Part V
Phase Separation in Homogeneous Hydrogenation

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38
Two-Phase Aqueous Hydrogenations

Ferenc Joó and Ágnes Kathó

38.1
Introduction

When a catalytic reaction is carried out in a mixture of two immiscible liquids it is often possible to separate the catalyst and the products (together with the unreacted starting materials) into the two liquid phases formed when stirring is stopped. Such two-phase catalytic processes retain all of the advantages of homogeneous catalysis (efficient use of the molecularly dispersed catalyst, high selectivity, possibility of tailoring the catalyst to the particular substrate by modification of the ligand environment) and combine those with the ease of recovery of a heterogeneous catalyst [1–4]. There are several organic solvents, which have limited miscibility with water and – in principle – these are suitable for two-phase catalysis. (Similarly, there are also water-immiscible ionic liquids (ILs) and supercritical fluids (SCFs), but in the general discussion aqueous-organic biphasic mixtures are used as examples.) Liquid organic substrates may form separate phases themselves. For an efficient recovery, the catalyst must be insoluble in one of the phases which, in turn, should preferentially dissolve the substrates and products. In general – though not always – the substrates and products of a catalyzed reaction are not especially soluble in water and partition to the organic phase (Scheme 38.1, A). In such cases, strongly hydrophilic catalysts are used, while for water-soluble substrates the catalyst should be dissolved in a water-immiscible organic solvent (Scheme 38.1, B). Ideally, the interaction of the catalyst with the substrates and products will not change its solubility properties and no leaching of the catalyst to the other phase takes place.

Water is a highly polar – and hence protic – solvent, the presence of which may strongly influence the chemistry of two-phase aqueous processes. Of course, all components of the reaction mixture should be stable to water, and to this end care must be taken with the choice of catalyst. Today, aqueous organometallic catalysis has become a mature field of chemistry, and a very wide choice of water-soluble and water-stable hydrogenation catalysts is available. It should also be borne in mind that water is a reactive solvent and may take part

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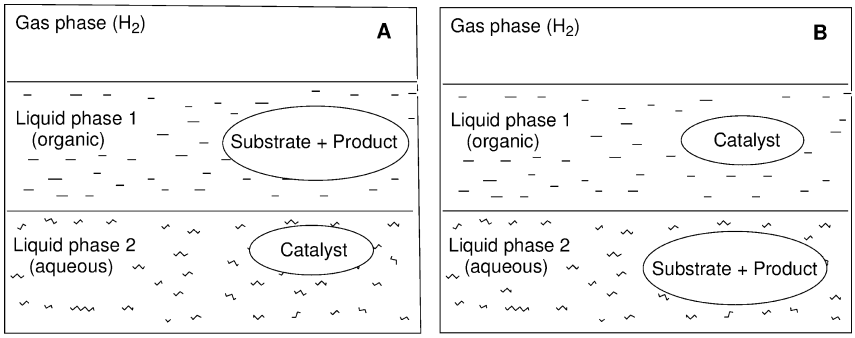
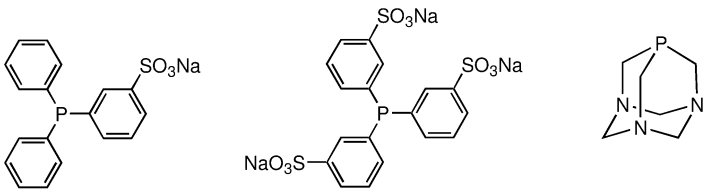


Scheme 38.1 General arrangements in aqueous two-phase hydrogenations.

