Asymmetric Organometallic-Catalyzed Reactions in Aqueous Media

Denis Sinou

Laboratoire de Synthèse Asymétrique, UMR 5622 associé au CNRS, CPE Lyon, Université Claude Bernard Lyon 1, 43, boulevard du 11 Novembre 1918, 69622 Villeurbanne Cédex, France
Fax: (+33)-4-72448160, e-mail: sinou@univ-lyon1.fr

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Abstract: This review provides an analysis of asymmetric organometallic-catalyzed reactions in aqueous media. The different methodologies for the preparation of chiral water-soluble ligands, and more particularly phosphorus derivatives, are summarized. The applications of these ligands in association with organometallic complexes in water only, as well as other conditions such as reaction in water in the presence of surfactants or in mixtures of water + organic solvents are described. Although asymmetric hydrogenation is one of the most studied catalyzed reactions in aqueous media, some preliminary results concerning asymmetric carbonylation, alkylation, oxidation, cyclopropanation, Diels–Alder reaction, and aldol reaction have appeared in the literature.

Keywords: aldol reaction; alkylation; asymmetric catalysis; carbonylation; hydrogenation; surfactants; water as solvent

1 Introduction

Homogeneous organometallic catalysis is now a well-used methodology in organic synthesis, and especially in the synthesis of fine chemicals.[1,2] This is mainly due to the high activities and selectivities (regio- and stereoselectivity) generally achieved in these processes, as well as the very mild conditions used in these metal-catalyzed transformations. However most of these developments have been carried out in organic solvents. Although chemical transformations in living systems occur in an aqueous environment, it was only in 1960's that a breakthrough was achieved in the use of water as a solvent and particularly in organometallic catalysis. The main goal in this case was the recycling of the expensive and sometimes toxic catalyst in hydroformylation, a very important industrial application. Nevertheless, this discovery induced researchers to try to perform many organic reactions in aqueous media, and the development of water-soluble organometallic catalysts has expanded significantly.[3]

Water has many advantages over the usual organic solvents. It is effectively one of the cheaper solvents and so one of the most economic. It is also safer than the usual solvents which are often inflammable and explosive. From an industrial point of view, the use of a two-phase system allows an easy separation of the products from the water-soluble organometallic catalyst by simple phase separation. Finally, water is environmentally friendly and could obviously diminish the problems of pollution by organic solvents.

During the last 20 years the use of soluble chiral organometallic catalysts has also led to important advances in asymmetric synthesis.[4-6] Now very good enantioselectivities, higher than 95%, have been obtained in many typical reactions such as hydrogenation of carbon-carbon or carbon-oxygen double bonds, isomerization, epoxidation, bishydroxylation, and allylic alkylation. However, one key challenge in these reactions is the separation of the expensive chiral catalyst for its recovery and its possible recycling. Although water-soluble catalysts were known and used since the 1960's, it is only recently that this methodology has been extended to the obtention of chiral compounds starting from prochiral ones.

However, water is a solvent quite different from the organic solvents. Rate enhancement of the reaction

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Denis Sinou was born in 1942 in Penmarch (France). He graduated from Ecole Supérieure de Chimie Industrielle de Lyon in 1965 and obtained his Ph. D. degree at the University of Lyon in 1971 under the direction of Professor G. Descotes in the field of heterocyclic chemistry. In 1974 he held a post-doctoral position in the University of Orsay (Professor H. B. Kagan). He returned to Lyon and obtained the position of professor at the University of Lyon 1 in 1983. His research interests involve organometallic catalysis in non-usual media (water, SAPC, micellar medium, perfluorinated solvents), principally in an asymmetric fashion, enantioselective organometallic-catalyzed formation of carbon-heteroatom bonds, and new synthetic methodologies in carbohydrate chemistry involving organometallic catalysis.

could be observed on going from an organic solvent to water. New selectivities, for example, regio- and enantioselectivity, could also sometimes be expected.

For performing organometallic-catalyzed reactions in water, the reactants need to be sparingly soluble in water. However, if the reactants are not soluble enough, a co-solvent can be added, as well as surfactants, in order to increase the solubilities in water.

This review will focus on asymmetric transformations performed in the presence of water, in an homogeneous way as well as in a two-phase system. After a survey concerning the synthesis of water-soluble ligands, catalyzed organometallic asymmetric reactions performed in the presence of water will be presented. However, only reactions using at least a stoichiometric or substoichiometric amount of water, without modification of the organometallic catalyst, will be reported.

2 Synthesis of Chiral Water-Soluble Ligands

The water-solubility of organometallic catalysts can be generally achieved by the modification of a ligand, and particularly by the introduction of polar groups such as sulfonate groups, quaternized aminoalkyl groups, hydroxyalkyl or polyether groups, carboxylated groups, etc., on a ligand. Another possibility is the introduction of the phosphino group on a chiral water-soluble molecule. Thus, a variety of chiral water-soluble ligands closely related to known chiral ligands has been prepared according to these methodologies.

2.1 Sulfonated Chiral Ligands

As a result of the successful applications and intensive investigations on the water-soluble ligand TPPTS or trisodium salt of tri-(*m*-sulfophenyl)phosphine,[7–9] a variety of water-soluble ligands were prepared by the introduction of a sulfonate group on a chiral ligand (Scheme 1). Sinou et al. prepared several chiral 1,2-, 1,3-, and 1,4-diphosphines by direct sulfonation of the corresponding chiral diphosphines **1a** – **4a** in sulfuric acid containing 30% SO_3 followed by subsequent neutralization and work-up.[10,11] The sulfonated Chiraphos **1b**, Prophos **2b**, BDPP **3b**, and Cyclobutanediop **4b**, were obtained using this methodology; as a rule, tetrasulfonated diphosphines were obtained, with the exception of Prophos **2**, where a mixture of tetrasulfonated and trisulfonated phosphines was obtained, together with some phosphine oxides, whatever the conditions used.

Since atropoisomeric C_2-symmetric ligands are among those inducing the highest ee's in organometallic catalysis, Davies et al. prepared sulfonated BINAP **5b**.[12,13] Treatment of BINAP **5a** in concentrated sulfuric acid with fuming sulfuric acid (40 wt % sulfur trioxide in concentrated sulfuric acid) for 3 days at 10 °C gave a mixture of tetra-, penta-, and hexasulfonated phosphines, structure **5b** being given to the major species (more than 85%).

Treatment of diphosphine **6a** with oleum in the presence of boric acid yielded the eight-fold sulfonated BINAS-8 **6b**.[14,15] Stirring BIFAP **7a** at 20 °C for 88 h with 5% SO_3 in H_2SO_4 gave enantiopure disulfonated BIFAPS **7b** almost quantitatively, although performing the reaction at 50 °C in sulfuric acid gave a racemic product.[16]

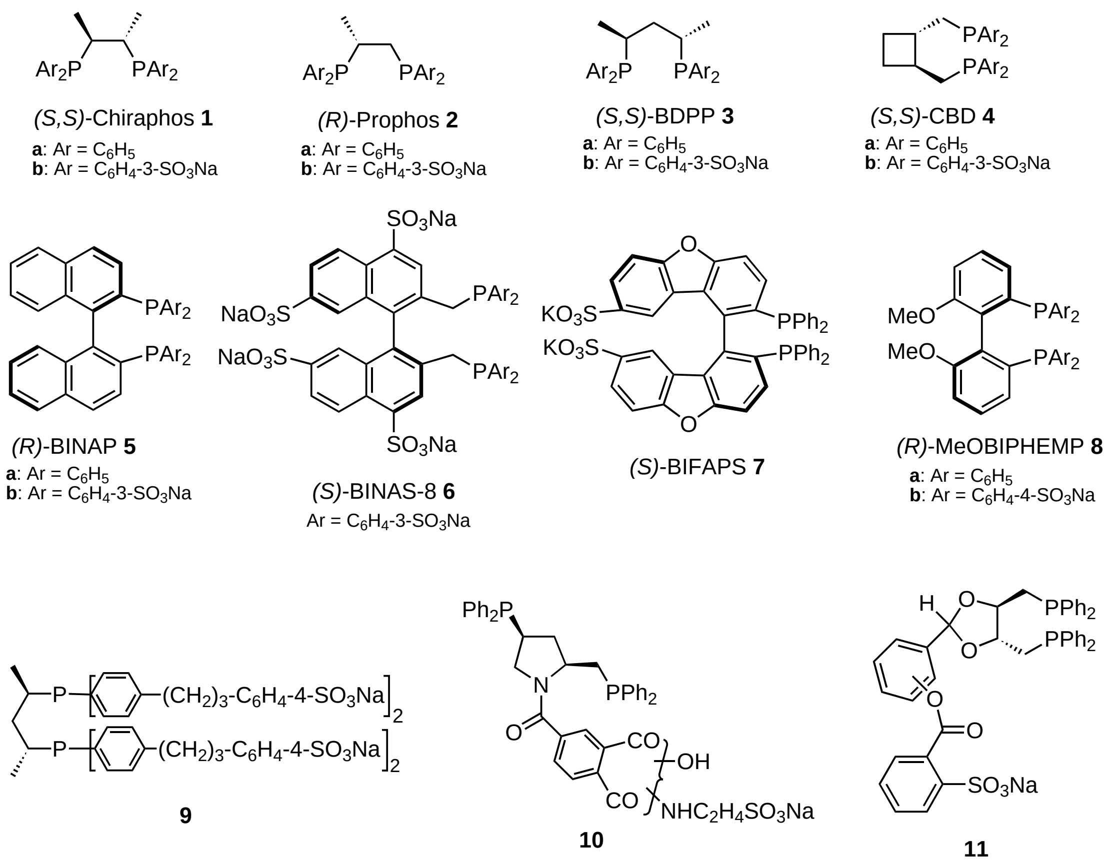
The tetrasulfonated atropisomeric ligand **8b**, an analogue of MeOBiphemp and bearing the sulfonate groups on the *para* position of the phenyl ring, was obtained by a five-step sequence.[17] Hanson et al. obtained the surface-active diphosphine **9b** by direct sulfonation of the BDPP analogue **9a**.[18]

