of the substrate carboxylate group, instead of its amide carbonyl, can also contribute to lower rate. This mode of coordination has previously been observed for acrylic acid under alkaline conditions [56]. Coordination of the substrate carboxylate group can also explain the lower enantioselectivity observed at pH 8. We are currently investigating these aspects using tetrasulfonated-1,4-bis(diphenylphosphino)-butane (DPPBTS) as model ligand which also forms a seven-membered chelate ring with rhodium [57].

*3.1.2.3. Biphasic reactions in water:ethyl acetate*. Catalytic reaction in the biphasic solvent system $H_2O$:EtOAc is, from the standpoint of catalyst recovery, more interesting than in neat solvent systems as water or methanol. Most of the investigations (entries 5–14, 19, 21, Table 2) have therefore been conducted in this solvent system.

*3.1.3. Effect of phosphine loading on the polymer*

Fig. 4 shows how the enantioselectivity varies with the phosphine loading on the polymer (ligands **A**, **B**, **C**, **D**, and **E**) in the hydrogenation of **1a**. From this figure, it is evident that the enantioselectivity is strongly dependent on ligand loading and the curve reaches a maximum at 1% phosphorus content (ligand **D**) giving an ee of 89%. The high enantioselectivity using $\mathbf{Cat_D}$ compares well with the best values reported earlier for biphasic hydrogenations of substrate **1a**. The ligands tetrasulfonated Chiraphos [43] or tetrakis-(paraquaternary amino) derivatives of Chiraphos [42] gave 88% and 92% ee, respectively.

The shape of the curve in Fig. 4 can be explained taking the complex forming properties of the chelating PPM ligand and the special concentration effects imposed by the polymer into account.

The chelate effect is most pronounced for five and six-membered rings while the chelate effect of seven-membered chelates, like the PPM ligand, are expected to be weak [58]. Theoretical considerations have also shown that both chelating and bridging bonding mode must be taken into account dealing with larger chelates [59]. Furthermore, the complex chemistry of rhodium dppb complexes has been shown to be very complicated giving complexes with normal bidentate coordination and complexes with dppb bridging two different rhodium atoms [60,61].

Taking both type of complexes, chelating and bridging, into account in the case of the PAA–PPM ligand the observed variations in the enantioselectivity can be explained. All reactions using ligand **A–E** (Fig. 4) have been performed at a constant phosphine concentration. However, even at the same total concentration there are

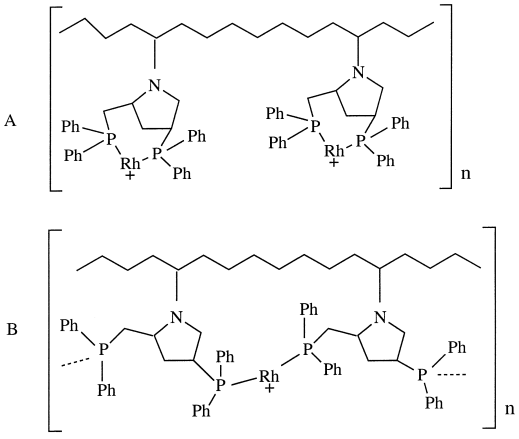


Fig. 3. Schematic representation of the complexes formed. **A**—Expected complex with bidentate coordination of the ligand; **B**—suggested complex aggregate with Rh coordinated to two different phosphine moieties.

large variations in local phosphine concentration due to ligand loading on the polymer, and it is the local concentration that determines the distribution between the two complexes and, thus, the enantioselectivity.

The phosphine moieties are less well separated at high loading than at low loading and consequently the local phosphine concentration increases with increased loading. It is likely that the chelating binding mode of the PPM ligand is preferred at low local concentration of phosphine moieties. Thus, the enantioselectivity is governed by the authentic chelate complex at low loading (Fig. 3A) while at high phosphine loading the enantioselectivity is partially determined by another type of complex (Fig. 3B).

Besides the phosphine loading on the polymer, the local concentration of phosphine moieties is also influenced by the physical shape of the polymer in solution which in turn is controlled by the polymer charge, the electrolyte concentration in solution and the concentration of polymer. The polymer charge and the ionic strength affects the configuration of the individual polymer chains while the concentration of polymer affects the interaction between individual polymers [62].

