Complex-Catalyzed Hydrogenation Reactions in Aqueous Media

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Abstract: The review summarizes recent work in the field of hydrogenation reactions catalyzed by transition metal complexes in aqueous media. This development was stimulated by the availability of water-soluble ligands and facilitated the recycling of the catalyst from multiphase systems. Another possibility is the immobilization of the catalytic system on insoluble or water-soluble polymers. The asymmetric hydrogenation of prochiral substrates was realized in several examples with remarkable success. An enhancement of enantioselectivity and activity was achieved in the hydrogenation of amino acid precursors in microheterogeneous (aqueous micellar) systems. Beside the reduction of the C=C bond, also reported are the reduction of C=O and C=N bonds including methods which involve transfer hydrogenation.

Keywords: amphiphiles; asymmetric catalysis; biphasic catalysis; catalyst immobilization; hydrogenation; transfer hydrogenation

Abbreviations: AH: (*Z*)-α-acetamidocinnamic acid (Table 1: **2**, $R^1 = H$, $R^2 = COOH$, $R^3 = Ph$, $R^4 = CH_3$); aH: (*Z*)-α-acetamidoacrylic acid (Table 1: **2**, $R^1 = H$, $R^2 = COOH$, $R^3 = H$, $R^4 = CH_3$); Alk: alkyl; AMe: methyl (*Z*)-α-acetamidocinnamate (Table 1: **2**, $R^1 = H$, $R^2 = COOCH_3$, $R^3 = Ph$, $R^4 = CH_3$); aMe: methyl (*Z*)-α-acetamidoacrylate (Table 1: **2**, $R^1 = H$, $R^2 = COOCH_3$, $R^3 = H$, $R^4 = CH_3$); Ar^S: sulfonated aryl; Ar^N: ammonio aryl; β-CD: β-cyclodextin; BH: (*Z*)-α-benzoylamidocinnamic acid (Table 1: **2**, $R^1 = H$, $R^2 = COOH$, $R^3 = Ph$, $R^4 = Ph$); BMe: methyl (*Z*)-α-benzoylamidocinnamate (Table 1: **2**, $R^1 = H$, $R^2 = COOCH_3$, $R^3 = Ph$, $R^4 = Ph$); $bmimPF_6$: *N*-butyl-*N*-methylimidazolium hexafluorophosphate; BOC (boc): *tert*-butyloxycarbonyl; BPPM: *N*-*tert*-butoxycarbonyl-2-diphenylphosphinomethyl-4-diphenylphosphinopyrrolidine; COD (cod): 1,5-*cis, cis*-cyclooctadiene; cy: cyclohexyl; DMPE: bis(dimethylphosphino)ethane; IH: itaconic acid (Table 1: **3**, $R^1 = H$, $R^2 = CH_2COOH$, $R^3 = H$, $R^4 = H$); IMe: methyl itaconate (Table 1: **3**, $R^1 = H$, $R^2 = CH_2COOCH_3$, $R^3 = H$, $R^4 = CH_3$); MAAC: methyl acetoacetate (Table 1: **10**, $R^1 = CH_3$, $R^2 = CH_2COOCH_3$); Pal: palmitoyl; PGSE-NMR: pulsed field gradient spin echo NMR; pro: prolyl; PTA: 1,3,5-triaza-7-phosphaadamantane; SAPC: supported aqueous phase catalysis; $scCO_2$: supercritical carbon dioxide; TOF: turnover frequency; TON: turnover number; tol: tolyl; Tp: hydrotrispyrazolylborate; TPPDS: triphenylphosphine disulfonated; TPPMS: triphenylphosphine monosulfonated; TPPTS: triphenylphosphine trisulfonated.

1 Introduction

Water is important as the typical solvent in physiological processes and is also a favored solvent of "green chemistry".[1] The use of water in complex-catalyzed reactions is a development of the last two decades and was made possible through the synthesis of water-soluble and water-resistant ligands. As a milestone, the hydroformylation with a sulfonated triphenylphosphine as a ligand for rhodium was developed by Rhône-Poulenc/Ruhrchemie in 1984[2] and demonstrated the technical feasibility of water as a component in a two-phase system. Like hydroformylation, the homogeneous hydrogenation occurs via intermediate transition metal hydrides and can be performed in water. One of the earliest hydrogenation-active complexes, the hydrido-

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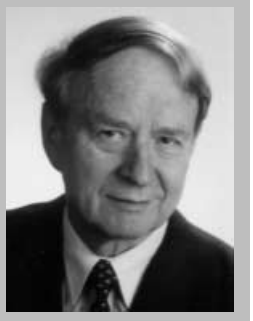
Torsten Dwars was born in Rostock, Germany in 1971. He studied chemistry and mathematics for the secondary teaching profession at the University of Rostock graduating in 1995. He did his Ph. D. work under the supervision of Günther Oehme at the Institute of Organic Catalysis Research in Rostock and his thesis was devoted to the synthesis of enantiomeric enriched α-aminophosphinic acid derivatives by asymmetric hydrogenation. After graduating in 1999 he moved for a short time as post-doctoral associate to the technical chemistry department of the University of Rostock and there he dealt with the reuse of chiral hydrogenation catalysts by ultrafiltration in a membrane reactor. Since 1999 he is scientific assistant at the Institute of Organic Catalysis Research and his research involves the synthesis of polymeric amphiphiles by plasma polymerization in aqueous systems and their use in micellar catalysis.



Günther Oehme was born in 1938 in Halle an der Saale, Germany. He studied chemistry in Köthen and Halle and received his Ph. D. with Alfred Schellenberger from the Martin-Luther-University Halle-Wittenberg in 1966. He then moved to Rostock at the Institute of Organic Catalysis Research in 1967 and worked on different fields of asymmetric catalysis and enantioselective analysis. In 1981 he joined as post-doc. the group of Steve L. Regen at Marquette University in Milwaukee, Wisconsin. In 1986 he became Professor at the Academy of Sciences of the GDR and was from 1987 till 1998 head of the Institute in Rostock. His work is directed to aqueous organometallic catalysis in microheterogeneous (micellar) systems, e. g., in asymmetric hydrogenation, C-C bond formation and photo-accelerated reactions.

pentacyanocobaltate, $[HCo(CN)_5]^{3-}$, is a water-soluble compound and useful in aqueous media.[3] The use of sulfonated phosphines in hydrogenation began in 1973 with a paper by Joo and Beck[4] and started a development in the field of homogeneous and biphasic aqueous hydrogenation with achiral and chiral catalysts.[5,6] A large number of transition metals is more or less active in hydrogenation, but the most important are Rh, Ru, Ir, Pd and recently Os.[7] While Rh, Ru, and Ir are preferently used in connection with water-soluble phosphines, phosphinites, and amines as ligands, the Pd is even connected with highly sulfonated dyes, e.g., Alizarin Red.[8] The number of papers dealing with aqueous phase hydrogenation is growing rapidly and a mini-review like the present has to be limited and should discuss the recent developments. A series of excellent reviews on the subject exists.[9–16] We will discuss the reduction of C=C, C=O, and C=N bonds with hydrogen or by transfer hydrogenation. The hydrogenolytic reduction of other functional groups will be mentioned only briefly. Owing to the limited space available, the review will focus on work published since 1990.

A number of different substrates can be hydrogenated with success. Only a part of these is water-soluble and thus suitable for hydrogenation in homogeneous aqueous systems, whereas the water-insoluble part is predestined for hydrogenation in a two-phase system. Table 1 shows a selection of substrates classified by structural types.

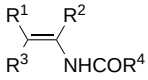
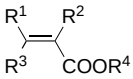
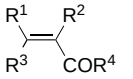
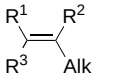
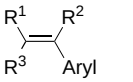
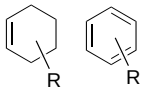
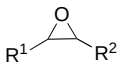
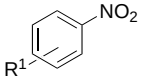
2 Hydrogenation of the C=C Bond in Aqueous Media

2.1 Homogeneous Systems

The term "homogeneous hydrogenation" means that substrate and catalyst are dissolved in the same liquid phase. Hydrogen is delivered from the gas-phase and is very sparingly soluble in the aqueous phase. The tailoring of the catalyst can be attained by a variation of the ligand. Table 2 contains an almost comprehensive selection of water-soluble phosphines suitable for achiral and chiral (asymmetric) hydrogenations.

Typical hydrophilic structural elements are sulfonate, phosphonate, carboxylate, hydroxy, ammonium, guanidinium, amine, and polyether groups. The phosphine groups are responsible for complexation. Other complex-forming ligands are collected in Table 3. Some of these ligands cause a high activity and their complexes are not sensitive to oxygen.

Table 1. Types of substrates for complex-catalyzed hydrogenation reactions in aqueous media.

Substrate class		Structure	Special examples	Type
alkynes				**1**
alkenes	enamides		amino acids precursors	**2**
	acrylic acid derivatives		ibuprofen and naproxen precursors	**3**
	unsaturated ketones and aldehydes		citral, citronellal, retinal,	**4**
	aliphatic alkenes			**5**
	styrenes		styrene	**6**
	cycloalkenes, aryl derivatives		benzene	**7**
	special alkenes		polybutadiene, oleic acids	**8**
aldehydes			aldoses	**9**
ketones				**10**
carbon dioxide		CO_2, HCO_3^-		**11**
epoxides				**12**
imines			folic acid	**13**
aromatic nitro compounds				**14**

2.1.1 Achiral Hydrogenation in Homogeneous Aqueous Phase

Table 4 gives an overview of achiral hydrogenations in the homogeneous aqueous phase. In an early paper Lee and Alper used $[HCo(CN)_5]^{3-}$ in the presence of ß-CD as catalyst for the hydrogenation of unsaturated carboxylic acids.[17] The yields were between 65 and 89%.

The hydrogenation of oct-1-ene with a rhodium-TPPTS (**15**) complex was reported by Hablot et al.[18] Allyl alcohols and maleic acid were hydrogenated with good yields using a rhodium complex with amine- and ammonium phosphines of type **16** as ligands.[19] Frediani et al.[20] reported the hydrogenation of a number of carbonyl compounds, unsaturated carbonyl compounds and hex-1-ene with a ruthenium-bipyridyl (**44)** complex at elevated temperature. Under the experimental conditions chosen the C=C bond was clearly favored.