Other chiral phosphines containing a sulfonate group were also obtained from BPPM by acylation with trimellitic anhydride followed by treatment with sodium taurinate, for **10**,[19] or by acylation of a chiral hydroxyphosphine with *o*-sulfobenzoic anhydride, for **11**.[20,21]

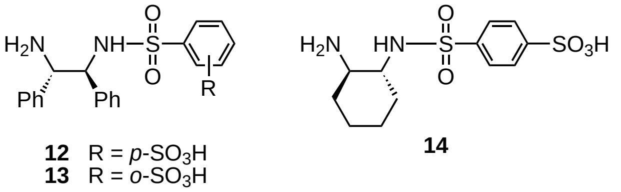
Recently, water-soluble analogues **12** – **14** of Noyori's *(1S,2S)-N-*(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine and Knochel's *(1R,2R)-N-*(*p*-tolylsulfonyl)-1,2-diaminocyclohexane, containing an additional sulfonic acid group, have been synthesized (Scheme 2).[22]

2.2 Other Chiral Water-Soluble Ligands

Among the other accesses to chiral water-soluble ligands, the introduction of a quaternary ammonium group is one of the most studied (Scheme 3).



Scheme 1. Water-soluble chiral sulfonated diphosphines.



Scheme 2. Water-soluble chiral sulfonated diamines.

Nagel et al.[23] prepared diphosphine **15** by quaternization of *(3R,4R)*-3,4-bis(diphenylphosphino-1-methylpyrrolidine with Me_3OBF_4 after protecting the phosphorus through complexation to rhodium.

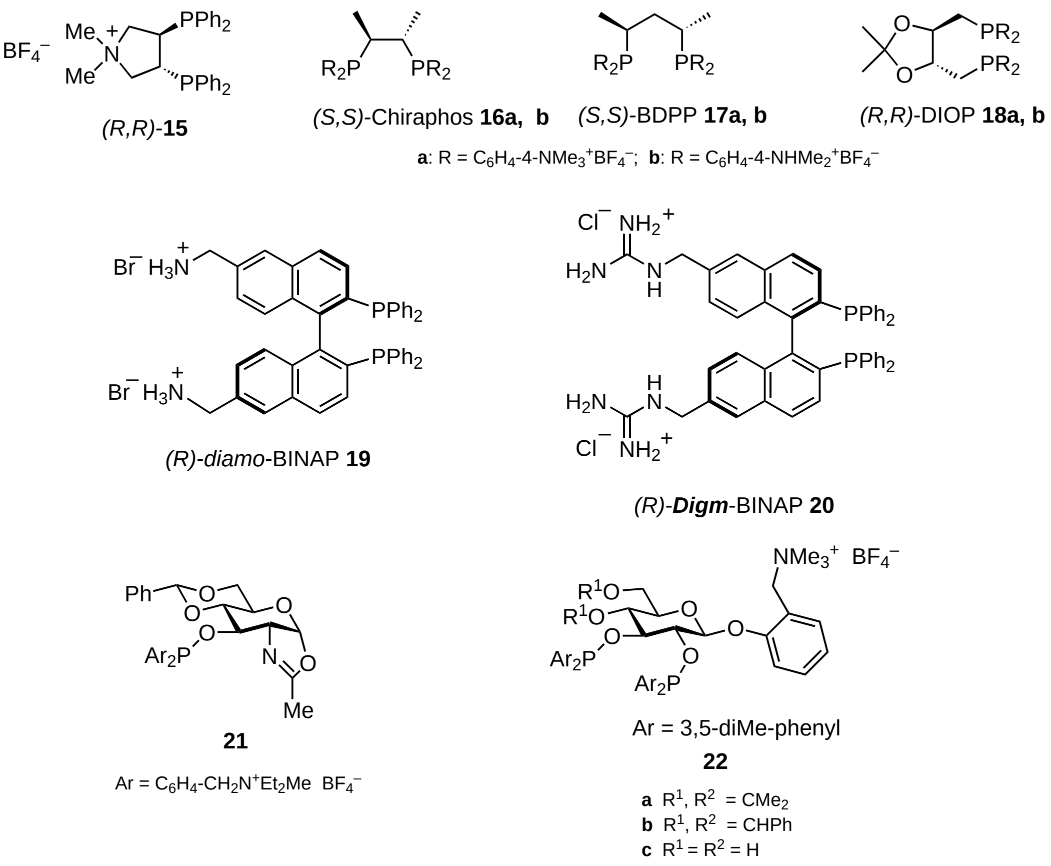
Toth and Hanson[24] synthesized tetraamine functionalized derivatives of the ligands Chiraphos **16**, BDPP **17**, and DIOP **18**; the water-solubility of these ligands was achieved by proton or methyl quaternization of their rhodium complexes, using HBF_4 or Me_3OBF_4, respectively.

BINAP analogues bearing aminoquaternized ammonium functions were simultaneously prepared by Lemaire's and Genêt's groups. Lemaire and co-workers[25] obtained the hydrobromide form **19** of *diamo*-BINAP or 6,6′-di(aminomethyl)-BINAP by treatment of this diaminophosphine with aqueous hydrobromic acid, while Genêt and co-workers[26] prepared the diguanidinium BINAP ligand **20** by reaction of *diam*-BINAP with *N,N′*-di-Boc-*N″*-triflylguanidine followed by addition of hydrochloric acid in methanol.

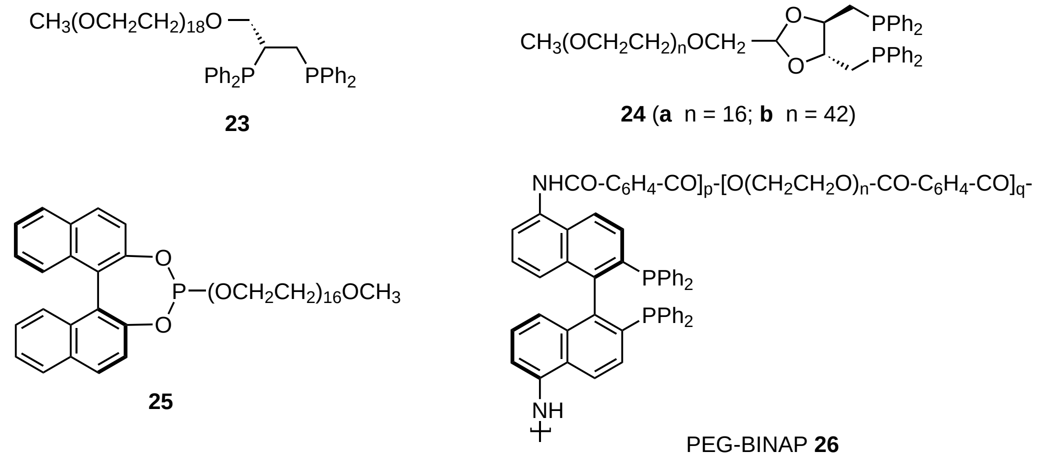
Finally, a phosphinite-oxazoline ligand **21**[27] and a bisphosphinite ligand **22**[28] bearing quaternary ammonium groups were prepared starting from natural D-glucosamine and 2-(hydroxymethyl)phenyl β-D-glucopyranoside, respectively, the last step being a quaternization of the corresponding amine with Me_3OBF_4.

Sinou et al. synthesized non-ionic, asymmetric polyoxa-1,2- and -1,4-diphosphines **23** and **24**, analogues of Prophos and DIOP (Scheme 4).[29,30] The chiral polyether-phosphite ligand **25** derived from *(S)*-binaphthol was prepared by Lemaire and co-workers,[31] while Chan et al. synthesized PEG-BINAP **26** through polycondensation of 5,5′-diamino-BINAP, polyethylene glycol and terephthalic chloride.[32]

Various groups also took advantage of the chirality and hydrophilicity of carbohydrates for the synthesis of various water-soluble non-ionic ligands. Oehme, Selke, and co-workers synthesized the water-soluble carbohydrate diphosphinites **27** having free hydroxy groups in the 4 and 6 positions of the hexoside (Scheme 5).[33,34] Diphosphinites **28** and **29** derived from α,α- and β,β-trehalose, which are more soluble in water than ligands based on monosaccharides, were also prepared.[35,36]



Scheme 3. Water-soluble chiral ligands bearing a quaternary ammonium group.