A linear charge-carrying polymer has a rod-like shape due to electrostatic repulsion between the charged groups (carboxylate in the present case) and the distances between evenly distributed phosphine moieties are thus only dependant on the substitution degree. Increasing the degree of phosphine ligand substitution on the polymer also decreases the number of charged groups which in its turn leads to a transformation to a more coiled shape. Although the total concentration of phosphorus in the solvent phase will remain constant, the net result is an increase in the local concentration of phosphine groups which tend to promote formation of complexes of the second type (Fig. 3B) giving lower enantioselectivity (Fig. 4). The electrostatic repulsion also decreases as positively charged metal moieties are bound to the ligands sites. A decreased electrostatic repulsion between the charged groups on the polymer, and a transformation of the polymer to a more coiled state, can also be achieved by increasing the ionic strength, e.g., by adding $NaClO_4$ to the reaction mixture. As can be seen by comparing the ee:s of entries 6, 10, 11, and 12 or entries 8, 13, and 14 in Table 2, there is a decline in enantioselectivity as the ionic strength increases which we suggest is related to changes of the polymer shape, increasing the local concentration of phosphine moieties and thus change of complex formation. It is also interesting to note that $\mathbf{Cat_D}$ with a lower loading is more sensitive to changes in the ionic strength than $\mathbf{Cat_B}$ with

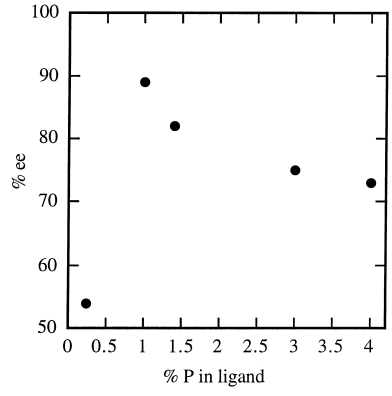


Fig. 4. Hydrogenation of **1a** using $\mathbf{Cat_{A-E}}$. Conditions: [Rh] = 1.5 mM, Rh: olefin 1:100, solvent $H_2O$/EtOAc, $H_2$ 1 bar, ambient temperature.

a higher loading. The enantioselectivity of **Cat$_B$** is not monotonously decreasing (Table 2, entries 6, 10) with increasing concentration of $NaClO_4$ and we refrain to speculate on the origin of this initial increase.

Seemingly the enantioselectivity of **Cat$_E$** falls outside that expected for low loading. One should, however, keep in mind that at such a low loading the total concentration of the charged polymer in the reactor is very high ($\sim$ 4% w/w). This is in the typical concentration range which characterise a cross-over from dilute to semidilute solutions. [2] A levelling-off in the observed enantioselectivity at a certain phosphine loading is not surprising if interchain interactions are taken into account.

The above reasoning is based on an assumption that the complex forming characteristics of the parent PPM ligand changes from pure bidentate to partly bridging as the local phosphine concentration increases. We have tried to verify this assumption spectroscopically but all attempts to show the existence of the suggested bridged complex (Fig. 3B) have failed. This failure demonstrates one of the drawbacks with the present ligand system, the polymer backbone makes a full spectroscopic and analytical characterisation of the complexes very difficult. $^{31}$P NMR is hampered by the broad resonances, previously described, and shift changes on going from a chelate bound to bridging rhodium atom are expected to be small (in the order of the half-line width of our spectra). The UV–VIS spectra of **Cat$_B$** and **Cat$_D$** are also identical, [3] thus giving no further information.

### *3.1.4. Comparison of different substrates and catalyst recycling*

It is well known that the enantioselectivity is substrate dependent and by comparing entries 6 and 19 or 8 and 21 it is obvious that the selectivity is lower for the ester relative to the acid for both **Cat$_B$** and **Cat$_D$**. It is also pleasing to note that the relative trend (**D** > **B**) in enantioselectivity is not substrate dependent but also holds in the case of substrate **1b.** The rather low enantioselectivity (53%) for catalysts based on ligand **B**, in the case of substrate **1b**, can be somewhat improved (58%) by adding benzene to the solvent mixture. A similar effect as a result of changes in the composition of the organic phase has also been observed earlier [41].

Although giving rather poor enantioselectivity the ester **1b** is by virtue of its low solubility in water well suited to demonstrate the feasibility of catalysts recycling and reuse. Taking **Cat$_D$** as an example entries 21a and b (Table 2) give 66% and 67% ee, respectively, clearly demonstrating that these catalysts are easily reused by simple extraction and recycling of the catalyst containing aqueous phase, causing no loss in enantioselectivity. It is also important to stress that no coloration of the organic phase can be seen in the extraction process so the extent of rhodium leakage must be low.

### *3.1.5. Reactions at high pressure*

A fast equilibrium between two diastereomeric olefin complexes and a subsequent rate-determining oxidative addition of $H_2$ to these two olefin complexes are the key reactions in the generally accepted mechanism for asymmetric hydrogenation of dehydroamino acid precursors by cationic Rh(I) complexes [63,64]. Mechanistically, the enantioselectivity relies on a difference in the rate of oxidative addition of $H_2$ to the two diastereomeric complexes and by virtue of a faster addition to the minor diastereomer this gives rise to the major enantiomer. A consequence of the mechanism is that any changes in the reaction conditions, which increases the rate of oxidative addition of $H_2$, will lead to changes in enantioselectivity and ultimately it will be determined by the relative stability of

[2] The crossover from a dilute to a semidilute polymer solution is described by the characteristic concentration $C*$. Values of $C*$ typically lies in the range of 0.1–10% (w/w).