Grzybek[21] synthesized a new water-soluble sulfonated phosphine of type **17** as ligand for the rhodium-catalyzed olefin hydrogenation and found an increase in the reaction rate on changing from water to a mixture of methanol-water (Scheme 1). A similar sulfonated but chelating phosphine was used by Baxley et al.[22]

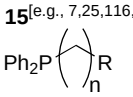
The hydrogenation of hex-1-ene, cyclohexene and allyl alcohol was reported by Pruchnik et al.[23] They applied water-soluble rhodium complexes with phosphines of the types **15** (TPPTS), **22**, and **28**. A series of unsaturated alcohols, aldehydes, ketones, carboxylic acids and nitriles was hydrogenated by Yang et al.[24] using the rhodium cluster, $[Rh_4(O_2C\text{-}n\text{-}C_3H_7)_4Cl_4(CH_3CN)_4]$ as catalyst.

Table 2. Water-soluble P^{III} ligands for complex-catalyzed hydrogenation reactions in aqueous media.

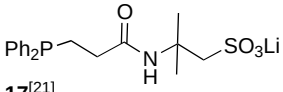
Monodentate achiral ligands

$Ph_{3-n}PAr^S_n$

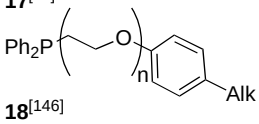
15[e.g., 7,25,116,187]



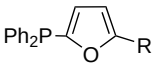
16[e.g., 48,60,81]



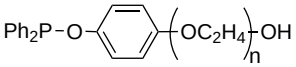
17[21]



18[146]



19[27]



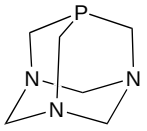
20

$P((CH_2)_nOH)_3$

21[53, 147]

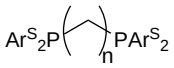
$P(CH_2CH_2CN)_3$

22[165]

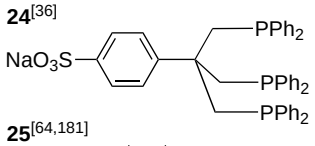


23[e.g., 63,178]

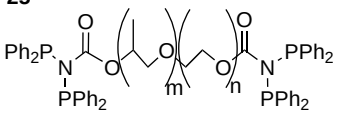
Bidentate achiral ligands



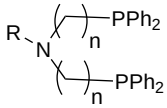
24[36]



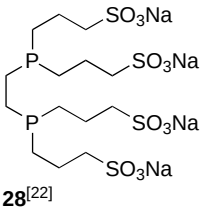
25[64,181]



26[126]

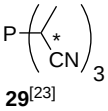


27[e.g., 128,190]



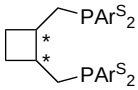
28[22]

Monodentate chiral ligands

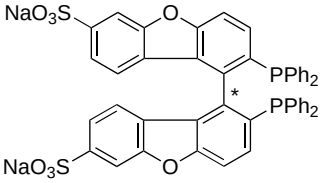


29[23]

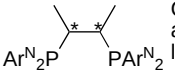
Bidentate chiral ligands



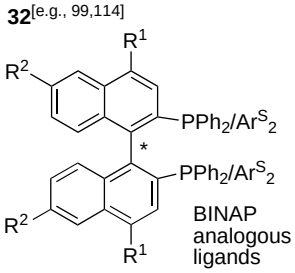
30[e.g., 77,79,176]



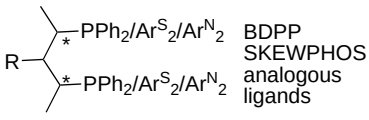
31[72]



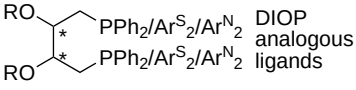
32[e.g., 99,114]



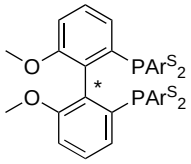
33[e.g., 76,113,159,202]



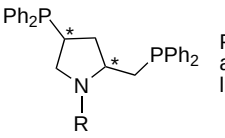
34[e.g., 75,167,169]



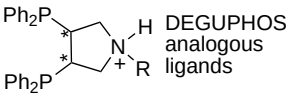
35[e.g., 93,99]



36[14]



37[e.g., 91,105,124]



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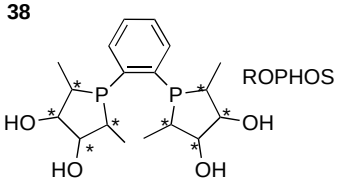
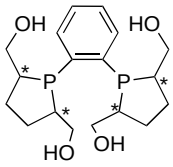


39[32,33]



40[31]

Ar^S sodium-3-phenylsulfonate
Ar^N 4-trialkylammonium-phenyl
R hydrophilic substituents (COONa, SO_3Na, PO_3Na_2, polyacrylic acid, etc.)

Table 3. Water-soluble ligands for complex-catalyzed hydrogenation reactions in aqueous media

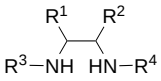
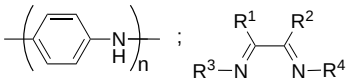
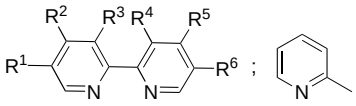
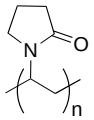
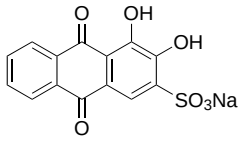
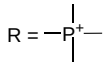
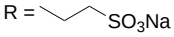
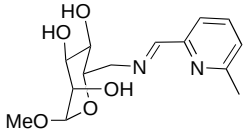
Ligand class		Structure	Type
N-ligands	amines		**41**[e.g., 158,160,192]
	imines		**42**[155]; **43**[26,192]
	pyridines		**44**[e.g., 131,152,154]; **45**[188]
	amides		**46**[129]
O-ligands		 alizarin S	**47**[e.g., 44,100]
other ligands		η^6-C_6H_6, η^5-C_5H_5, η^5-C_5Me_5, CH_3CN, $C_3H_7COO^-$, amino acids	

Table 4. Achiral hydrogenation in homogeneous aqueous phases.

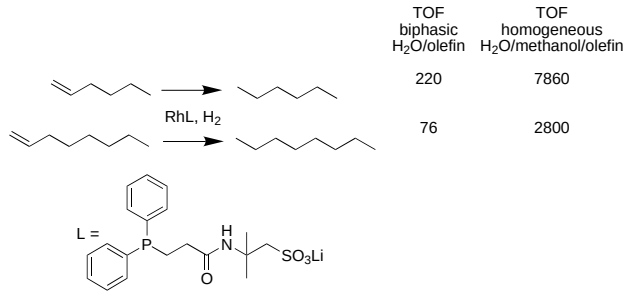
Metal	Ligands[a]	Substrates[b]	Conditions	Selectivity [%]	Ref.
Co	CN^-	**3**	β-CD, H_2O	(65–89)	[17]
Rh	TPPTS	oct-1-ene	H_2O-EtOH	(20)	[18]
Rh	**16**, R = 	allylic alcohol	H_2O	(40–100)	[19]
Rh	**44**	**1**, **4**, hex-1-ene	H_2O, H_2O-MeOH	hexane (97), benzylideneacetone (52)	[20]
Rh	**17**	**7**, other alkenes	H_2O, H_2O-MeOH	TOFs up to 7860 h^{-1}	[21]
Rh	TPPTS, 16, R = 	**4**, hex-1-ene	H_2O-THF	with **15** (4), with **16** (100)	[22]
Rh	TPPTS, **23**	**7**, hexene-1, allylic alcohol	H_2O	TOF 21–143 h^{-1}	[23]
Rh (cluster)	CH_3CN, butyric acid	**3**, **4**	H_2O	(66–100)	[24]
Ir	TPPMS	unsaturated C_{18}-carboxylic acids	H_2O	(7–57)	[25]
Pd	see Formula 1	unsaturated nitriles	H_2O	(100)	[26]
Rh	**19**, R = COONa, PO_3Na, SO_2Li	**2**, AH	H_2O-MeOH	(0–100)	[27]

[a] See Tables 2 and 3.
[b] See Table 1.

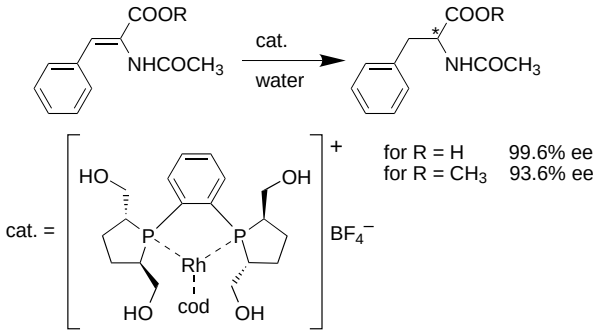
The ratio of isomerization and hydrogenation in long-chain unsaturated fatty acids was investigated by Kovacs et al.[25] with an iridium-TPPMS complex. Boriello et al.[26] used a palladium complex of a ligand shown in Formula 1. The ligand is derived from a carbohydrate, but gave no chiral induction with methacrylonitrile.



Formula 1. Ligand in accordance with Ref.[26]



Scheme 1. Biphasic and homogeneous hydrogenation of olefins.[21]



Scheme 2. Asymmetric hydrogenation in water.[31]

Eymery et al.[27] developed water-soluble furylphosphines for an achiral reduction of α-acetamidocinnamic acid.

2.1.2 Asymmetric Hydrogenation in Homogeneous Aqueous Solution

Only a few papers (see Table 5) are available for an enantioselective hydrogenation in an aqueous medium.

Wan and Davis investigated in two papers the asymmetric hydrogenation of α-amino acid precursors with a Ru-sulfonated BINAP (**33**)[28] or a Rh-**30** complex[29] but the enantioselectivities were only moderate. Shin and RajanBabu[30] used ligands derived from α,α′-trehalose and obtained with the rhodium complex up to 70% ee. A real milestone in aqueous enantioselective hydrogenation was realized in investigations by Holz et al.[31] (Scheme 2), Li et al.[32] and recently RajanBabu et. al.[33] with DUPHOS analogues **39** and **40** as ligands in rhodium complexes. These groups achieved enantioselectivities with itaconic acid, α-acetamidoacrylic acid, (Z)-α-acetamidocinnamic acid and their methyl esters between 93 and 99% ee.