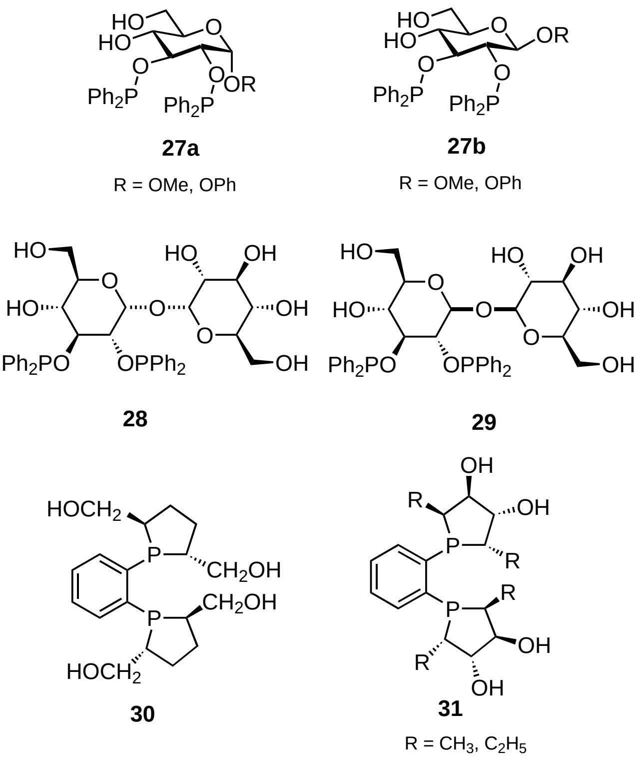


Scheme 4. Chiral non-ionic water-soluble ligands.

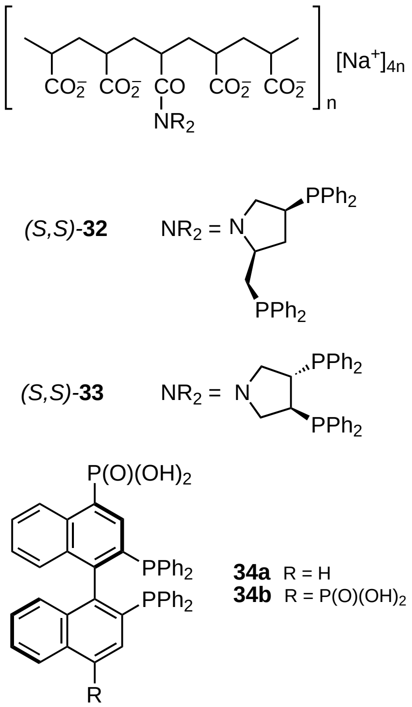
Finally, chiral tetrahydroxydiphosphines **30** and **31**, analogues of Duphos, were synthesized from readily available D-mannitol in quite good yields.[37,38]

Carboxylate groups were also used to achieve water-solubilization. Acylation of the diphosphine *(2S,4S)*-4-diphenylphosphino-2-[(diphenylphosphino)methyl]-pyrrolidine (PPM) and *(R,R)*-3,4-bis(diphenylphosphino)pyrrolidine (Pyrphos) with polyacrylic acid gave very easily the hydrophilic macroligands PAA-PPM **32** (Scheme 6)[39,40] and PAA-pyrphos **33**.[41]

Recently, mono- and bisphosphorylated BINAP derivatives **34** have been obtained; the sodium salts of the phosphonic acid derivatives are soluble in water.[42]



Scheme 5. Water-soluble carbohydrate-based ligands.



Scheme 6. Chiral carboxylic and phosphonic water-soluble ligands.

3 Hydrogenation in Aqueous Media

Hydrogenation of prochiral substrates such as α-acetamidoacrylic acids, α,β-unsaturated acids, β-ketoesters, and imines, in water or in a two-phase system, is one of the most studied reactions.

3.1 Hydrogenation of α-Acetamidoacrylic Acids

3.1.1 Ionized Ligands

Hydrogenation of prochiral substrates in water or in a two-phase system, and particularly of α-amino acid precursors, is one of the most studied reactions. Rhodium complexes of water-soluble 1,2-diphosphines such as **15**,[23] sulfonated Chiraphos **1b** and Prophos **2b**,[10,11] and aminoquaternized ammonium diphosphines **16a**, **b**[43,44] effectively reduced unsaturated α-amino acid precursors in water or in a two-phase system under pressure with high enantioselectivities, very close to the values obtained in organic media (Table 1). Reduction of (*Z*)-α-acetamidocinnamic acid in the presence of sulfonated ligands **1** and **2** gave the corresponding amino acids with enantioselectivity of up to 87% ee in a two-phase system, while an enantioselectivity up to 94% ee was obtained in water only using **16a** as the ligand. Methyl (*Z*)-α-acetamidocinnamate was also reduced with enantioselectivities in the range 67 – 81% ee using the water-soluble 1,2-ligands in a two-phase system. The unsaturated precursor of the Dopa was hydrogenated with an ee of up to 88% in a two-phase system in the presence of ligand **1**, while an ee of up to 93% was obtained in water in the presence of ligand **16**.

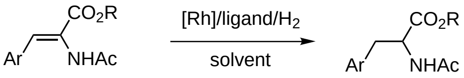
In the reduction of the same precursors, rhodium complexes of water-soluble 1,3-diphosphines **3b**, **17a** or **17b** derived from BDPP, gave enantioselectivities from 40 to 80% ee, lower than the values obtained with the non-water-soluble analogues or even with ligands **17a**, **b** in methanol (Table 2).[10,11,43–45] Finally, the catalysts obtained from tetrasulfonated CBD **4b**, or aminoquaternized ammonium DIOP **18a**, **b**, although the most active, gave lower enantioselectivities, with values from 8 to 67% ee (Table 3).[10,11,43,44]

It is to be noted that the reuse of the catalyst solution was possible in the cases of sulfonated or aminoquaternized diphosphines, with no loss of enantioselectivity.

The concept of supported aqueous-phase catalysis has been extended to the asymmetric hydrogenation of some amino acid precursors by the use of the [Rh(COD)(**16b**)]BF_4 and [Rh(COD)(**17b**)]BF_4 immobilized on silica, enantioselectivity of up to 55% ee being reached using a mixture of AcOEt/benzene (1/1) as the solvent;[46] however, some deactivation and rhodium leaching was observed upon recycling.

The water-soluble catalyst [Rh(COD)(**5b**)]ClO_4 gave enantioselectivities up to 70% in the reduction of α-acetamidoacrylic acid and its methyl ester,[12] while the catalyst obtained by mixing [$Ru(C_6H_6)Cl_2$]$_2$ with sulfo-

Table 1. Asymmetric reduction of some enamides in the presence of rhodium complexes containing water-soluble 1,2-diphosphines.

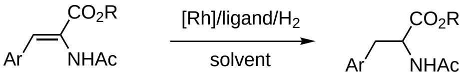


Ar	R	Ligand	Solvent	P_{H_2} [atm]	ee [%]	Ref.
C_6H_5	H	**15**	H_2O	1	90[a]	[23]
		1b	H_2O/AcOEt (1/2)	10	87	[11]
		2b	H_2O/AcOEt (1/2)	10	70[b]	[11]
		16a	H_2O	14	94	[44]
		16b	H_2O	14	90	[44]
C_6H_5	CH_3	**1b**	H_2O/AcOEt (1/1)	10	81	[11]
		2b	H_2O/AcOEt (1/1)	10	67[b]	[44]
		16a	H_2O	14	68	[44]
		16a	H_2O/AcOEt/C_6H_6 (2/1/1)	14	77	[44]
		16b	H_2O/AcOEt/C_6H_6 (2/1/1)	14	74	[44]
3-MeO-4-AcO-C_6H_3	H	**1b**	H_2O/AcOEt (1/1)	10	88	[11]
		2b	H_2O/AcOEt (1/1)	10	80[b]	[11]
		16a	H_2O	14	93	[44]
		16b	H_2O	14	88	[44]

[a] Reduced as the sodium salt.

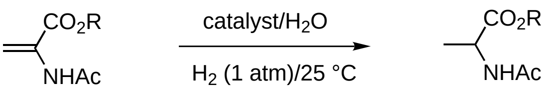
[b] As a mixture of 60% tetrasulfonated diphosphine and 40% trisulfonated diphosphine.

Table 2. Asymmetric reduction of some enamides in the presence of rhodium complexes containing water-soluble 1,3-diphosphines.