in proton exchange, hydration, telomerization and so forth as side reactions to hydrogenation. Engineering aspects are also important. In practice, the two liquids are not completely "immiscible" but have limited miscibility in each other. For example, the solubility of ethyl acetate in water at 20 °C is 6.1 wt.%, while that of water in EtOAc is 3.3 wt.%. Very similar numbers were determined for Et_2O in H_2O (6.9 wt.%) and H_2O in Et_2O (3.3 wt.%). (For other mutual miscibility data with water as one of the phases, see [5] and for general solvent properties [6].) Usually, saturation of both liquids with the other component of the biphasic mixture does not lead to appreciable volume changes when the catalyzed reaction takes place in a batch reactor. However, in a flow system the mobile phase (the solution of the substrates and products) may gradually carry away the solvent of the catalyst-containing stationary phase. The solubility of hydrogen in water (0.81 mM at 20 °C) is somewhat less than in the common organic solvents (e.g., in methanol 3.75 mM, benzene 2.94 mM, toluene 3.50 mM; all data at 20 °C) [7]. Lower concentrations of dissolved H_2 usually lead to lower reaction rates, but it has also been shown [8] that the selectivity of a catalytic hydrogenation may be strongly influenced by the hydrogen pressure – that is, by the concentration of dissolved hydrogen.

Since the overwhelming majority of the important substrates of hydrogenation are insoluble in water, it is the catalyst that should be applied in the aqueous phase. Some of the catalysts are water-soluble due to their ionic nature, such as $[Co(CN)_5]^{3-}$, or the chloro-aqua complexes of ruthenium(III) or rhodium (III) obtained by dissolution of $RuCl_3 \cdot aq$ or $RhCl_3 \cdot aq$ in aqueous hydrochloric acid. However, by far the most common approach is the solubilization of well-known transition metal-based hydrogenation catalysts by substitution of their tertiary phosphine (or other) ligands with analogous but highly water-soluble ligands. The best-known examples are the mono- and trisulfonated triphenylphosphines (3-diphenylphosphinobenzenesulfonic acid, *m*tppms, and 3,3′,3″-phosphinetriylbenzenesulfonic acid, *m*tppts, respectively) (Scheme 38.2). Functionalization with alkylene sulfate, phosphonate, carboxylate, ammonium, and phosphonium groups is also used for making phosphine ligands water-soluble.



*m*tppms *m*tppts pta

Scheme 38.2 Frequently used water-soluble tertiary phosphines.

Some phosphines are easily soluble in water due to their strong hydrogen-bonding capacity. Representatives of these ligands are 1,3,5-triaza-7-phosphaadamantane (pta), the polyoxyethylene-substituted and the carbohydrate-derived phosphines. A detailed compilation of water-soluble phosphines (together with the known solubilities) can be found in [4].

Catalytic hydrogenation is an important synthetic process, but studies on such reactions of simple olefins were frequently performed with the aim of characterizing new catalysts. Many of these investigations were carried out in homogeneous aqueous solutions and therefore fall outside the scope of this chapter. Nevertheless, important conclusions could be drawn with regard to the mechanisms of hydrogenations catalyzed by transition metal complexes in water. Water, as a polar solvent, may stabilize polar transition states and in doing so may facilitate the activation of dihydrogen. Strong hydration of H^+ makes the energetics of heterolytic splitting of H_2 comparable to that of its homolytic activation [9]. The balance of these two processes – that is, the formation of monohydrido- or/and dihydrido-complexes – is strongly influenced by the pH of the aqueous solutions [10, 11]. These mechanistic features of dihydrogen activation have their consequences in the reaction rates and selectivities of the catalyzed hydrogenations.

Several books [1–4, 12] and reviews [13–20] are available on transition metal complex-catalyzed hydrogenations in aqueous systems, but only a few cover biphasic aqueous processes specifically. In the following sections of this chapter, only two-phase reactions are described, which have been arranged according to the functional groups involved in the hydrogenation. Most of the results are compiled into tables and are not discussed individually in the text. The catalytic activities are expressed as *turnover frequencies* (TOF, h^{-1}) defined as mole reacted substrate (mol catalyst · h)$^{-1}$. In most cases, TOF values were calculated from the experimental conditions (conversion, reaction times, concentrations) given in the original paper, and often represent the lowest limit of the catalytic activity.

Table 38.1 Aqueous-organic two-phase achiral hydrogenation of alkenes.