Less successful was the diastereoselective hydrogenation of a (*S*)-proline modified anthranilic acid as substrate (74% de).[34]

2.1.3 Mechanistic Investigation

The mechanism of the hydrogenation of amino acid precursors was developed by Halpern and co-workers[35] and is shown in Figure 1.

As to be expected with transition metal hydrides as intermediates, the pH plays an important role in aqueous medium with respect to activity and selectivity.

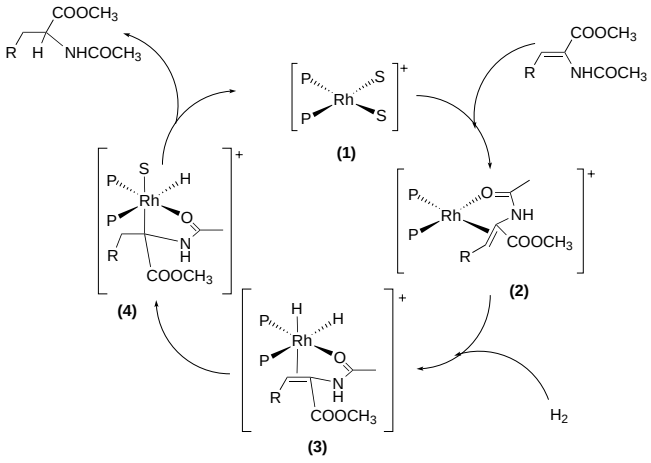


Figure 1. Mechanism of the homogeneous hydrogenation.[35]

Table 5. Chiral hydrogenations in homogeneous aqueous systems.

Metal	Ligand[a]	Substrates	Conditions	Enantioselectivity [% ee]	Ref.
Rh	**30**	aH, aMe	H_2O	(70)	[28]
			H_2O-MeOH	(55 – 67)	
Ru	**33** with Ar^S	aH, aMe, AH	H_2O, H_2O-MeOH	(2 – 88)	[29]
Rh	diphosphinites, derivatives of α,α'-trehalose	aH, aMe, AH, AMe	H_2O	(49 – 59)	[30]
Rh	**39**	aH, aMe	H_2O	aH (>99), aMe (94)	[31]
Rh	DUPHOS-similarity derived from d-mannitol	IH, IMe	H_2O-MeOH	(99)	[32]
Rh	DUPHOS-similarity	AH, AMe, aH, aMe	H_2O, H_2O-MeOH	(99)	[33]
Rh, Ru	η^5-C_5Me_5, η^6-C_6H_6	proline modified anthranilic acid	H_2O-EtOH	with $[Ru(C_6H_6)Cl]_2$ (74 de)	[34]

[a] See Table 2.

For instance, Malmström et al.[36] found in the rhodium-catalyzed hydrogenation of (Z)-α-acetamidoacrylic acid a strong pH effect on the reaction rate, and several authors could show that there is a pH dependence of the chemoselectivity on the hydrogenation of α,β-unsaturated carbonyl compounds[37,38,39] (for an example, see Scheme 3).

A mechanistic investigation of the rhodium- and ruthenium-catalyzed reaction has been reviewed by Joo, Papp, and Katho.[40]

Several authors applied homogeneous hydrogenation-active complexes of rhodium[41,42,43] or palladium[44] in a regioselective deuteriation of unsaturated substrates.

Beside the use of D_2 it is also possible to insert D from D_2O which is used instead of H_2O in a hydrogenation reaction.[45] The importance of this CH/CD exchange for mechanistic studies will be discussed in Section 2.2.

2.2 Multiphase Systems

It is not easy to distinguish between homogeneous and biphasic (multiphase) hydrogenation in aqueous systems because in many cases the substrates are not soluble in water and form a second phase. Besides, the gas phase would be also a different phase. We will define a biphasic system as a system with two liquid phases. Table 6 summarizes a selection of achiral hydrogenation reactions predominantly catalyzed by rhodium and ruthenium complexes.

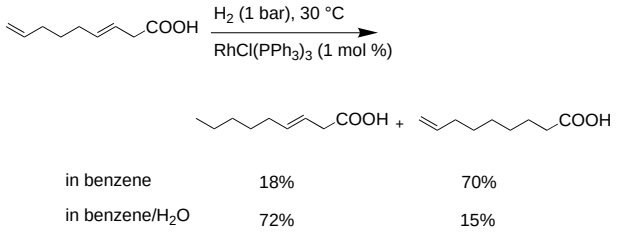
Lee and Alper[46] used $[HCo(CN)_5]^{3-}$ with lanthanides (La, Ce, Yb salts) as promotors in a water/benzene system with β-cyclodextrin as mediator and reduced dienes selectively to monoenes. The same working group[47] hydrogenated the C=C bond in unsaturated carbonyl compounds with moderate to good selectivities by means of the rhodium-hydrido-cyclohexylphosphine complex $[RhH(Pcy_3)_2Cl_2]$. Hex-1-ene was hydrogenated under catalysis by rhodium complexes with diphenylalkylphosphines containing phosphonium groups as hydrophilic parts.[48]

Okano et al.[49] applied Wilkinson-analogous rhodium complexes for the regioselective hydrogenation of twofold unsaturated carboxylic acids (Scheme 4).

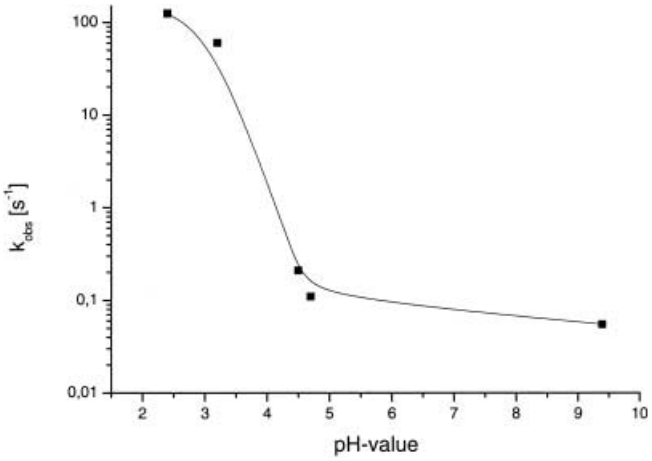
A Russian group reported that rhodium-[50] or platinum-amine complexes[51] form active catalysts for the hydrogenation of linear and cyclic alkenes in the presence of water. Applying the water-soluble ruthenium-benzene complex, $[Ru(\eta^6\text{-}C_6H_6)(CH_3CN)]BF_4$, Chan et al.[52] developed an aqueous biphasic system for the hydrogenation of alkenes and α,β-unsaturated carbonyl compounds.

Ruthenium-arene complexes were used also by other authors with success.[53,54] An activity in arene hydrogenation was found[55] in the case of ruthenium-clusters.

Favored ligands for ruthenium and rhodium are the in the *meta*-position mono- and trisulfonated triphenylphosphines, TPPMS and TPPTS. The complexes are active in the hydrogenation of alkenes and cycloalkenes,[56] unsaturated carbonyl compounds,[57] and dimethyl itaconate which was investigated in a continuous flow reactor.[58] It seems to be of interest to hydrogenate unsaturations in polymers, e.g., polybutadiene, styrene-butadiene copolymers and nitrile-butadiene copolymers.[59,60,61] In a recent paper by Guo and Rempel[61]



Scheme 4. Regioselectivity in homogeneous and biphasic systems.[49]



Scheme 3. Dependence of activity on the pH.[36]

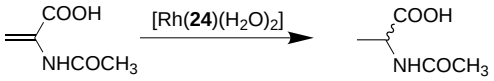
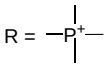


Table 6. Achiral hydrogenation in multi-phase aqueous systems.

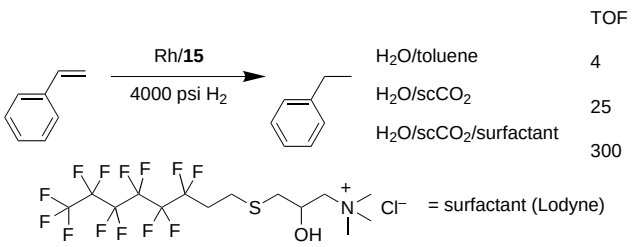
Metal	Ligand[a]	Substrates[b]	Conditions	Selectivity [%]	Ref.
Co (La, Ce, Yb)	CN^-	**5**, **7**	β-CD, H_2O/benzene	diene → monoene (49 – 100)	[46]
Rh	Pcy_3	**4**	H_2O/benzene (xylene)	alkene → alkane (15 – 96)	[47]
Rh	**16**, R = 	**5**	H_2O/ether (CH_2Cl_2)	alkene → alkane (23 – 89)	[48]
Rh	PPh_3. $Ptol_3$	dienecarboxylic acids	H_2O/benzene	diene → monoene (75 – 81)	[49]
Rh	Trioctylamine	**5**, **7**	H_2O/alkene	TOF up to 26000 h^{-1}	[50]
Ru	η^6-C_6H_6	**10**	H_2O/benzene	alkene → alkane (68 – 87)	[52]
Ru	TPPMS	**6**, **7**	H_2O/decaline	ethylbenzene (97), cyclohexene (25)	[56]
Pt	Amines	**1**, **5**, **7**	H_2O/alkene	TON up to 10000	[51]
Ru	TPPTS	**9**, **10**	H_2O/toluene (CH_2Cl_2)	alkene → alkane (6 – 96)	[57]
Rh	16, n = 5, 7, R = SO_3Na	**5**, **6**, **8**	H_2O/toluene	alkene → alkane (84 – 100)	[59]
Rh	TPPTS, 16, n = 5, R = COONa	**8**	H_2O/toluene	(45 – 84)	[60]
Ru	PPh_3, Pcy_3	**8**	H_2O/polymer-emulsion, different solvents	(95 – 99)	[61]
Ru	η^5-C_5H_5, **16**	sorbic acid	H_2O/heptane	diene → alkane (22 – 92)	[53a]
Ru	η^6-C_6H_6	**7**	H_2O/arene	arene → cyclohexane (63 – 100)	[54]
Ru	**16**	sorbic acid	H_2O/MeOAc	diene → alkane (81)	[53b]
Rh	TPPDS	styrene	H_2O/$scCO_2$, surfactants	TOF up to 300 h^{-1}	[62]
Rh	**23**	**3**, **4**	H_2O/olefin	TOF up to 300 h^{-1}	[63]
Ru	**25**	**5**, **6**, **8**	H_2O-MeOH/*n*-heptane	(97 – 100)	[64]
Ru	DMSO	hex-1-ene	H_2O/hexene	(78)	[65]
Rh	TPPTS	IMe	H_2O/cyclohexane	continuous	[58]
Rh	η^4-C_7H_8, PPh_3	2-butyne-1,4-diol	H_2O/ionic liquid	2-butene-1,4-diol (66), 2-butane-1,4-diol (33)	[66]
Ru	η^6-C_6H_6, η^6-C_6Me_6	**7**	H_2O/arene	(74 – 100)	[55]

[a] See Table 2.
[b] See Table 1.

the influence of different stabilizers of water- polymer emulsions was studied.