Ar	R	Ligand	Solvent	P_{H_2} [atm]	ee [%]	Ref.
C_6H_5	H	**3b**	H_2O/AcOEt (1/1)	15	65	[11]
		17a	H_2O	14	67	[44]
		17a	H_2O	91	65	[44]
		17b	H_2O	14	71	[44]
		17b	H_2O/CH_3OH (2/1)	14	70	[44]
		17b	H_2O/CH_3OH (1/1)	14	64	[44]
		17b	H_2O/EtOAc/C_6H_6 (2/1/1)	14	73	[44]
C_6H_5	CH_3	**3b**	H_2O/AcOEt (1/1)	15	45	[11]
		17a	H_2O	14	40	[44]
		17a	H_2O/AcOEt/C_6H_6 (2/1/1)	14	45	[44]
		17b	H_2O/AcOEt/C_6H_6 (2/1/1)	14	50	[44]
3-MeO-4-AcO-C_6H_3	H	**3b**	H_2O/AcOEt (1/1)	10	58	[11]
		17a	H_2O	14	76	[44]
		17b	H_2O	14	79	[44]

nated BINAP **5b** (Scheme 7) gave an enantioselectivity as high as 88% ee, quite close to the values obtained in neat methanol;[13] it is to be noted in these cases that the direction of enantioselection was the opposite using the rhodium or the ruthenium catalyst, as that observed in organic solvents. The hydrogenation of *(Z)*-acetamidocinnamic acid with BIFAPS **7** as the ligand instead of **5b**, in a two-phase system of water/ethyl acetate, resulted in the product with 72% ee, but with low conversion (18%).[16]

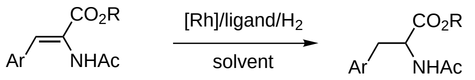


R = H	cat [Rh]/*(R)*-**5b**	ee 70% *(S)*
	cat [Ru]/*(R)*-**5b**	ee 68.5% *(R)*
R = CH_3	cat [Rh]/*(R)*-**5b**	ee 69.5% *(S)*
	cat [Ru]/*(R)*-**5b**	ee 82% *(R)*

Scheme 7. Reduction of α-acetamidoacrylic acid derivatives in the presence of [Rh]/ and [Ru]/*(R)*-**5b** catalysts.

The other sulfonated diphosphines such as **10** and **11** associated with rhodium complexes[19,21] gave lower enantioselectivities in the reduction of α-acetamidoacrylic acid and its methyl ester in water: 34% and 7 – 27% ee in the case of the unsaturated acid, respectively, and 0 – 17% ee for the methyl ester using ligand **11**.

Table 3. Asymmetric reduction of some enamides in the presence of rhodium complexes containing water-soluble 1,4-diphosphines.



Ar	R	Ligand	Solvent	P_{H_2} [atm]	ee [%]	Ref.
C_6H_5	H	**4b**	H_2O/AcOEt (1/1)	1	34	[11]
		18a	H_2O	14	25	[44]
		18b	H_2O	14	34	[44]
C_6H_5	CH_3	**4b**	H_2O/AcOEt (1/1)	1	20	[11]
		18a	H_2O	14	8	[44]
		18b	H_2O/AcOEt/C_6H_6 (2/1/1)	14	25	[44]
3-MeO-4-AcO-C_6H_3	H	**4b**	H_2O/AcOEt (1/2)	1	37	[11]
		18a	H_2O	14	42	[44]
		18b	H_2O	14	67	[44]

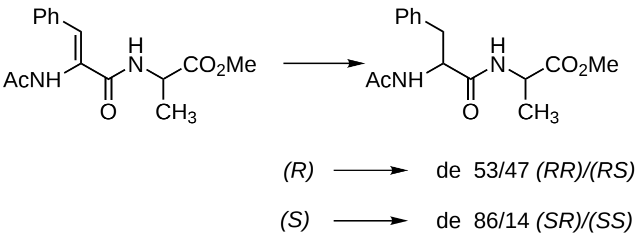
Ligand **9** associated with $[Rh(COD)Cl]_2$ acted as a surface-active ligand and reduced methyl (*Z*)-α-acetamidocinnamate in a two-phase system, AcOEt/water, with an enantioselectivity up to 69%, quite similar to the values obtained using non-sulfonated BDPP; however, improved reactivity was observed.[18]

Reduction of (*Z*)-α-acetamidocinnamic acid was also performed by hydrogen transfer from formate catalyzed by $[Rh(COD)Cl]_2$ in the presence of ligand **4b** affording the saturated product with 43% ee.[47]

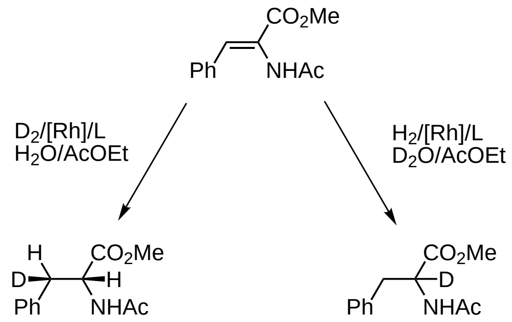
RajanBabu and co-workers[28] used a series of water-soluble, chelating bis-phosphinite ligands **22** derived from D-salicin and bearing a quaternized ammonium function as ligand in the hydrogenation of some acetamidoacrylic acid derivatives in aqueous or biphasic media. The enantioselectivities obtained in neat aqueous or biphasic media are generally lower than those observed in organic medium; for example, reduction of methyl α-acetamidoacrylate using **22a** as the ligand afforded the saturated product with 2 and 90% ee in water or in a mixture water/methanol (1/1), respectively, while reduction in water only using **22c** as the ligand gave the product with 61% ee, recycling of the catalyst being not possible.

This hydrogenation process was extended to the reduction of dehydropeptides in a two-phase system, water/ethyl acetate, using $[Rh(COD)Cl]_2$ associated with tetrasulfonated ligands **3b** and **4b** (Scheme 8);[48] the diastereomeric excess (de) of the obtained dipeptide was strongly dependent on the absolute configuration of the unsaturated substrate. Reduction of Ac-Δ-Ph-(*S*)-Ala-OCH_3 in the presence of [Rh]/**4b** gave a de as high as 72% in favour of the (*R,S*) diastereoisomer, while a de of 6% was obtained in the reduction of Ac-Δ-(*R*)-Ala-OCH_3 in favour of the (*R,R*) diastereoisomer.

The lower enantioselectivity observed in water for the reduction of amino acid precursors using water-soluble diphosphines in association with rhodium complexes was attributed to solvent effects and to the different reaction kinetics in the two solvents;[49] effectively a drop in enantioselectivity was observed going from the true organic system to the aqueous phase, a linear relationship being found between log (%*S*/%*R*) and the solvophobicity parameter, S_p, of various solvents. However, another possibility could be the presence of a different mechanism than the usual one, occurring, for example, *via* a monohydride species. Effectively, although the biphasic hydrogenation of α-amino acid precursors using rhodium complexes was shown to be a truly homogeneous process,[50] a very high amount of regiospecific monodeuteration at the position α to the acetamido and the ester functions was observed in the reduction of α-acetamidocinnamic acid in AcOEt/D_2O, the amount of deuterium incorporation depending on the nature of the substrate and on the ligand (Scheme 9).[51,52] Hydrogen incorporation occurred at



Scheme 8. Reduction of Ac-Δ-Ph-Ala-OCH_3 in a two-phase system AcOEt/H_2O in the presence of $[Rh(COD)Cl]_2$ + *(S,S)*-**3b** at 25 °C under 20 atm of hydrogen.



Scheme 9. Deuterium (or hydrogen) incorporation using H_2 (or D_2) in a two-phase system D_2O (or H_2O)/AcOEt.

the same position when the reduction was performed under a deuterium atmosphere in the presence of water.

3.1.2 Non-Ionic Ligands

Polyoxadiphosphines or carbohydrate-based ligands have been used, in association with rhodium complexes, in the reduction of unsaturated amino acid precursors in water. While enantioselectivity lower than 32% ee has been obtained in the reduction of α-acylaminoacrylic acids using **23** or **24** as the chiral ligands,[29,30] diphosphinites or diphosphines **27** – **31** derived from carbohydrates and associated with rhodium complexes afforded very high enantioselectivities.

Selke and co-workers used various deprotected D-hexopyranoside-2,3-*O*-bis(diphenylphosphinite) carrying free hydroxy groups in 4,6-positions of the hexoside in the reduction of (*Z*)-α-acetamidocinnamic acid and its methyl ester in water.[53] The ligands having the β-configuration gave the highest enantioselectivity (up to 80% ee for the β-anomer compared to 60% ee for the α-anomer); these enantioselectivities are quite close to those obtained when performing the reaction in methanol. However, the ligands carrying a phenyl group as the aglycone showed extremely long reaction rates compared to the methyl analogue.

The rhodium complex [Rh(COD)(**30**)]BF_4 reduced 2-acetamidoacrylic acid and its methyl ester in water as solvent with a high rate and enantioselectivity of up to 99.6 and 93.6% ee, respectively.[37]

The bisphosphinite **28** and **29**, derived from the corresponding α,α- or β,β-trehalose, have been transformed into cationic rhodium complexes which are soluble in water and are efficient catalysts for the asymmetric hydrogenation of dehydroamino acids and their esters in water or in an aqueous/organic biphasic medium (Table 4).[35,36,54] The reduction of methyl α-acetamidocinnamate using the diphosphinite **28** proceeded in H_2O or in a biphasic system H_2O/AcOEt to give moderate selectivity (55% and 68% ee, respectively); addition of methanol increased the enantioselectivity to 75% ee. The hydrogenation in water using diphosphinite **29** as the chiral ligand gave an enantioselectivity up to 88%; hydrogenation carried out in H_2O/AcOEt biphasic system gave an enantioselectivity of up to 87% ee, while this value was improved to 98% ee when the reaction was carried out in H_2O/CH_3OH/AcOEt. Several dehydroamino acid derivatives were also hydrogenated with good enantioselectivities (90 – 98% ee) under the above conditions.