Entry	Catalyst	Substrate	TOF [h^{-1}]	Solvent, conditions and remarks	Reference
1	$[RhCl(m\text{tppms})_3]$ [a]	1-hexene	38.1	H_2O, 25 °C, 3 bar H_2	21
		cyclohexene	9.1		
2	$RhCl_3 + m\text{tppms}$, 1:3	1-octene	85	H_2O/benzene, 35 °C, P_{tot}=1 bar	22
3	$RhCl_3 + m\text{tppms}$, 1:6	cyclohexene	50	H_2O, 50 °C, P_{tot}=1 bar, co-solvents	23
4	$[\{RhCl(COD)\}_2]$ + DSPrPE, [b),c)] 1:1.5	1-hexene	up to 25	H_2O/THF 6/1, 60 °C, 3.5 bar H_2	24
5	$[\{RhCl(COD)\}_2]$ + DHPrPE, [d)] 1:1.5	1-hexene	up to 25	H_2O/THF 6/1, 60 °C, 3.5 bar H_2	24
6	$[\{RhCl(COD)\}_2]$	1-hexene	220	H_2O, r.t., P_{tot}=1 bar	25
	$+ Ph_2P(CH_2)_2CONHC(CH_3)_2CH_2SO_3Li$	1-octene	76		
		cyclopentene	48		
		cyclohexene	60		
		cyclooctene	40		
		carvone	36	both double bonds are hydrogenated	
		limonene	21	both double bonds are hydrogenated	
7	$[RhCl(pta)_3]$ [e)]	allylbenzene		H_2O, 50 °C, P_{tot}=1 bar	26
		cinnamaldehyde			
8	$[Rh(NO)(m\text{tppts})_3]$ [f)]	cyclohexene	2.8	H_2O, 25 °C, 1 bar H_2	27
		cyclohexene	1.0	H_2O/*i*PrOH, 25 °C, 1 bar H_2	
		cyclooctene	2.7	H_2O, 25 °C, 1 bar H_2	
9	$[Rh(acac)(CO)(PR_3)]$ [g)]	1-hexene		H_2O, 30 °C, 1 bar H_2	28
	$PR_3 = m\text{tppts}$, pta, cyep [h)]	cyclohexene			
10	$[Rh(amphos)(MeOH)_2]^{3+}$ [i)]	1-hexene		H_2O/CH_2Cl_2, Et_2O,or *n*-pentane	29
		styrene		r.t., P_{tot}=1 bar	
11	$[Rh(NBD)(n\text{-phophos})]^{3+}$ [j),k)]	1-hexene	up to 150	H_2O/CH_2Cl_2 or Et_2O, 25 °C, 3 bar H_2	30
	n=2, 3, 6, 10				

12	$[Rh(COD)_2][BF_4]+Na_2[Ph_2P(CH_2)_{12})PO_3]$, 1:3	1-decene		H_2O, r.t., P_{tot}=1 bar, metal deposition with 1-hexene and cyclohexene	31
13	$[RuHCl(m\text{tppms})_3]$	1-hexene	18.9	H_2O, 25 °C, 3 bar H_2	21
		cyclohexene	8.9		
14	$[RuCl_2(m\text{tppms})_2]$	1-hexene	18.0	H_2O, 30 °C, P_{tot}=1 bar	32
15	$[RuHCl(m\text{tppms})_3]$	styrene	10.8	H_2O, 60 °C, P_{tot}=1 bar	32
16	$[RuH(OAc)(m\text{tppms})_3]$	styrene	25.0	H_2O, 60 °C, P_{tot}=1 bar	32
17	$[RuHCl(CO)(m\text{tppms})_3]$	styrene	3.0	H_2O/decalin 1/1 100 °C, 70 bar H_2	33
		cyclohexene	1.1		
18	$[RuH(CO)(m\text{tppms})_3(CH_3CN)]^+$	1-hexene	10.5	H_2O/*n*-heptane 1/1, 80 °C, 28 bar H_2	34
		1-decene	3.0		
		cyclohexene	3.3		
		styrene	5.5		
19	$[Ru(H)_2(CO)(m\text{tppms})_3]$	1-hexene	6.8	H_2O/*n*-heptane 1/1, 100 °C, 28 bar H_2	35
		1-decene	5.1		
		cyclohexene	1.6		
		styrene	4.0		
20	$[Ru(CO)_3(m\text{tppms})_2]$	1-hexene	7.0	H_2O/*n*-heptane 1/1, 100 °C, 28 bar H_2	35
		1-decene	5.4		
		cyclohexene	1.8		
		styrene	4.0		
21	$[RuCl(Cp)(m\text{tppms})_2]$ [l]	1-hexene	85	H_2O/toluene 1/1, 100 °C, 35 bar H_2	36
22	$[RuCl_2(m\text{tppms})_3(DMSO)]$ [m]	1-hexene	98	H_2O/toluene 1/1, 80–100 °C, 35 bar H_2	37
		cyclohexene	64		
23	$[RuCl_2(DMSO)_4]$	1-hexene	82	H_2O, 80 °C, 28 bar H_2	38