As an interesting new alternative, Jacobson et al.[62] checked a system consisting of water and supercritical CO_2. They observed an important enhancement of the reaction rate with a number of special phase-transfer reagents (example, see Scheme 5).

The hydrogenation of unsaturated carbonyl compounds with a water-soluble rhodium hydride complex



Scheme 5. Enhancement of hydrogenation rate by use of a surfactant in the biphasic system water/$scCO_2$.[62]

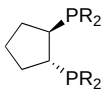
containing monoalkylated PTA, **23**, as ligand was reported by Pruchnik et al.[63] A ruthenium complex with the tridentate ligand **25** was active in hydrogenation but under relatively harsh conditions (30 bar H_2, 140 °C).[64] Sometimes really simple complexes, e.g., [$RuCl_2$(dmso)], could be used with success for the hydrogenation of alkenes.[65]

A temperature-controlled ionic liquid/water system with [$Rh(\eta^4$-$C_7H_8)(PPh_3)_2]BF_4$ as catalyst and 2-butyne-1,4-diol as substrate was described recently by Dyson et al.[66] The system is biphasic at room temperature and becomes homogeneous above 80 °C.

Early work about asymmetric hydrogenation in aqueous liquid/liquid systems was reviewed by Sinou.[11,67] Obviously, enantioselectivities were lower in water than in organic media, especially methanol. As mentioned in Section 2.1, some authors could recently obtain very high inductions in water. Novel results in chiral hydrogenations are summarized in Table 7.

Toth et al.[68] hydrogenated (*Z*)-α-acetamidocinnamic acid (AH) and (*Z*)-α-benzoylamidocinnamic acid and

Table 7. Chiral hydrogenations in multi-phase aqueous systems.

Metal	Ligand[a]	Substrates[b]	Conditions	Enantioselectivity [% ee]	Ref.
Rh	**34** with Ar^N	AH, AMe, BMe	H_2O H_2O/EtOAc/benzene	AH (95), AMe (40) AH (67), AMe (44), BMe (54)	[68]
Rh	**32**, **34**, **35** with Ar^N	AH, AMe, BMe	H_2O H_2O/EtOAc	AH (94), AMe (68) AH (73), AMe (77), BMe (67)	[69]
Rh	**34** with Ar^S	AMe	H_2O/EtOAc	(69)	[70]
Rh	**34** with different Ar^S	AMe, IMe	H_2O/EtOAc	AMe (87), IMe (28)	[71]
Ru	**31**	AH, MAAC	H_2O/EtOAc H_2O-HCl	AH (72) MAAC (85)	[72]
Ru		AH	H_2O H_2O/toluene	(22) (80)	[73]
Ru	**33**	**3** with $R^1 = H$, $R^2 = COOH$, R^3, $R^4 = Me$	H_2O/ionic liquid ($bmimPF_6$)	(92)	[74]
Rh, Ir	**34**, $R = CH_2PhSO_3Na$	IMe	H_2O-MeOH/hexane	Rh (76), Ir (66)	[75]
Rh	**33**, $R^2 = H$, $R^1 = PO(OH)ONa$	IMe	H_2O-EtOH/hexane	(79)	[76]

[a] See Table 2.
[b] See Table 1.

their methyl esters in water and in a biphasic system containing water/ethyl acetate and benzene with a rhodium complex, derived from ligand type **34** with $Ar^N = C_6H_4(p\text{-}N^+Me_3)$. Surprisingly, the enantioselectivity in water was better for AH (95% ee) than under biphasic conditions (67% ee). Similar results were observed in a second investigation with DIOP, BDPP, and modified CHIRAPHOS as ligands.[69] The same group[70] modified BDPP, **34**, with $Ar^S = C_6H_4$ (*m*-SO_3Na) and as amphiphile with $Ar^S = C_6H_4\text{-}(CH_2)_3\text{-}C_6H_4(p\text{-}SO_3Na)$. The rhodium complex of this amphiphilic ligand yielded in the biphasic system water/ethyl acetate the highest chiral induction (69% ee).

The dependence of the enantioselectivity on the degree of sulfonation in rhodium-BDPP complexes was investigated by Lensink et al.[71] for amino acids, α-methylsuccinic acid and amine precursors. In the imine hydrogenation and in the hydrogenation of dimethyl itaconate the monosulfonated ligand gave the best enantioselectivities, two- and three-fold sulfonated ligands caused practically racemic products. This effect was missing with dehydroamino acids and their esters as substrates (Figure 2).

Gelpke et al.[72] used a ruthenium complex of the atropisomeric diphosphine BIFAPS (**31**) in the hydrogenation of (*Z*)-α-acetamidocinnamic acid and methyl acetoacetate (MAAc). The amino acid was synthesized in a two-phase system (water/ethyl acetate) with 72% ee, MAAc gave low enantioselectivities in water (22% ee) but showed enhanced values in the presence of sulfuric acid (86% ee) or hydrochloric acid (85% ee).

An expanded *trans*-bis(diphenylphosphino)cyclopentane (Formula 2) was synthesized and checked as

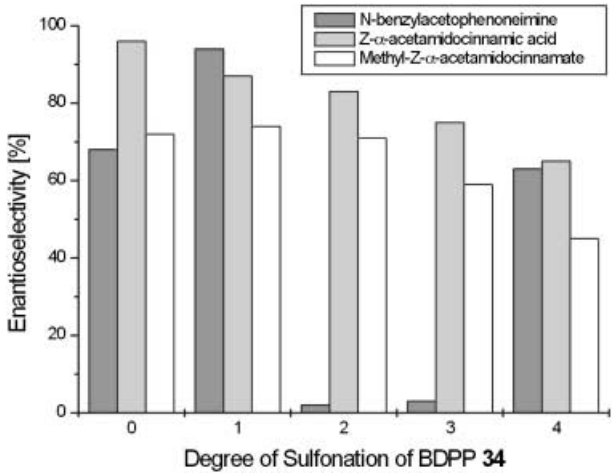
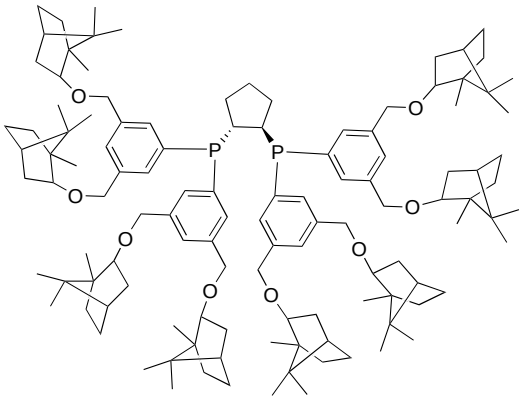


Figure 2. Dependence of the enantioselectivity in hydrogenation on the degree of sulfonation and on the type of substrate.[71]

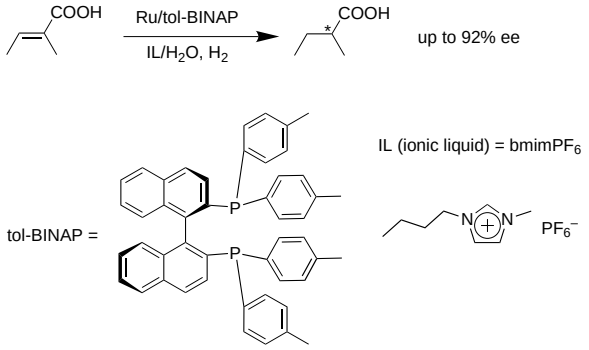
rhodium complex by Brunner et al.[73] The hydrogenation of AH resulted in 22% ee in water, but in water/toluene mixtures showed enhanced enantioselectivity of 80% ee.

The high enantioselectivity of 92% ee was achieved with a ruthenium complex of the BINAP type and α-methylcrotonic acid in a two-phase system of butylmethylimidazolium hexafluorophosphate and water[74] (Scheme 6).

Bianchini et al.[75] used a ligand of the type **34** with $R = C_6H_4(p\text{-}SO_3Na)$ in rhodium and iridium complexes and obtained in the hydrogenation of methyl itaconate in water-ethanol/hexane 76% and 66% ee.



Formula 2. Chiral ligand developed by Brunner et al.[73]



Scheme 6. Asymmetric hydrogenation in biphasic systems containing an ionic liquid.[74]

Recently, Köckritz et al.[76] prepared hydrophilic analogues of BINAP with phosphonate groups and applied them as rhodium complexes in aqueous hydroformylation and hydrogenation reactions. Dimethyl itaconate was reduced with 79% ee in a two-phase system of water-ethanol/hexane.