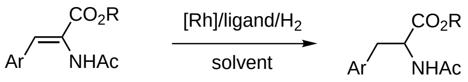
3.1.3 Water-Soluble Polymers

Anderson and co-workers used rhodium complexes of water-soluble polymer ligand **32** and **33** in the reduction of α-acetamidocinnamic acid and its methyl ester in water and in a two-phase system, AcOEt/water.[39–41] The corresponding amino acids were obtained in moderate to good ee's, the best enantioselectivity being obtained for α-acetamidocinnamic acid (ee of up to 89%) (Scheme 10). However, the enantioselectivity in the case of ligand **32** is dependent on the phosphorus loading on the polymer, being high at low loading and low at high loading, although catalyst based on ligand **33** gave an enantioselectivity up to 83% ee, the enantioselectivity being unaffected by the phosphorus loading.

3.1.4 Reduction in the Presence of Surfactants

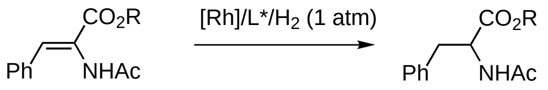
Asymmetric hydrogenation was also performed in water as solvent using rhodium complexes associated with non-water-soluble chiral ligands, and particularly BPPM **35a**, in the presence of micelle-forming amphi-

Table 4. Asymmetric reduction of some enamides in the presence of rhodium complexes associated with carbohydrate-based ligands.



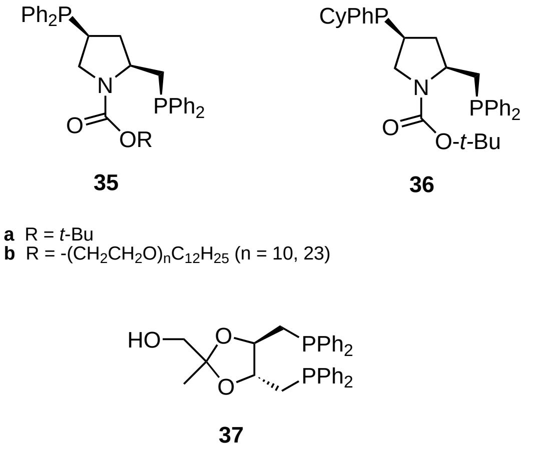
Ar	R	Ligand	Solvent	ee [%]	Ref.
C_6H_5	CH_3	**28**	H_2O	55	[35,36]
			H_2O/AcOEt (1/1)	68 (66)[a]	[35,36]
			H_2O/CH_3OH/AcOEt (6/4/10)	76	[35]
C_6H_5	CH_3	**29**	H_2O	88	[35]
			H_2O/AcOEt (1/1)	87 (85)[a]	[35]
			H_2O/CH_3OH/AcOEt (6/4/10)	98	[35]
C_6H_5	H	**29**	H_2O/CH_3OH/AcOEt (6/4/10)	96	[35]
4-MeO-C_6H_4	CH_3	**29**	H_2O/CH_3OH/AcOEt (6/4/10)	98	[35]
2-naphthyl	CH_3	**29**	H_2O/CH_3OH/AcOEt (6/4/10)	96	[35]
H	CH_3	**29**	H_2O	80	[35]

[a] The ee obtained from the recycling of the catalyst aqueous solution is shown in brackets.



R	L*	Solvent	ee
R = H	L* = **32**	H_2O	70% ee
	L* = **32**	$AcOEt/H_2O$	89% ee
	L* = **33**	$H_2O/EtOH$	83% ee
R = Me	L* = **32**	H_2O	24% ee
	L* = **32**	$AcOEt/H_2O$	66% ee

Scheme 10. Reduction of α-acetamidocinnamic acid derivatives in the presence of [Rh]/**32** and [Rh]/**33** catalysts.



35 **36**

a R = *t*-Bu
b R = $-(CH_2CH_2O)_nC_{12}H_{25}$ (n = 10, 23)

37

Scheme 11.

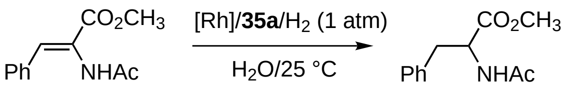
philes (Scheme 11). Oehme et al.[55,56] showed that, using the catalyst $[Rh(COD)_2]BF_4$ + BPPM **35a** in the reduction of some α-amino acid precursors in water, both activity and enantioselectivity were enhanced significantly in the presence of surfactants, and that the enantioselectivities obtained are quite comparable to those obtained in methanol (96% ee) (Scheme 12). These effects were found with non-ionic, zwitterionic, as well as anionic and cationic surfactants, and depended on the critical micelle concentration (CMC), the change in activity and enantioselectivity being maximal near the CMC.

Various carbohydrate amphiphiles have been also used in the hydrogenation of methyl (*Z*)-α-acetamidocinnamate with this catalyst;[57] activity and enantioselectivity were increased in comparison to the values found for pure water, enantioselectivity of up to 96% ee with a half-life of 5 min being obtained. This study using carbohydrate amphiphiles possessing alkyl chains of different lengths suggested that these effects were due to micelle formation, hydrophilic-lipophilic balance, and hydrogen bonding in the head group. It is to be noted that some carbohydrate amphiphiles induced also some enantioselectivity, although in a low amount (up to 6% ee) using non-chiral rhodium complex as the catalyst.

The same trends were observed in the reduction of some prochiral dialkyl 1-benzamido-2-phenyl-ethenephosphonates in water (Scheme 13).[58,59] Enantioselectivities up to 99% ee were obtained using $[Rh(COD)_2]BF_4$ and BPPM **35a** in the presence of surfactants, or amphiphilized BPPM **35b**. Some enantioselectivity (11% ee) was also observed using an achiral rhodium catalyst in the presence of carbohydrate amphiphiles.

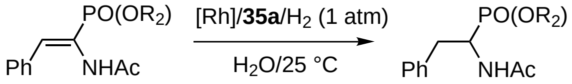
The use of metallosurfactants $[Rh(COD)_2]BF_4$ + **35b** gave also the reduced product with enantioselectivity up to 91%, while 96% ee was obtained in mixed micelles by addition of a very small amount of SDS (sodium dodecyl sulfonate) to the above catalyst.[60,61] Polymer-bound amphiphiles based on an inorganic support have also been successfully used, giving the same enantioselectivity;[57] it is to be noticed that recycling processes were possible with constant enantioselectivity, but with decreasing activity. Recently, a micellar enlarged Rh/BPPM catalyst was used in a membrane reactor equipped with an ultra-filtration membrane, the catalyst being reused several times with no loss of activity and enantioselectivity.[62]

Oehme et al.[63] investigated the effect of amphiphiles on the CH/CD exchange in the reduction of methyl (*Z*)-α-acetamidocinnamate in an aqueous micellar medium. The amount of incorporation was strongly influenced by the nature of the amphiphile, values of up to 37%, 40%, 10%, and 28% being obtained with non-ionic, cationic, anionic, and zwitterionic amphiphiles, respectively.



Surfactant	t/2[min]	ee [%]
no	90	78
Brij 56	7	96
Tween 40	5	95
DDAPS	5	93
SDS	6	94
$CTAHSO_4$	5	94

Scheme 12. Reduction of α-acetamidocinnamic acid using [Rh]/**35a** as the catalyst in the presence of surfactants.



	Solvent	t/2 [min]	ee [%]
R = CH_3	H_2O	720	91
	CH_3OH	6	96
	H_2O + SDS	7	98
R = C_2H_5	H_2O	600	93
	CH_3OH	12	95
	H_2O + SDS	4	98
R = *i*-C_3H_7	H_2O	no hydrogen	
	H_2O + SDS	13	99

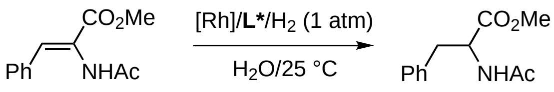
Scheme 13. Reduction of dialkyl 1-benzamido-2-phenylethene phosphonates using [Rh]/**35a** as the catalyst in the presence of surfactants.

The presence of surfactants also enhanced significantly the activity and enantioselectivity in the hydrogenation of unsaturated amino acid precursors in the presence of [Rh(COD)(**36**)]BF_4.[64] Complexes containing carbohydrate-based ligands have also been used in water in the presence of various surfactants;[53,65] catalysts [Rh(COD)(**27β**]BF_4 and [Rh(COD)(**27α**)]BF_4 reduced α-amino acid precursors in water in the presence of SDS with enantioselectivity up to 98% ee, exceeding the values obtained in methanol.

Hydroxydiphosphines showed a particular behaviour in water. While [Rh(COD)(DIOP)]BF_4 showed a very low enantiomeric enhancement in the reduction of unsaturated amino acid precursors in water in the presence of surfactants, the enantioselectivity using the rhodium/**37** chelate as catalyst was influenced by the amphiphile to an unprecedented degree (Scheme 14).[66] Reduction in water without surfactant using Rh/**37** gave low ee (15% ee), while the enantioselectivity jumped to 76.6% ee in the presence of SDS, higher than the value obtained in pure methanol (50% ee).

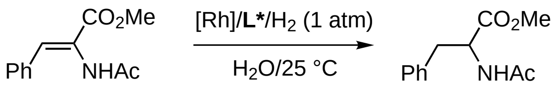
Uemura and co-workers[54] noticed also a huge increase in enantioselectivity in the reduction of methyl α-acetamidocinnamate in water in the presence of SDS, using water-soluble ligands **28** and **29** (Scheme 15).