Table 38.1 (continued)

Entry	Catalyst	Substrate	TOF [h^{-1}]	Solvent, conditions and remarks	Reference
24	$[RuCl(CO)(Cp^*)(PR_3)]$ [n)] $[Ru(CO)(Cp^*)(PR_3)][CF_3SO_3]$ $R=CH_2OH$, $(CH_2)_3OH$, C_6H_4-3-SO_3Na	sorbic acid	up to 16	H_2O/*n*-heptane, 80 °C, 50 bar H_2	39
25	$[\{RuCl_2(PR_3)\}_2]$, $R=(CH_2)_3OH$	sorbic acid	192	H_2O/ethyl acetate, 80 °C, 50 bar H_2	40
26	$[Ru_3(CO)_{12-x}(m\text{tppms})_x]$, x=1, 2, 3	1-octene	45–95	H_2O, 60 °C, 60 bar H_2	41
		1-decene	32		
		cyclohexene	39–252		
		styrene	490		
27	$[Ru(\eta^6\text{-}C_6H_6)(CH_3CN)_3]^{2+}$	1-octene	min. 250	H_2O/benzene, 110 °C, 40 bar H_2	42
		1-decene	min. 250		
		1-dodecene	min. 250		
		styrene	min. 250		
28	$[Ru(6,6'\text{-}Cl_2bipy)_2(H_2O)_2][CF_3SO_3]_2$ [o)]	1-octene	min. 500	H_2O, 130 °C, 40 bar H_2	43
		1-decene	min. 500		
		cyclohexene	430		
		styrene	min. 500		
29	$[RuCl(Cp)(pta)_2]$	benzylidene-acetone	9.5	H_2O/*n*-octane, 80 °C, 32 bar H_2, selective hydrogenation to 4-phenyl-butan-2-one	44
	$[RuCl(Cp^*)(pta)_2]$		2.6		45
	$[Ru\{Cp(CH_2)_2NEt_2\}(pta)_2][PF_6]$		2.4		
	$[Ru\{Cp(CH_2)_2NEt_2\}(pta)_2(MeCN)][PF_6]$		3.3		
	$[Ru(Cp)(pta)(CH_3CN)_2][\ PF_6]$		9.5		
	$[Ru(Cp)(pta)_2(CH_3CN)][\ PF_6]$		6.2		
	$[Ru(Cp^*)(pta)_2(CH_3CN)][\ PF_6]$		6.4		

30	$Na_3[RuCl(\eta^6\text{-arene})(dppbts)]$ [p]	styrene		H_2O/substrate, 100 °C, 45 bar H_2	46
	arene = *p*-cymene [q]		1100		
	arene = [2.2]-paracyclophane		2000		
31	$[Co_2(CO)_8(m\text{tppts})_2]$	cyclohexene	1.8	H_2O, 20 °C, 30 bar H_2	27
		1-decene	11.9	H_2O, 100 °C, 70 bar H_2/CO 1/1, no aldehyde formation	
32	$[W(CO)_3(m\text{tppms})_2(CH_3CN)]$	styrene	10	H_2O/*n*-heptane, 140 °C, 70 bar H_2, Et_2NH	47