Only moderate chiral induction (up to 87% de) was observed in the asymmetric hydrogenation of unsaturated dipeptide precursors with rhodium complexes of the phosphines **30**, **32**, and **34** containing *m*-sulfonated arenes as hydrophilic groups.[77]

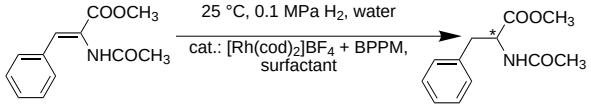
The mechanistic role of water in homogeneous and multiphase hydrogenation reactions was investigated mainly in the groups of Sinou[78] and Joo[40] by means of deuteriation experiments with amino acid precursors and unsaturated carboxylic acids. Hydrogenation in D_2O or *vice versa* deuteriation in H_2O gives CH/CD-exchange. The effect depends on the type of substrate, the transition metal and the type of ligand.[79] In accordance with the Halpern mechanism shown in Figure 1 the exchange should occur in step 4 between the metal hydride and D_2O (H_2O) as coordinated solvent. Obviously, the exchange takes place preferently in the α-position to the carboxylic group and some scrambling to a small extent was explained due to a competition between a rapid ß-elimination and a slower reductive elimination process. More deuterium than expected was incorporated by use of palladium-Alizarin Red complexes in the hydrogenation of unsaturated carboxylic acids.[44] Ideas about the existence of different metal hydride species in aqueous systems were developed by Joo and co-workers and applied on selectivity problems.[39,80] An active share of water in the coordination sphere of rhodium-phosphine complexes was concluded by Bischoff and Kant.[81] They observed exclusively the hydrogenated product and its hydrolysis derivative in the aqueous phase hydroformylation of 2,5-dimethoxy-2,5-dihydrofuran with a rhodium-TPPTS complex.

2.3 Hydrogenation in Microheterogeneous (Colloidal) Systems

Amphiphiles or surfactants with a special structure can assemble in aqueous media at a characteristic temperature and a critical concentration.[82] These spherical aggregates are micelles of colloidal size. The interior of micelles has an extreme polarity gradient and excellent solubilization properties for non-polar and polar compounds. Micelles present versatile reaction phases in a microheterogeneous range.[83] The suitability for hydrogenation reactions should be good because of the high solubility of hydrogen in surfactants. It was found that the asymmetric hydrogenation of amino acid precursors by means of water-insoluble rhodium complexes can be realized in an aqueous micellar medium with high activities and excellent enantioselectivities.[84,85] The effect is significant above the critical micelle concentration (CMC) and is coupled to the existence of micellar aggregates. Instead of self-organized supramolecular assemblies of surfactants the use of polymerized macromolecular micelles gave almost similar effects.[86,87] The influence of amphiphiles on the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate is illustrated in Table 8.

Very different amphiphiles – anionic, cationic, zwitterionic, and non-ionic – gave an enhancement in activity and enantioselectivity. The isolation of the product is quite simple by extraction with an organic solvent, whereas the catalyst remains in the micelle and can be reused. With polymerized or polymeric (derived from amphiphilic polymers) micelles[88] the system could be transferred into a membrane reactor to save the extraction step.[89] The effect of amphiphiles on activity and enantioselectivity was found with different amino acid precursors [90] and related compounds like esters of dehydroaminophosphonic[91] and dehydroaminophosphinic acids.[92] Sometimes a surprisingly high increase of the enantioselectivity was observed[93,94] and even the inversion of configuration is possible. For a correct evaluation of the improvement of enantioselectivity

Table 8. Asymmetric hydrogenation in the presence of different types of amphiphiles.



Surfactant	$t_{1/2}$ [min]	optical yield [% ee]
none in water	90	78
none in methanol	2	90
anionic sodium dodecyl sulfate	6	94
cationic cetyltrimethylammonium hydrogen sulfate	5	95
zwitterionic *N*-dodecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate	5	93
non-ionic polyoxyethylene(10)hexadecyl ether (Brij 56)	7	95

Selke[95] recommended as a measure beside the enantiomeric excess (ee), also the use of the enantiomeric ratio ($E_R/E_S = er$). In some cases the enantioselectivity in aqueous micellar systems exceeds the values obtained in methanol, which is one of the best organic solvents for homogeneous hydrogenations.

One advantage of the aqueous micellar system is the direct transfer of catalyst and substrate from the organic solvent into the aqueous medium without any hydrophilization, a disadvantage can be the sometimes difficult separation of organic and water phases after the extraction of the product, because of the surface activity of the amphiphile. Some proposals to avoid this surface effect will be given in Section 2.4.

The reason for enantioselectivity in these examples is the chiral catalyst. Some investigations were undertaken to check an optical induction due to chiral amphiphiles. The amphiphiles were derived from cholesterol,[96] carbohydrates[97] or amino acids.[98] Unfortunately, the induction was small in all cases studied and attained as a maximum up to 11% ee. Especially *N*-acylprolines and prolylproline derivatives were investigated systematically. The results are presented in Figure 3.

The connection between configuration of the amphiphile and configuration of the product is unambiguous. In the case of prolylproline head groups the configuration of the prolyl part decides the configuration of the products. It seems to be a precondition for chirality transfer to the substrate that chirality exist near the transition of the polar head group to the non-polar tail. The reaction should occur in this region of the micelle which is designated as the "palisade layer". The experiments with chiral amphiphiles are not useful for asymmetric synthesis but are informative with respect to the mechanism of the micellar effect. Other indications about the intramicellar reaction were concluded from ***p***ulsed field ***g***radient ***s***pin ***e***cho-NMR (PGSE-NMR) measurements.[99] This method allows the measurement of an average diffusion coefficient of the catalyst below and above the critical micelle concentration and gives also information about the incorporation of substrates.

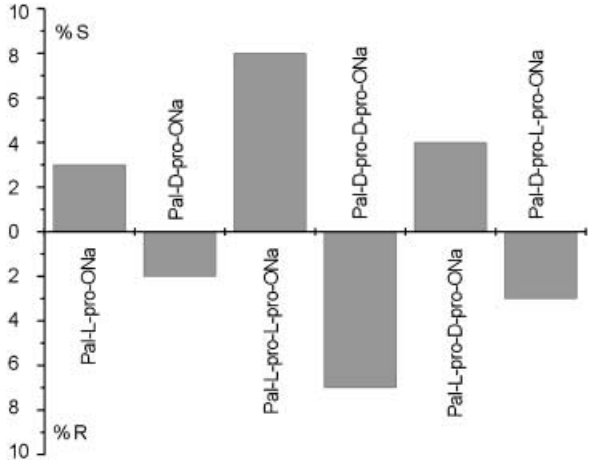


Figure 3. Chiral induction in micelles of *N*-acylprolines and *N*-acylprolylprolines. Rh:amphiphile:AMe = 1:20:100, Pal-L-pro-ONa = palmitoyl-L-proline sodium salt, Pal-L-pro-L-pro-ONa = palmitoyl-L-prolyl-L-proline sodium salt.

The CH/CD exchange in the α-position of the α-amino acid derivatives in the hydrogenation in D_2O as medium can be influenced by amphiphiles.[100,101] Anionic amphiphiles have an exceptional position and inhibit the exchange. The effect was observed even at concentrations below the CMC of the amphiphile and seems to be a non-micellar effect. Anionic amphiphiles enable also an extension of the pH range of enantioselective (asymmetric) hydrogenations.[102] It is possible that the aqueous micelles of anionic amphiphiles are more compact than those of cationic, zwitterionic, and non-ionic amphiphiles.

The kinetics of the standard reaction (see at the top of Table 8) in aqueous micellar medium with SDS as

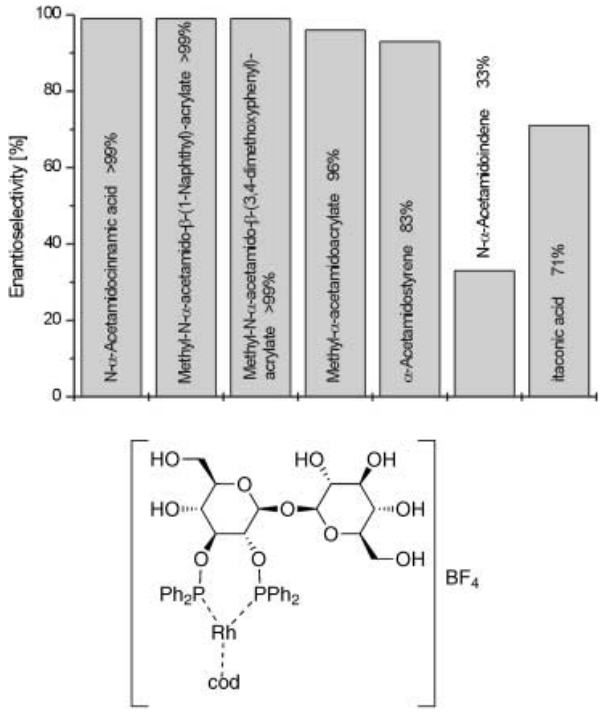


Figure 4. Asymmetric hydrogenation in aqueous micellar medium (different amounts of SDS).[104]

micelle-forming amphiphile was investigated by Weitbrecht and Schomäcker.[103] The equilibrium between catalyst and substrate is almost on the side of the catalyst-substrate complex, and the insertion of hydrogen is rate-determining. The activation energy was found to be lower than in methanol as the medium. The reason for the increase of enantioselectivity in micelles is not clear in all details, but probably depends on the regularity of the interior, especially due to the folding of the hydrophobic tails. A micellar effect could be observed also with water-soluble rhodium-phosphinite complexes derived from carbohydrates[104] (Figure 4).

Some experiments were performed with amphiphilized ligands in rhodium catalysts but their influence was optimized in mixture with a "standard amphiphile".[105]

Amphiphilic self-organized catalysts were also tested in biphasic aqueous systems with success.[70]

2.4 Immobilization

Numerous attempts have been made to combine the advantages of homogeneous catalytic systems (high activity, high selectivity, excellent reproducibility) with the advantages of heterogeneous catalytic systems (long life, recycling, continuous application). The "classical" method of immobilization is the anchoring of homogeneous systems on organic or inorganic supports.[106,107] The support can be a solid or a water-soluble polymer.