According to experiments with chiral amphiphiles in water, Oehme et al. [56,67] suggested that the achiral catalysts were located in the region between the chiral head groups and the hydrophobic tails of micelles formed by the amphiphiles. A recent study of Selke[68] using pulse field gradient spin echo NMR spectroscopy to determine the average diffusion coefficients of the catalyst clearly showed that the increase in enantioselectivity was coupled with an aggregation of the catalyst to the micelles; this aggregation in the micelles led to the formation of a colloidal phase in the aqueous solution. The enantioselectivity depends strongly on the place where the hydrogenation occurs; if it takes place exclusively inside the micelles, the enantioselectivity will be high, while if the catalyst is not completely embedded in the micelles, the enantioselectivity will be lower.



L*	SDS	ee [%]
37	no	1.5
	yes	76.6
DIOP	no	10
	yes	45

Scheme 14. Reduction of methyl α-acetamidocinnamate using [Rh]/**37** as the catalyst in the presence of surfactants.



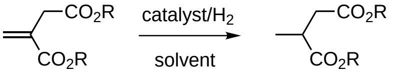
L*	SDS	ee [%]
28	no	55
	yes	90
29	no	88
	yes	>99

Scheme 15. Reduction of methyl α-acetamidocinnamate using [Rh]/**28** and **29** as the catalyst in the presence of surfactants.

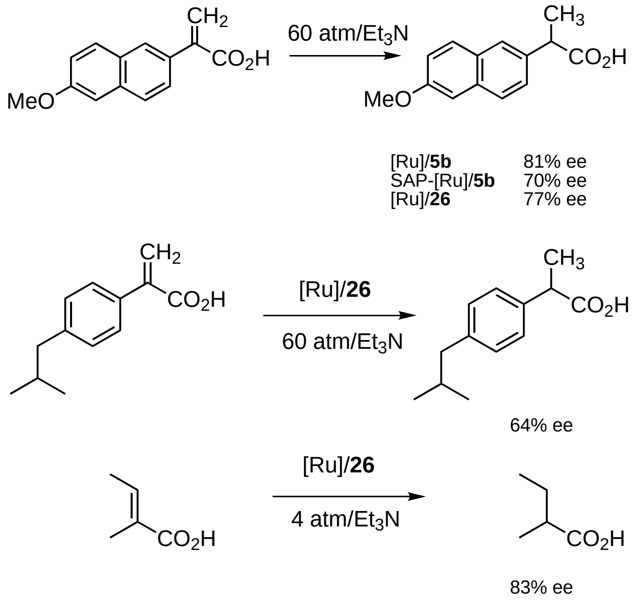
3.2 Reduction of Other Unsaturated Substrates

Itaconic acid and its dimethyl ester have been reduced using rhodium or ruthenium complexes associated with various water-soluble ligands (Table 5). Although sulfonated diphosphines gave low enantioselectivities whatever the metal used in water only or in a two-phase system (ee lower than 50%),[11,13] these compounds were smoothly hydrogenated in mixtures of water and

Table 5. Asymmetric reduction of itaconic acid derivatives in the presence of rhodium complexes containing water-soluble diphosphines.



R	Catalyst	Solvent	ee [%]	Ref.
CH_3	$[Rh(COD)Cl]_2$ + **1b**	AcOEt/H_2O (1/1)	29	[11]
	$[Rh(COD)Cl]_2$ + **2b**	AcOEt/H_2O (1/1)	8	[11]
	$[Rh(COD)Cl]_2$ + **3b**	AcOEt/H_2O (1/1)	43	[11]
CH_3	$[Rh(COD)_2]PF_6$ + **31**	MeOH/H_2O (9/1)	> 99	[38]
	$[Rh(COD)_2]PF_6$ + **31**	MeOH/H_2O (1/1)	> 99	[38]
CH_3	$[RuCl_2(p\text{-cymene})]_2$ + **34b**	EtOH/H_2O/hexane (5/1/5)	79	[42]
H	$[Rh(COD)_2]PF_6$ + **31**	MeOH/H_2O (1/1)	> 99	[38]
	$[Rh(COD)_2]PF_6$ + **31**	MeOH/H_2O (3/97)	> 99	[38]
H	$[Ru(C_6H_6)Cl_2]_2$ + **5b**	H_2O	50	[13]



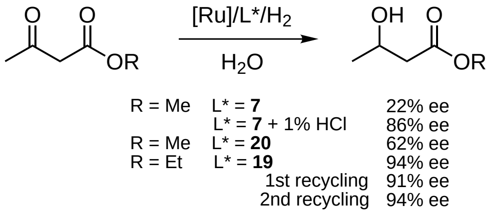
Scheme 16. Hydrogenation of some α,β-unsaturated acids in AcOEt/H_2O at 25 °C.

methanol in the presence of the catalyst obtained from $[Rh(COD)_2]PF_6$ and **31**,[38] or in a mixture of water/EtOH/hexane (5/1/5) in the presence of $[RhCl_2($*p*-cymene$)]_2$ and **34b**,[69] giving the saturated product with an enantioselectivity as high as 99% ee.

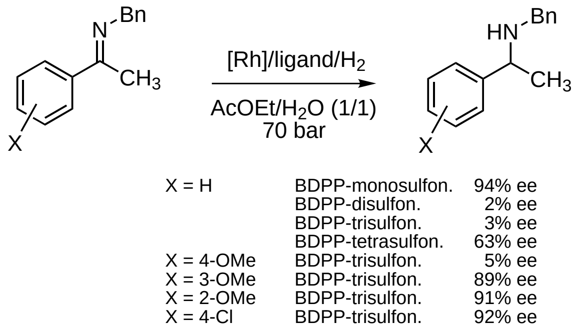
Reduction of 2-(6′-methoxy-2′-naphthyl)acrylic acid in a two-phase system, AcOEt/H_2O, using the $[Ru(C_6H_6)$-(**5**)Cl]Cl catalyst allowed the preparation of naproxen in 81% enantioselectivity, ee values over the range 78 – 83% being obtained over several recycles of the catalytic solution (Scheme 16).[70] The supported catalyst SAP-Ru-BINAP(4-SO_3Na) was also prepared and used in this reduction; an enantioselectivity of up to 70% ee was obtained in ethyl acetate saturated with water as the solvent. The recycling of the catalyst was easily achieved without any leaching of ruthenium in the organic phase.

Ruthenium complexes based on the polymeric ligand **26** were also efficient catalysts for the asymmetric hydrogenation of various prochiral α,β-unsaturated carboxylic acids in the ethyl acetate/water two-phase system (Scheme 16).[32] It is to be noticed that the activity and/or enantioselectivity in the two-phase system were observed to be higher than those obtained in a homogeneous system.

The hydrogenation of various β-keto esters proceeded also in water in the presence of ruthenium complexes associated with the water-soluble ligands BIFAPS **7**,[16] diamo-BINAP **19**,[25] and digm-BINAP **20**,[26] affording the β-hydroxy ester with an enantioselectivity of up to 94% ee (Scheme 17). It is to be noticed that catalyst/substrate ratio as high as 1,000 could be used, and that the aqueous catalyst solution could be reused after extraction of the product with pentane without loss of enantioselectivity.



Scheme 17. Hydrogenation of some ketoesters at 25 °C.



Scheme 18. Reduction of imines using [Rh]/BDPP as the catalyst.

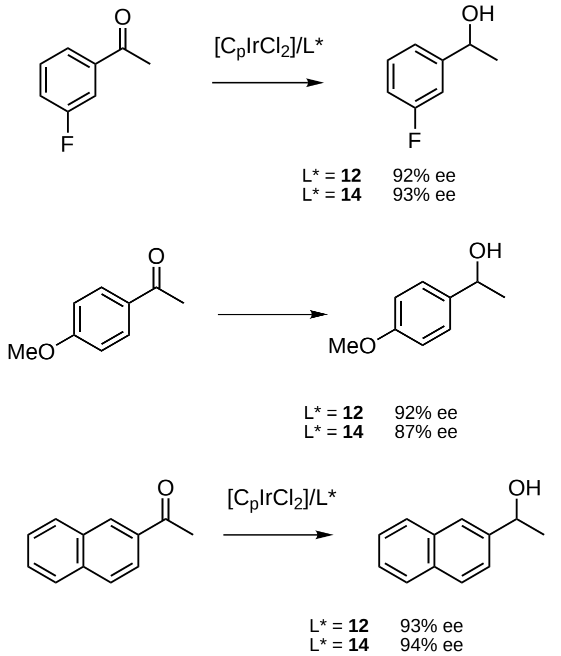
Sinou[71] and de Vries[72,73] reported the drastic influence of the degree of sulfonation of chiral BDPP **3a** on the enantioselectivity in the reduction of prochiral imines (Scheme 18). Hydrogenation of various imines in a two-phase system, AcOEt/H_2O, with the catalyst obtained by mixing $(Rh(COD)Cl]_2$ and the monosulfonated BDPP yielded the corresponding amines with an enantioselectivity of up to 94% ee, while the reduction using the di- or the trisulfonated BDPP as the ligand proceeded with practically no enantioselectivity. As mixtures of mono-, di-, and trisulfonated BDPP gave almost 94% ee, comparison of reaction rates confirmed the kinetic superiority of the monosulfonated catalyst which was found to be about five times faster in this hydrogenation than the catalyst based on the di- or trisulfonated analogues.