a) *m*tppms = monosulfonated triphenylphosphine.
b) COD = 1,5-cyclooctadiene.
c) DSPrPE = C_2H_4-1,2-$[P(CH_2CH_2CH_2SO_3Na)_2]_2$.
d) DHPrPE = C_2H_4-1,2-$[P(CH_2CH_2CH_2OH)_2]_2$.
e) pta = 1,3,5-triaza-7-phosphaadamantane.
f) *m*tppts = trisulfonated triphenylphosphine.
g) acac = 2,4-pentanedionate.
h) cyep = $P(CH_2CH_2CN)_3$.
i) amphos = $[Ph_2PCH_2CH_2NMe_3][NO_3]$.
j) n-phophos = $[Ph_2P(CH_2CH_2)_nPMe_3][NO_3]$.
k) NBD = bicyclo[2.2.1]hepta-2,5-diene.
l) Cp = η^5-C_5H_5.
m) DMSO = $(CH_3)_2SO$.
n) Cp* = η^5-$C_5(CH_3)_5$.
o) bipy = 2,2′-bipyridine.
p) dppbts = C_6H_4-1,2-$[P(C_6H_4\text{-}4\text{-}SO_3)_2]_2$.
q) *p*-cymene = 4-isopropyltoluene.

38.2
Two-Phase Hydrogenation of Alkenes, Alkynes, and Arenes

Several copper, silver, ruthenium, rhodium, and cobalt compounds (e.g., $RuCl_3 \cdot aq$, $[RuCl_4(bipy)]^{2-}$ (bipy = 2,2′-bipyridine), $RhCl_3 \cdot aq$, *bis*(dimethylglyoximato)cobalt derivatives (cobaloximes), etc.) have been found to catalyze hydrogenations in aqueous solutions [9]. Although important for the early research into homogeneous catalysis, these catalysts did not gain synthetic significance.

Several examples of achiral biphasic hydrogenations are shown in Table 38.1. It can be seen, that the activity of the various phosphine complexes of precious metals rarely exceeds 100 h^{-1} under mild conditions. In many cases hydrogenation is accompanied by isomerization of the olefinic substrates.

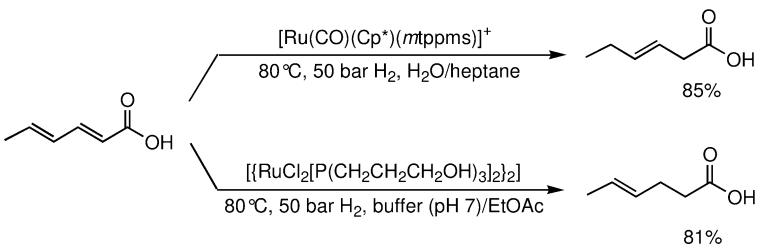
$[CoH(CN)_5]^{3-}$ is readily formed under mild conditions from $Co(CN)_2$, KCN and H_2; [Eqs. (1) and (2)]. It is an active catalyst for the hydrogenation of a variety of unsaturated substrates, and in fact in the first documented examples of two-phase hydrogenations this catalyst was used [48, 49]. The catalysis suffers from several drawbacks such as rapid "aging" with a loss of activity, and the need to use highly basic aqueous solutions.

$$Co(CN)_2 + 3\,KCN \rightleftharpoons K_3[Co(CN)_5] \quad (1)$$

$$2\,K_3[Co(CN_5] + H_2 = 2\,K_3[CoH(CN)_5] \quad (2)$$

Conjugated dienes (such as 1,3-cyclohexadiene, cyclopentadiene, 2,4-hexadienoic-sorbic-acid) and polyenes can be selectively hydrogenated to monoenes; unactivated alkenes are totally unreactive [20]. Unfortunately, the possibilities for modification of the catalyst by ligand alteration or by the use of additives are very limited [50, 51].

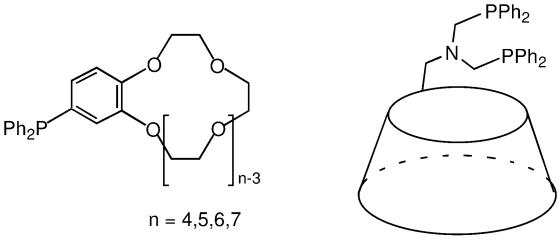
The various isomeric hexenoic acids are useful starting materials for the production of fine chemicals, and the stereoselective hydrogenation of sorbic acid has attracted considerable interest. It was shown recently that this reaction could be catalyzed by [Ru(CO)(Cp*)(*m*tppts)][CF_3SO_3] (Cp* = η^5-C_5Me_5) in a water:*n*-heptane biphasic mixture to yield *trans*-3-hexenoic acid with up to 85% selectivity [39] (Scheme 38.3). Conversely, the use of $[\{RuCl_2(PR_3)_2\}_2]$ (R = $CH_2CH_2CH_2OH$) as catalyst precursor led to the selective formation of 4-hexenoic acid [40].