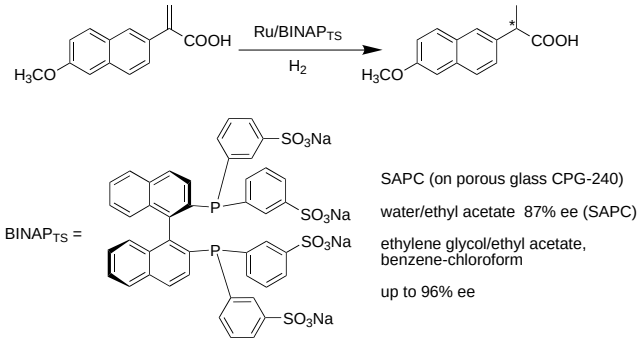
Brunner et al.[108] tried the immobilization of rhodium-DIOP and rhodium-NORPHOS complexes on different supports like barium sulfate, cellulose, silica, DOWEX ion exchanger, alumina, active charcoal, and SERDOLIT, partly in alcohol-water mixtures. In comparison to homogeneous systems a loss of enantioselectivity was observed at least with the rhodium NORPHOS complex.

Toth et al. quaternized amino groups containing chiral phosphines (**34**, **35**) with tetrafluoroboric acid[109] and with strongly acidic ionic exchangers[110] and checked these as catalysts in the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate and the corresponding cinnamic acid in water and water-containing solvent mixtures. The acidified homogeneous system led with cinnamic acid to high enantioselectivities (up to 97% ee) and bound to the ionic exchanger to medium enantioselectivities (up to 47% ee).

In 1989 proposed Arhancet et al.[111] ***s***upported ***a***queous ***p***hase ***c***atalysis (SAPC) as a new convenient method to fix homogeneous catalytic systems on small wet particles of silica. These particles adsorb water and organic solvents in different areas and take up the water-soluble catalyst and hydrophobic (soluble in organic solvents) substrates. The small particles play the role of microreactors and are reusable. SAPC experiments in hydrogenation with rhodium complexes were published by Wan et al.[112,113] using sulfonated Ru-BINAP complexes on porous glass as supports. The enantioselectivity was moderate in water-containing systems (up to 83% ee), whereas in an ethylene glycol/ethyl acetate mixture naproxen resulted with 95% ee from the hydrogenation of 2-(6′-methoxy-2′-naphthyl)acrylic acid (Scheme 7).

Toth et al.[114] compared results in biphasic asymmetric hydrogenation of AMe with those of SAPC and observed a significant decrease in case of immobilization.

The chemoselective hydrogenation of α,β-unsaturated aldehydes to allyl alcohols with Ru-TPPTS complexes in SAPC systems was investigated by Fache et al.[115] in relation to a supported Ir-phosphine complex.



Scheme 7. Asymmetric hydrogenation of a naproxen precursor with a catalyst adsorbed on porous glass.[112,113]

The authors found good alternatives to homogeneous systems with the chance of easy recovery. Interestingly, Bhanage et al.[116] obtained in the hydrogenation of cinnamic aldehyde in liquid/liquid phase systems (water/toluene and water/scCO_2) and in SAPC experiments with Ru-phosphine complexes mainly the allyl alcohol. Rhodium and palladium complexes gave mainly the β-phenylpropionaldehyde.

Another type of embedding was developed by Flach et al. They bound anionic, cationic and non-ionic amphiphiles to organic[117] and inorganic[118] supports. The polar/non-polar layer seems to be a good medium for asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate with a rhodium-BPPM complex as catalyst and resulted in high enantioselectivities and high activities. In some cases it was possible to recycle the catalyst up to ten times. No leaching of rhodium could be indicated in the aqueous phase.

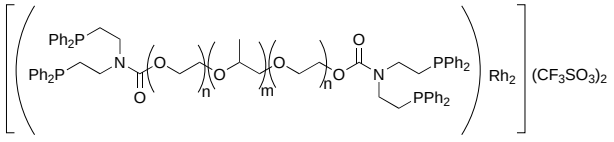
Mesoporous silica and sol-gel beds for Ru-BINAP and Rh-BPPM complexes were used in the hydrogenation of (Z)-α-acetamidocinnamic acid or their methyl ester by Jamis et al.[119] Enantioselectivities were only moderate and could not be increased by a modification (surface deactivation) of the silica.[120] Methanol-water mixtures were typical media.

Anderson et al.[121] bound rhodium-phosphine complexes by impregnation in VPI-5 (aluminium phosphate) micropore material.

Another kind of immobilization shall be mentioned here. In a series of papers Malmström et al.[122–124] described the anchoring of achiral and chiral (PPM) rhodium complexes on water-soluble polyacrylic acid and polyacrylamide. The hydrogenation of the chiral systems were checked with (*Z*)-α-acetamidocinnamic acid and its methyl ester as substrate and yielded the highest enantioselectivities with the acid (up to 89% ee). Change from water as medium to the biphasic system water/ethyl acetate gave an advantage, whereas on addition of benzene the enantioselectivity decreased.

Comparable systems were proposed by Bergbreiter et al.[125] They used supports with temperature coefficients as shown in Formula 3 ("smart" ligands[126]).

Another principle was to apply poly(*N*-isopropylacrylamide) as support in a thermomorphic biphasic system of aqueous ethanol/hexane. The mixture became homogeneous above 70 °C and the reaction occurred. On cooling back to room temperature the product was dissolved in the hexane phase and the catalyst remained in the water-alcohol phase.[127]



Formula 3. "Smart" ligand for hydrogenation in aqueous medium.[126]

In some work the water-soluble polymers were used to protect small particles of transition metals.[128,129]

Fan et al.[130] synthesized a water-soluble amphiphilic ligand through polycondensation of a 5,5′-diamino-BINAP, polyethylene glycol, and terephthaloyl chloride and used the Ru complex in aqueous biphasic systems for an effective enantioselective hydrogenation of prochiral carboxylic acids (e.g., a precursor of naproxen). Here also we should mention the use of polymer-detergent complexes in hydrogenation reactions by Fuhrmann et al.[87] and the work by Steckhan and co-workers[131] who applied PEG-bound rhodium-bipyridyl complexes for the continuous preparation of NADH in a membrane reactor.

3 Hydrogenation of C=O and C=N Bonds in Aqueous Media

Various hydrogenations of C=O or C=N functionalities in aqueous media are known. Especially ruthenium and rhodium (less so iridium, palladium and osmium) are the active metals in these reactions. Most complexes are prepared by combination of the metal and a water-soluble ligand (see Tables 2 and 3). Favored substrates are aldehydes, ketones, carbon dioxide, epoxides, and imines. In the case of the reduction of ketones and imines the preparation of enantiomerically enriched products is possible by use of optically active catalysts. Most of the reactions were carried out in biphasic systems, but there are also examples for homogeneous hydrogenations, or sometimes transfer hydrogenations in water.

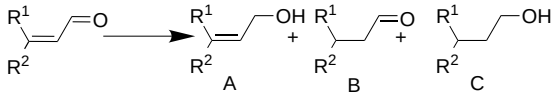
3.1 Hydrogenation of the C=O Bond and Epoxides

3.1.1 Hydrogenation of Aldehydes

The combination of ruthenium and TPPTS (**15**, n = 3) under biphasic[132] and homogeneous conditions[133,134] showed activity in the hydrogenation of simple aliphatic aldehydes. Aromatic aldehydes and unsaturated aldehydes were reduced selectively to the corresponding alcohols by ruthenium catalysts in water/arene two-phase systems.[52,135–139]

Especially, the selective hydrogenation of the C=O bond in unsaturated aldehydes **4** is well examined.[40] Table 9 summarizes recent results in this field and shows the effectivity of the catalysts used in aqueous media. Most of all, the combinations of ruthenium and sulfonated phosphines seems to be successful to hydrogenate the carbonyl bond and not the olefinic double bond. Joo and co-workers reported that the pH value[140,141] of the solution and the metal [37] are decisive for the conversion and chemoselectivity of the reaction (Figure 5).

Table 9. Selective C=O-bond hydrogenation in unsaturated aldehydes.



Metal	Ligand[a]	Conditions	Selectivity [%A/%(B+C)]	Ref.
Ru	TPPMS, TPPTS	$R^1 = H$, $R^2 = Ph$, water, water/chlorobenzene	95/5	[140]
Ru	PPh_3, TPPTS	$R^1 = H$, $R^2 = Ph$, water/toluene, water/$scCO_2$	up to 99/1	[116]
Ru	TPPTS	$R^1 = H$, Me, $R^2 = Ph$, Me, water/organic solvents, biphasic, transfer hydrogenation with formates, recycling of the catalyst	up to 99/1	[141]
Ru	TPPTS	$R^1 = H$, $R^2 = Ph$, water/organic solvents, biphasic	up to 97/3	[57]
Ru	TPPTS	$R^1 = H$, Me, $R^2 = Ph$, Me, water/toluene, recycling of the catalyst	up to 99/1	[144]
Ru	**18**	$R^1 = Me$, $R^2 = Me$, water/2-propanol	97/3	[146]
Ru	TPPMS, TPPTS	$R^1 = H$, $R^2 = Ph$, water/toluene	up to 100/0	[7]
Ru, Os	TPPMS	$R^1 = H$, $R^2 = Ph$, water/toluene	up to 95/5 for Ru, 100/0 for Os	[145]
Ru, Ir	TPPTS	$R^1 = Me$, $R^2 = Me$, water/hexane, SAPC, recycling of the catalyst	up to 95/5	[115]
Ir	TPPTS	$R^1 = Me$, $R^2 = Me$, water	up to 95/5	[143]
Ir	$P(CH_2OH)_3$	$R^1 = H$, $R^2 = Ph$, water/benzene	97/3	[147]

[a] See Table 2.

Mercier and co-workers[142-144] showed the possibility of recycling the water-soluble catalyst in the highly selective iridium-catalyzed hydrogenation of unsaturated aldehydes.[143]

Sanchez-Delgado et al.[145] reported that osmium complexes catalyze the aldehyde reduction under suitable conditions with remarkable selectivities, but with poor conversions. Other water-soluble phosphines (Table 2), are also active in the hydrogenation of unsaturated carbonyl compounds.[146,147]

Fache et al.[115] used SAPC for their ruthenium- and iridium-catalyzed hydrogenations of methylcrotonaldehyde and retinal. They found selectivities up to 95% for the corresponding alcohol.