A range of aromatic ketones was reduced under hydrogen transfer conditions in the presence of $[CpRhCl_2]$ or $[CpIrCl_2]$ associated with water-soluble ligands **12** and **13** in systems containing up to 51% water with high catalytic activities and enantioselectivities in the range of 87 – 95% ee (Scheme 19).[74]

4 Other Reactions

4.1 Carbonylation Reaction

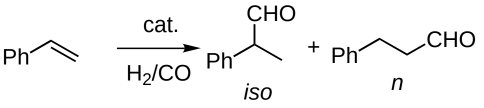
The carbonylation reaction of organic compounds catalyzed by organometallic complexes is a useful tool in organic synthesis for the preparation of carbonyl



Scheme 19. Reduction of ketones by hydrogen transfer.

compounds. From an industrial point of view, hydroformylation of propene in a two-phase system using the highly water-soluble RhH(CO)(TPPTS)$_3$ was developed by Ruhr-Chemie AG.[7–9,75–77] However asymmetric hydroformylation or carbonylation in a two-phase system is still an unresolved problem with few examples being reported in the literature, the enantioselectivity being generally low.

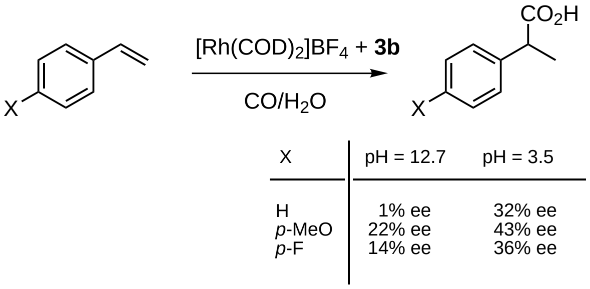
No asymmetric induction was observed in the hydroformylation of styrene, Equation (1), in a two-phase system water-organic solvent using PtCl$_2$(**17a**) as the catalyst, while the SAP catalyst provided enantioselectivity up to 14% ee;[46] however the catalyst activity was poor.



(1)

Hydroformylation of styrene in the biphasic system CH$_3$OH/H$_2$O/toluene in the presence of the catalyst Rh(CO)$_2$(acac) and BINAS **6** proceeded with good regioselectivity in 2-phenylpropanal (95%) and an enantioselectivity up to 18% ee.[15] Enantioselectivities of up to 17% and 14% ee were obtained using the catalyst precursor [Rh(μ-OMe)(COD)]$_2$ associated with chiral sulfonated **1b** and **3b**, respectively, in water;[78] however conversion and selectivity were moderate.

Recently, the catalyst obtained by mixing [Rh(COD)$_2$]BF$_4$ with the chiral polyether-phosphinite ligand **25** gave an enantioselectivity up to 25% ee in the hydroformylation of styrene under thermoregulated phase-transfer conditions.[79]



X	pH = 12.7	pH = 3.5
H	1% ee	32% ee
p-MeO	22% ee	43% ee
p-F	14% ee	36% ee

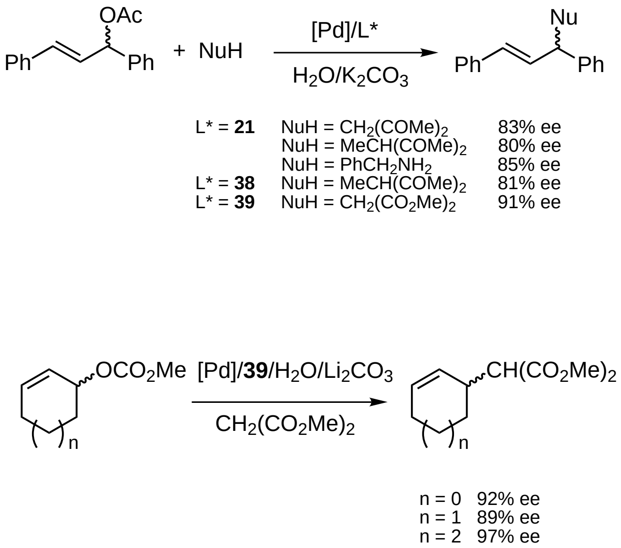
Scheme 20. Hydrocarbonylation of vinylarenes.

Hydrocarboxylation of various vinylarenes proceeded in the presence of Pd(OAc)$_2$ and tetrasulfonated BDPP **3b** or CBD **4b** with enantioselectivity up to 43% ee (Scheme 20);[80] an acidic medium stabilizes the catalyst, recycling being possible with no loss in activity and enantioselectivity.

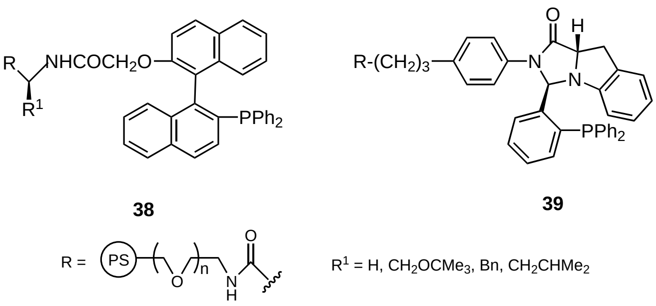
4.2 Alkylation Reaction

Palladium-catalyzed alkylation is now a common tool in organic synthesis, enantioselectivity of up to 99% being obtained in carbon-carbon as well as in carbon-heteroatom bond formation.

The complex obtained from [Pd(η^3-C$_3$H$_5$)Cl]$_2$ and ligand **21** is soluble in water and is an efficient catalyst for asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate in water or in an aqueous/organic biphasic medium, enantioselectivity up to 85% ee being obtained (Scheme 21);[27] recycling of the catalyst was possible.



Scheme 21. Allylic substitution.



Scheme 22. Some chiral amphiphilic ligands.

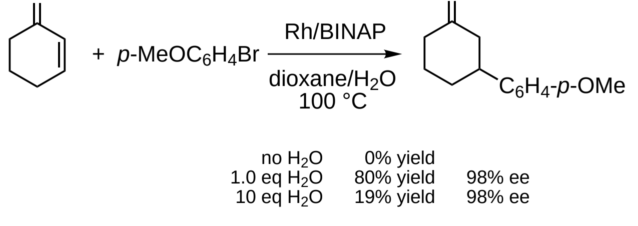
Uozumi and co-workers prepared the amphiphilic resin-supported MOP ligand PEP-MOP **38**[81] and *P,N*-chelating ligand PS-PEG *P,N* **39** (Scheme 22).[82] The palladium complexes of these ligands were found to be effective as catalysts for the asymmetric π-allyl substitution of both cyclic and acyclic substrates in water with enantioselectivity of up to 98% ee (Scheme 21). The catalyst could be recovered by simple filtration and reused without any loss of activity and enantioselectivity.

Sinou and co-workers studied the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate in water in the presence of surfactants, using K_2CO_3 as the base and chiral non-water-soluble ligands.[83] The highest enantioselectivies, up to 92% ee, were observed using cetyltrimethylammonium hydrogen sulfate as the surfactant and chiral atropoisomeric diphosphines such as BINAP **5a** or analogues as the ligand; higher activity was also observed in the presence of surfactant.

4.3 1,4-Addition

Rhodium-catalyzed asymmetric addition of aryl borates to α,β-unsaturated ketones gave the corresponding β-aryl ketones with an enantioselectivity of up to 99% ee in the presence of BINAP **5a** as the ligand (Scheme 23).[84] However, in the absence of water, the reaction is very sluggish, giving low yields; the addition of 1.0 equivalent of water is essential for the obtention of high yields, while too much water disturbs the reaction *via* hydrolysis of the aryl-boron bond.

A high level of enantioselectivity as well as catalytic activity was also found in the addition of a variety of arylboronic acids to cycloalkenones using the same conditions and BINAP **5a** or an amidomonophosphine as the ligand.[85] This 1,4-addition was extended to various 1-alkenylphosphonates under the above conditions, giving an enantioselectivity of up to 97% ee, and high yields.[86]



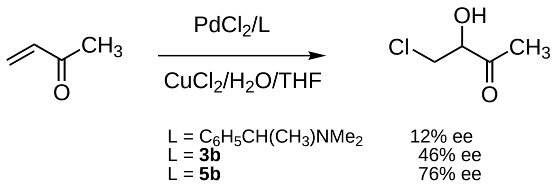
Scheme 23. Asymmetric 1,4-addition.