[3] Absorption at 330 and 470 nm.

the two diastereomeric olefin complexes. The rate of oxidative addition can basically be influenced in two ways: intrinsically by alterations which changes the rate constant for the oxidative addition or extrinsically by changing the effective concentration of $H_2$. Fully in accordance with the mechanism, the enantioselectivity of cationic Rh(I) complexes of the BPPM ligand have been shown to be very pressure dependent up to a limiting level [50]. Moreover, rhodium complexes of chiral phosphines, designed to oxidatively add $H_2$ fast, have been shown to give lower chiral induction and to be less pressure sensitive [65], i.e., the share of the product derived from the major diastereomer is substantial already at 1 atm.

Slurry hydrogenation of **1a** with $\mathbf{Cat_C}$ at different pressures give an initial decrease in enantioselectivity, as the pressure is increased, but above 22 bar the enantioselectivity is pressure independent (Fig. 5). A limiting value of 22 bar is considerably lower than that previously observed for catalysts based on the parent BPPM ligand in methanol and is probably a reflection of a faster oxidative addition of $H_2$ in aqueous solvent than in methanol. Recent experimental results provide clear support for this conclusion, i.e., the oxidative addition of $H_2$ to a Ir–TPPMS complex was found to be 40 times faster in water than in toluene due to a more stable polar transition state in the more polar solvent [66,67].

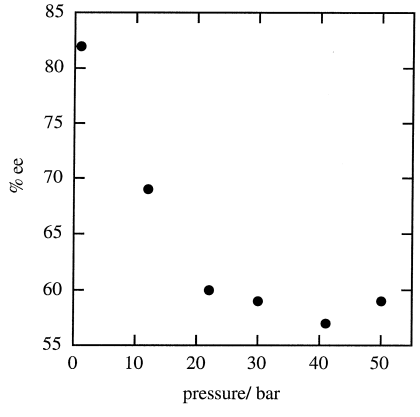


Fig. 5. Hydrogenation of **1a** at different $H_2$ pressure. Conditions: $\mathbf{Cat_C}$, [Rh] = 1.5 mM, Rh: olefin 1:50, solvent $H_2O$.

Additionally we have compared the enantioselectivity of $\mathbf{Cat_A}$ and $\mathbf{Cat_D}$ in hydrogenation of **1a** applying the conditions (14 bar, 60°C) used in a previous study with the BDPP ligand [42], in which case 71% ee (*R*) was observed. $\mathbf{Cat_A}$ gave the product with 61% ee (*R*), while 74% ee (*R*) was obtained with $\mathbf{Cat_D}$, thus showing that the relative trend in enantioselectivity discussed above, depending on phosphorus loading on the polymer, also holds at higher pressure.

The feasibility of catalyst recycling has also been tested at more forcing conditions. Slurry hydrogenation of **1b** at 14 bar pressure using $\mathbf{Cat_B}$ give **2b** in 100% yield but with very poor enantioselectivity, only 24%. The aqueous phase containing the catalyst is, however, easily reused by filtration and washing of the aqueous phase with carefully degassed EtOAc. Applying this water phase in a second run give the product in 27% ee and 100% yield (Table 2 entry 22a and b). Carrying out the same reaction under biphasic conditions (organic phase EtOAc/$C_6H_6$) give **2b** in 27% ee which upon recycling of the catalyst increases to 30% ee (Table 2 entry 23a and b). The increase in the enantioselectivity when the catalyst is reused have been observed before [41]. The organic phase is in the latter case slightly yellow indicating rhodium leakage into the organic phase. Analyses of the combined organic phases from the two hydrogenations for Rh showed 0.16% rhodium which corresponds to a leakage of approximately 6.7% of the total amount of rhodium into the organic phase.

## 4. Conclusions

The water-soluble ligand PAA–PPM is easily synthesised and the method utilising water soluble polymers as charge carrying units can be expanded to other ligands and/or polymers. The phosphorus loading on the polymer have

been found to have a profound effect on enantioselectivity and a maximum ee of 89% have been observed at 1.0% phosphorus loading. We suggest that the variation in enantioselectivity, with respect to ligand loading on the polymer, is due to interaction of metal sites with different phosphine moieties thus forming complexes that do not contribute to the enantioselectivity. The enantioselectivity decreases with increasing $H_2$ pressure but stabilises at approximately 22 bar. Recycling experiments show that catalysts based on the ligands bound to water-soluble phosphines can be reused easily with no loss in enantioselectivity. The ligand with 1% P is most suitable since the higher carboxylate to phosphine ratio makes this ligand completely insoluble in organic solvent thus preventing rhodium leakage into the organic phase.

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