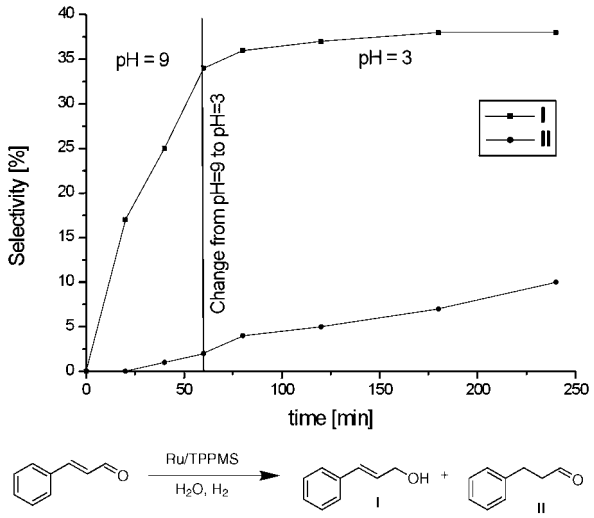


Figure 5. Dependence of regioselectivity on pH.[140,141]

Chemoselective hydrogenations (99%) in systems of $scCO_2$ and water were reported by Bhanage et al.[116]

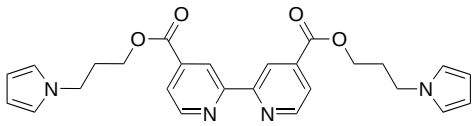
Apart from simple aldehydes, the hydrogenation of aldoses with ruthenium catalysts has also been described. High yields of the corresponding alditols were found in homogeneous catalytic hydrogenation with TPPTS as ligand and dihydrogen[148] or formates[149] as hydrogen source and in aqueous mixed or biphasic systems.[150]

3.1.2 Hydrogenation of Ketones

Numerous attempts for ketone reduction in aqueous media with several complexes containing different metals are reported in the literature. Mainly rhodium, and to a less extent, ruthenium and iridium are active metals for the hydrogenation of various ketones in combination with water-soluble bipyridyl ligands (**44**). Frediani et al.[20] found more than 80% yield for acetone reduction in aqueous alcohol at room temperature and full conversion at 140 °C, whereas Lau et al. carried out ketone hydrogenations in biphasic systems with 85% yield[151] and up to 90% yield in water-THF. [152]

Tingry and co-workers[153] reported that in electrocatalytical hydrogenations of cyclohexanone in ethanol-water mixtures 91% of the corresponding alcohol resulted if a combined Rh-bipyridyl ligand (**44**) was used (Formula 4).

Recently, Penicaud et al.[154] obtained yields up to 99% of aryl methyl carbinols in rhodium- and iridium-catalyzed reactions in water. Anthraquinone derivatives were reduced with the considerable TOF of 377 h^{-1} in a



Formula 4. Bipyridyl-derived ligand for electrocatalytical hydrogenations.[153]

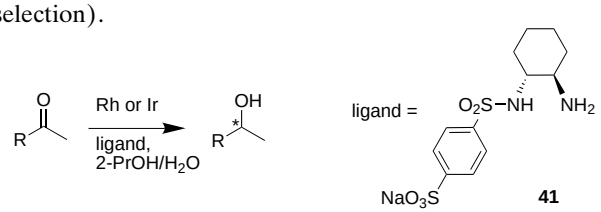
biphasic water/xylene system. Drelinkiewicz et al.[155] used palladium in combination with polyaniline **42** for this reaction.

Watanabe and co-workers reported that the hydrogenation[38] or transfer hydrogenation[156] of simple aliphatic ketones with $[Ir(cp)(H_2O)_x]$ in water was possible. Similar to the attempts mentioned for hydrogenation of aldoses, Hamersak et al.[157] reduced 2,5-diketo-D-gluconic acid with a Ru-TPPTS complex in water.

Table 10 shows the results of asymmetric hydrogenations of ketones in aqueous systems. Especially rhodium in combination with ligands containing nitrogen moieties (see Table 3) and ruthenium-BINAP (**33**) complexes are active hydrogenation catalysts for carbonyl compounds. Whereas 50% ee was found with a rhodium catalyst in aqueous alcohols,[158] for ruthenium catalysts the value reported recently was up to 94% ee.[159]

Table 11 summarizes the results of transfer hydrogenation of numerous aryl alkyl ketones. Thorpe et al.[160] examined reactions with regard to the dependence of the enantioselectivity on the water content. In general, the high ee values decrease slightly if the water content increases. They used water-soluble chiral amine-sulfonamide-ligands (**41**)[161] in combination with rhodium and iridium as hydrogenation catalysts.

Table 11. Asymmetric hydrogenation of various ketones[160] (selection).

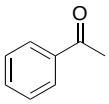
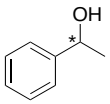
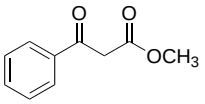
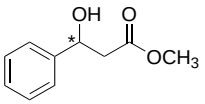
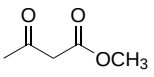
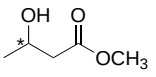
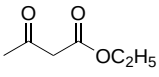
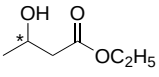


R	Metal	Water content [%]	Yield [%]	ee [%]
Phenyl	Ir	15	88	96
	Rh	15	94	95
3-CF_3-Phenyl	Ir	15	98	93
	Rh	15	99	94
4-OCH_3-Phenyl	Ir	15	80	95
		34	76	92
		51	89	87
	Rh	15	65	95
Naphthyl	Ir	15	96	96
		34	92	95
		51	92	94
	Rh	15	95	96

3.1.3 Hydrogenation of Carbon Dioxide

The hydrogenation of carbon dioxide to formic acid in aqueous systems is an interesting and important transformation in the use of this feedstock. Table 12 shows recent results. The reported attempts are different in the use of water as solvent or only as additive. Gassner et al.[162] found the best results for the production of formic acid from carbon dioxide in water as solvent. The TON′s were more than 3400 for the catalyst system Rh-TPPTS in the presence of a secondary amine. Joo and co-workers[163] recently obtained similar results for rhodium and showed also the application of Ru-PTA (**23**) as

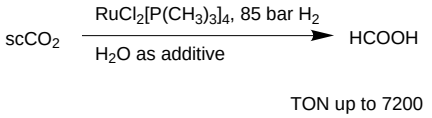
Table 10. Ketone reduction in aqueous systems (selection).

Substrate	Product	Catalyst[a]	Solvent	Yield [%]	ee [%]	Ref.
		Rh/**44**	water-ethanol	94	15	[193]
		Rh/**41**	water-methanol	99	50	[158]
		Ru/**33**	water	100	62	[194]
		Ru/**33**	water	100	94	[159]

[a] See Tables 2 and 3.

Table 12. Hydrogenation of CO_2 to formic acid in aqueous systems.

Metal	Ligand	Conditions (S: solvent, A: additive, T: time)	TON [mol formic acid/mol metal]	Ref.
Rh	TPPTS	S: water, A: $NHMe_2$, 25 °C, 12 h	up to 3439	[162]
Rh	PPh_3	S: EtOH-H_2O 5/1, A: NEt_3, 60 °C, 5 h	up to 210	[195]
Rh	$PhPMe_2$	S: THF, A: water, 25 '°C, 24 h	up to 64	[196]
Rh, Ru	TPPMS, PTA	S: water, A: $NaHCO_3$, 25 – 50 °C, 2 h (Rh), 456 h (Ru)	up to 524 (Rh), 358 (Ru)	[163]
Ru	PPh_3, PMe_3, DMPE	S: $scCO_2$, A: water, NEt_3, alcohols, amines, 50 °C, 47 h	up to 7200	[164]
Ru	PPh_3, Tp	S: THF-H_2O 7/1, A: none, 100 °C, 16 h	up to 760	[197]
Ru	PTA	S: water, A: none, 80 °C, –	initial TOF 800 h^{-1}	[198]



Scheme 8. Hydrogenation of supercritical carbon dioxide.[164]

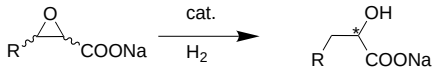
catalyst in the CO_2 hydrogenation, but ruthenium is less active than rhodium. TON values were determined lower than 1000 for aqueous organic solvents.

Noyori and co-workers[164] found the interesting role of water as additive in supercritical CO_2. With various Ru catalysts they obtained TON′s up to 7200 for the hydrogenation of carbon dioxide to formic acid under supercritical conditions in the presence of 0.1 mmol water (Scheme 8).

Pruchnik et al.[165] reduced carbon monoxide to methane with water-soluble ruthenium-phosphine complexes, but they found only 5% of the desired product.

3.1.4 Hydrogenolysis of Epoxides

The asymmetric hydrogenolysis of epoxides **12** leads, in contrast to the hydrolytic ring opening, to enantiomerically enriched monoalcohols. Chan et al.[166] obtained disodium hydroxysuccinate (Scheme 9, R = COONa) in rhodium-catalyzed hydrogenations of the corresponding water-soluble epoxide with an enantiomeric excess up to 30%. They carried out the reaction with a series of chiral phosphine ligands in aqueous methanol. Bakos et al.[167] tried the same reaction some years later with the water-soluble complex of sulfonated rhodium-SKEWPHOS (**34**) complex in water, in aqueous methanol and in a biphasic system (water/ethyl acetate). They found a maximum ee of 39%. The hydrogenation to the sodium 1-hydroxy-2-phenylpropionate (Scheme 9, R = Ph) yielded only 29% ee.



Scheme 9. Asymmetric hydrogenolysis of water soluble epoxides **12**.

3.2 Hydrogenation of C=N Bonds

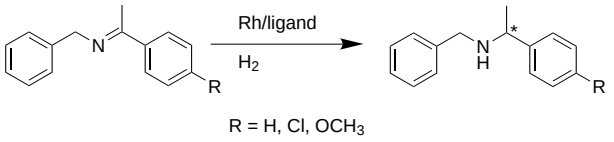
In contrast to the hydrogenation of C=O bonds in aqueous systems there exist only few reports on imine hydrogenation. Most of them deal with the model reaction as shown in Scheme 10.

Bakos et al.[168] found enantioselectivities up to 96% ee in biphasic systems by use of an Rh-SKEWPHOS (**34**) analogue as catalyst. The best aqueous/organic solvent system was water/ethyl acetate.