4.4 Oxidation

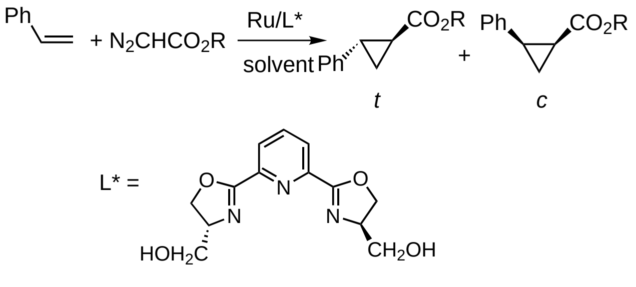
Chlorohydrins have been obtained in the palladium(II)-catalyzed oxidation of various alkenes in aqueous solution using pyridine as a ligand and $CuCl_2$ (Scheme 24). The replacement of pyridine by the chiral monoamine $C_6H_5CH(CH_3)NMe_2$ gave a catalyst which produced the chlorohydrin with enantioselectivity up to 12% ee.[87–89] However, an enantioselectivity of up to 76% ee was obtained in the presence of chelating sulfonated diphosphines such as **3b** and **5b**. This enantioselectivity jumped up to 94% ee using bimetallic catalysts containing a β-triketone and bridging chiral diphosphine and diamines.

4.5 Cyclopropanation

Cyclopropanation of styrene with various diazoacetates occurred in aqueous-organic media using chiral bis(hydroxymethyldihydrooxazolyl)pyridine-ruthenium catalyst, giving high enantiomeric excess up to 96–97% and *trans/cis* stereoselectivity up to 97/3 (Scheme 25).[90]



Scheme 24. Asymmetric synthesis of chlorohydrins.



Solvent	Yield (%)	ee (%) *t*	ee (%) *c*
THF	39	8	30
THF + H_2O	46	78	45
Toluene	38	8	28
Toluene + H_2O	56	88	51

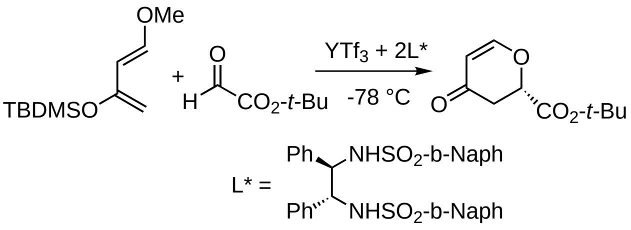
Scheme 25. Asymmetric cyclopropanation.

Addition of water in this case dramatically increased the enantioselectivity. It is to be noted that performing the reaction in H_2O-toluene allowed a recycling of the catalyst with no loss of enantioselectivity.

4.6 Diels–Alder Reaction

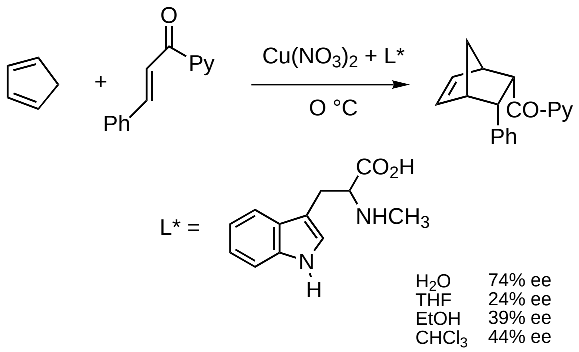
Lewis acids have been used as catalysts in Diels–Alder reactions. The beneficial use of water as an additive in the Lewis acid-catalyzed reaction was reported.[91–95] Condensation of Danishefsky's diene with butyl glyoxylate in toluene in the presence of the chiral lanthanide bis(trifluoromethanesulfonyl)amides Y/L* gave the corresponding cyclized product in 74% yield and 54% ee (Scheme 26). Addition of 11 equivalents of water to the mixture increased the enantioselectivity to 66% ee and the yield to 88%.[96]

Engberts et al.[97] have also shown the beneficial effect of water on both the activity and enantioselectivity in the condensation of cyclopentadiene with an unsaturated ketone in the presence of copper complexes of various chiral α-amino acids such as valine, leucine, phenylalanine, etc. (Scheme 27). The Diels–Alder adduct was obtained in yields generally exceeding 90%, and enantioselectivity of up to 74% ee. This enantioselectivity is higher than those observed in organic solvents, and one reason could be the less efficient arene-arene interaction in organic solvent than in water. It is to be noticed that the catalyst solution can be reused without any decrease in enantioselectivity.



toluene	74% yield	54% ee
toluene + H_2O	88% yield	66% ee

Scheme 26. Asymmetric catalytic Diels–Alder reaction.



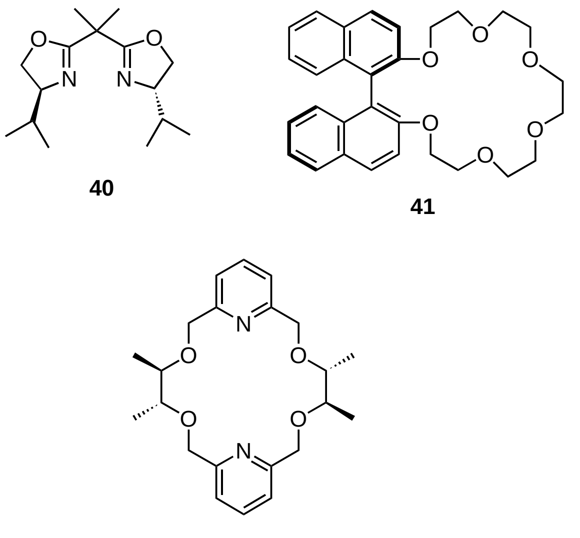
H_2O	74% ee
THF	24% ee
EtOH	39% ee
$CHCl_3$	44% ee

Scheme 27. Cu(II)-α-amino acids-catalyzed asymmetric Diels–Alder reaction.

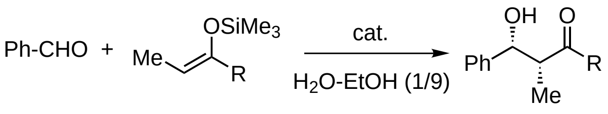
4.7 Aldol Condensation

The catalytic aldol reaction is a powerful carbon-carbon bond formation process leading to useful chiral β-hydroxy ketones and esters. Good chemical and optical yields (up to 73% ee) have been obtained in the addition of various silyl enol ethers to aldehydes in wet DMF in the presence of a palladium(II)-BINAP catalyst.[98]

Kobayashi and co-workers [99,100] carried out catalyzed asymmetric aldol reactions in aqueous media, the catalyst being obtained by mixing $Cu(OTf)_2$ and a chiral bis-(oxazoline) (Scheme 28). Very high chemical yields as well as diastereo- and enantioselectivities (up to 85% ee) have been obtained at –10 °C (Scheme 29). Aromatic, α,β-unsaturated, heterocyclic, and aliphatic aldehydes reacted smoothly under these reaction conditions. $Pb(OTf)_2$[101] and more important $Ln(OTf)_3$-crown ether[102] (Scheme 28) were shown to be very efficient chiral catalysts for asymmetric aldol reaction in aqueous media. The desired aldol adducts were obtained in high yields, with high diastereo- (*syn/anti* » 9/1) and enantioselectivities (in the range of 47 – 87% ee) depending on the structure of the aldehyde (Scheme 29). However,



Scheme 28. Some chiral ligands used in aldol reaction.



catalyst	R	yield [%]	ee [%]
$Cu(OTf)_2$ + **40**	Et	81	81
	Ph	74	67
	i-Pr	95	77
$Pb(OTf)_2$ + **41**	Ph	62	55
$Ln(OTf)_3$ + **42**	Ph	85	78

Scheme 29. Enantioselectivities observed in aldol condensation.

slight changes in ionic diameters of the lanthanide cations greatly affected the diastereo- and enantioselectivities of the aldol adducts, the large cations such as La, Ce, Pr, and Nd, giving high selectivities, while the smaller cations such as Sc and Yb showed no enantioselection.

5 Conclusions and Outlook

Considerable interest has developed recently in asymmetric organometallic catalysis in water. One of the first goals was the recycling of the toxic and often costly catalyst *via* the use of a two-phase system water-organic solvent; the organometallic catalyst is soluble in the aqueous phase by association with water-soluble ligands, while the reactants and the product(s) of the reaction are soluble in the organic phase. This approach has resulted in the synthesis of a large number of chiral water-soluble ligands. The second and more recent goal was to use a safe, non-toxic, and cheap solvent such as water in order to realize a green chemical process. However, this approach needs special techniques in order to solubilize the catalyst and the products in the aqueous phase; catalysts also have to be stable under these conditions and particularly against hydrolysis .

Asymmetric hydrogenation of prochiral substrates has been one of the most studied reactions under the above conditions. It occurs in a two-phase system or in water only in the presence of surfactants with enantioselectivities as high as those obtained in organic media; higher activities and enantioselectivities are sometimes observed in water in the presence of surfactants.

These approaches have also been successfully applied to carbonylation, oxidation, alkylation, 1,4-addition, cyclopropanation, Diels–Alder reaction and aldol condensation. If only low enantioselectivities have been obtained at this time in carbonylation or oxidation, very high enantioselectivities have been reached in water in palladium-catalyzed alkylation in the presence of surfactants, and in Diels–Alder reaction and aldol condensation in the presence of Lewis acids; in these last examples, higher activities are also observed in water than in organic solvents.

It is obvious that in the coming years the unique properties of water will be employed in other asymmetric organometallic-catalyzed reactions. However, in order to optimize these processes for fine tuning of enantioselective control of the reaction, much work has also to be devoted to the nature of the interactions, such as hydrogen bonds or hydrophobic interactions, occurring in aqueous media.

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