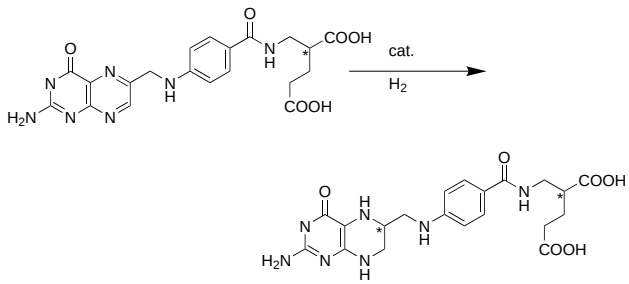
Lensink et al.[169] obtained similar results for the hydrogenation of *N*-benzylacetophenone imine. They used a rhodium catalyst of SKEWPHOS-similarity (**34**) with a different degree of sulfonation.

Buriak and Osborn[170] studied the catalytic asymmetric imine hydrogenation in the presence of reverse micelles. They described attempts with an Rh-SKEWPHOS complex in benzene and the reverse micellar system containing AOT [aerosol OT: disodium bis(2-ethylhexyl)-sulfosuccinate] and water. Moderate yields and ee's up to 87% were found.

Brunner et al. used folic acid as a special substrate for the rhodium-catalyzed hydrogenation of C=N bonds (Scheme 11). They reported numerous attempts at asymmetric hydrogenation in buffered aqueous solu-



Scheme 10. Asymmetric hydrogenation of C=N bonds.



Scheme 11. Hydrogenation of folic acid.[171,172]

tions. BPPM (**37**, R = Boc) as ligand was the most effective (41% de), whereas water-soluble ligands like hydroxy-DIOP or PEG-DIOP (**35**) gave only small optical yields (< 15% de).[171] Rh-phosphine complexes immobilized on silica showed better enantioselectivities (up to 53%) and could be reused several times.[172]

With the aim of producing primary amines Beller and co-workers[173] used the iridium-catalyzed hydrogenation of terminal imines (**13**, $R^1 = H$, $R^3 = H$) as an intermediate step in water/organic solvent two-phase systems. A rhodium-catalyzed hydroformylation of terminal alkenes to the corresponding aldehydes followed by conversion with ammonia to imines, and the reduction with hydrogen leads to the product. The overall selectivity of the primary amine was found as 91% for TPPTS and 87% for BINAS (**33**, Ar^S) as ligands used.

4 Transfer Hydrogenation in Aqueous Media

Because of the good water solubility of the frequently used hydrogen sources for the transfer hydrogenation, 2-propanol and formates, recent work includes reactions of that kind in aqueous media. Examples are reported with ruthenium and rhodium as catalytically active metals and unsaturated carboxylic acids (**2**, **3**) and carbonyl compounds (**4**, **9**, **10**) as substrates.

Apart from achiral hydrogenations of model substrates like α-acetamidocinnamic acid and itaconic acid and their derivatives,[136,174–176] the asymmetric transfer hydrogenation of olefinic substrates is successful in aqueous systems. Sinou and co-workers[176] reported ee values of 10 and 43% for the hydrogenation of phenylalanine precursors and itaconic acid, respectively, with a Rhn-**30** complex and ammonium formate.

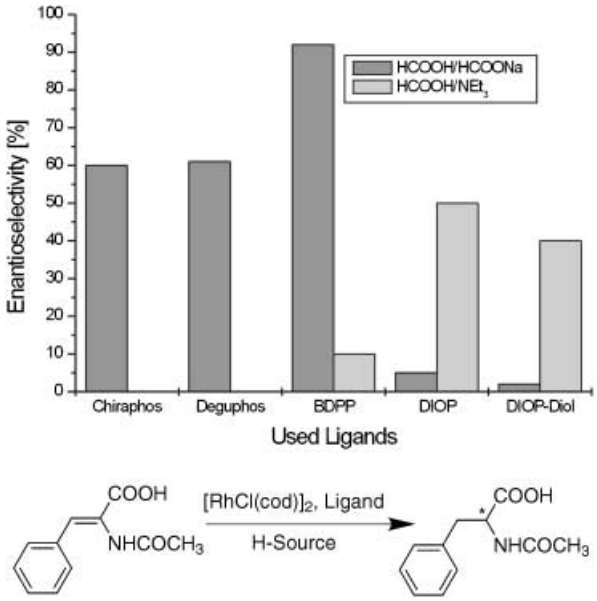
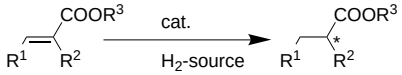


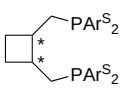
Figure 6. Dependence of enantioselectivity on the type of ligand and the H-source in asymmetric transfer hydrogenation.[177]

Rocha Gonsalves et al.[177] found better results with the system formic acid-sodium formate and complexes of rhodium with chiral ligands like SKEWPHOS, DEGUPHOS, and CHIRAPHOS. They obtained up to 92% ee for the hydrogenation of (*Z*)-α-acetamidocinnamic acid and 57% ee for itaconic acid (Figure 6; see also Table 13).

Darensbourg et al.[178] reported attempts on the transfer hydrogenation of allylbenzene with an Rh-PTA (**23**) complex in chlorobenzene/water. In contrast to the hydrogenation with hydrogen (51% hydrogenation, 47% isomerization) the reduction with sodium formate gave only 12% hydrogenation, but 71% isomerization.

Table 13. Transfer hydrogenations of C=C bond in unsaturated carboxylic acid **2**, **3** derivatives (selection).



Metal/Ligand	H_2-Source	R^1	R^2	R^3	Yield [%]	ee [%]	Ref.
Ru-P(C_4H_9)$_3$	$HCOOCH_3$	H	H	CH_3	100	–	[174]
Rh-TPPTS **15**	HCOONa	H	CH_2COOCH_3	CH_3	95	–	[175, 136]
Rh-TPPTS **15**	$HCOONH_4$	H	CH_2COOH	H	100	–	[176]
	$HCOONH_4$	Ph	$NHCOCH_3$	H	87	–	[176]
Rh-**30**	$HCOONH_4$	H	CH_2COOH	H	50	10	[176]
	$HCOONH_4$	Ph	$NHCOCH_3$	H	65	43	[176]
Rh-SKEWPHOS **34**	HCOOH-HCOONa	Ph	$NHCOCH_3$	H	100	92	[177]
Rh-CHIRAPHOS **32**	HCOOH-HCOONa	Ph	$NHCOCH_3$	H	100	60	[177]
Rh-DEGUPHOS **38**	HCOOH-HCOONa	Ph	$NHCOCH_3$	H	100	91	[177]
Rh-DEGUPHOS **38**	HCOOH-HCOONa	H	CH_2COOH	H	100	57	[177]
Rh-DEGUPHOS **38**	HCOOH-HCOONa	COOH	CH_3	H	100	11	[177]

Transfer hydrogenations of carbonyl compounds are known for ruthenium[135,136,179] and iridium.[136,156,160] Joo and co-workers[139] and Grosselin et al.[143] reported high yields and chemoselectivities in the case of the hydrogenation of unsaturated aldehydes **4**. Willner et al.[180] reduced benzil in a H_2O/CH_2Cl_2 biphasic system using Ru-TPPTS (**15**, n = 3), -TPPMS (**15**, n = 1) and Rh-bpy (**44)** catalysts. They reported that different formates in combination with the redox-system NAD-NADH are a useful hydrogen source.

Kolaric et al.[150] found yields up to 95% and selectivities up to 85% for the reduction of glucose to sorbitol in various aqueous solutions. The reactions were carried out with $RuCl_2(PPh_3)_3$ as catalyst and different alcohols like 2-propanol and cyclohexanol as transfer-hydrogenation reagents.

The synthesis of enantiomerically enriched alcohols by transfer hydrogenation with 2-propanol were reported by Bubert et al.[161] recently. Enantioselectivities up to 95% were reached for the hydrogenation of numerous methyl aryl ketones with ruthenium and water-soluble aminosulfonamide ligands **41**. Amino acids as chiral ligands in the transfer hydrogenation of acetophenone were used by Carmona et al.[138] A series of ruthenium, rhodium and iridium catalysts with L-proline as chiral modifier gave the best results with up to 71% ee.

5 Miscellaneous and Trends

Apart from the hydrogenation of C=C, C=N, and C=O bonds some articles describe the reduction of nitro- and haloarenes to the corresponding anilines and arenes. Bianchini et al.[181] reported recently the hydrogenolysis of the C-S-bond in benzothiophene in an aqueous biphasic system with a rhodium complex of the tridentate phosphine **25** with 91% selectivity. The deoxygenation of allyl alcohols[182] and the hydrogenolysis of haloarenes[183,184] succeeded under basic conditions. Many metals[185] were found to be active in the hydrogenation of nitroarenes to anilines. Especially, the palladium-catalyzed reaction[186,187] showed excellent results (yield 40 to 100%). Rhodium[188–190] (up to 96% yield) and to a lesser extent ruthenium[191,192] (23 – 50% yield) were also used successfully in aqueous systems.

Asymmetric homogeneous hydrogenation was the first significant use of a transition metal complex in an enantioselective process with industrial applications.[199] The most recent achievement is the metolachlor process.[200]

The trend to use water as solvent in hydrogenation reactions is obvious.[201]

Concluding our review, we find major achievements in homogeneous and multiphase aqueous hydrogenation systems. Transferring the enantioselective hydrogenation of amino acid precursors into water as medium would be relatively simple. An offer of suitable chiral ligands by different suppliers should help this effort. The application can be important for water-dispersible substrates in biochemistry. Some results with immobilized catalysts are encouraging, and attempts with water-soluble polymers as supports have been demonstrated.

New directions with respect to amphiphilic ligands and the combination of common catalysts with amphiphiles[202] continue to emerge. The development of convenient liquid-liquid two-phase systems seems to be most important for a catalyst recycling.[203] The potential for fine tuning aimed to improving selectivity for the hydrogenation of α,β-unsaturated carbonyl compounds should be of great interest. So is the environmentally benign reduction of nitro compounds.[6,16]

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