Scheme 38.3

Such selectivity changes were also observed on the effect of water. For example, the hydrogenation of 3,8-nonadienoic acid catalyzed by $[RhCl\{P(p\text{-tolyl})_3\}_3]$ in benzene (30 °C, 1 bar H_2, one phase) afforded 3-nonenoic acid (up to 75% selectivity), whereas in the presence of a separate aqueous phase 8-nonenoic acid was obtained with 98% selectivity [52]. It should be noted that, in this reaction, the catalyst was dissolved in the organic phase (see Scheme 38.1, B); in fact, the first report of aqueous two-phase catalysis with tertiary phosphine complexes of Rh(I) [23] also described the hydrogenation of butenediol (in the aqueous phase) catalyzed by $[RhCl(PPh_3)_3]$ dissolved in benzene. The organic solvent can also be replaced by a supercritical fluid dissolving the catalyst. Itaconic acid (in the aqueous phase) was hydrogenated with $[Rh(COD)_2][BF_4] + P(C_6H_4\text{-}3\text{-}CH_2CH_2C_6F_{13})_3$ dissolved in supercritical CO_2 ($scCO_2$) [53] (COD = 1,5-cyclooctadiene). Since the catalyst is insoluble in water, there is no leaching when the aqueous phase is removed from the reactor and replaced by a fresh solution of the substrate.

In two-phase aqueous hydrogenations the catalyst and the substrates are found in the separate liquid phases, and the reaction rate depends on the solubility of the substrates in the catalyst-containing phase (or on the size of the interfacial area in case the reaction takes place at the phase boundaries). Mass transfer between the phases and interaction of the catalyst with the substrates can be facilitated by proper modification of the ligands, for example by attaching crown ether [54] or cyclodextrin [55] moieties to the tertiary phosphine ligands. $[\{RhCl(COD)\}_2]$ combined with 3n-diphenylphosphinobenzo-[3n-crown-n] ethers (n = 4, 5, 6, and 7; Scheme 38.4 a) showed high catalytic activities towards the catalytic hydrogenation of potassium and lithium cinnamates in water : benzene biphasic mixtures. At 30 °C, under 1 bar H_2 pressure, TOFs as high as 720 to 4440 h^{-1} were determined. The latter value is 50 times higher than that observed with $[\{RhCl(COD)\}_2] + PPh_3$ + benzo-[18-crown-6], and the catalytic activity varied in parallel with the ability of the crown-modified phosphine ligand to extract K- and Li-cinnamate from the aqueous into the benzene phase. Both observations relate to the active role of the crown-ether unit built into the ligand in bringing together the Rh(I) center of the catalyst and the substrate [54]. Similarly, β-cyclodextrin was attached to bis(2-diphenylphosphinoethyl)amine [55]. The reaction of the resulting bidentate phosphine (Scheme 38.4 b) with $[Rh(COD)_2][BF_4]$ afforded a highly water-soluble catalyst which showed enhanced activity (factor of 3 to 6) in the hydrogenation of higher olefins compared to $PhN(CH_2PPh_2)_2/[Rh(COD)_2][BF_4]$ in



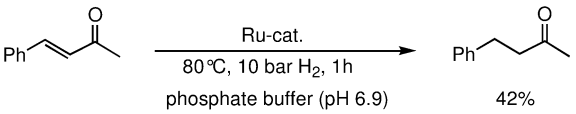
a **b** **Scheme 38.4**

water:substrate biphasic systems. Moreover, in a 1:1 mixture of Ph-$(CH_2)_2$-$CH=CH_2$ and C_8H_{17}-$CH=CH_2$, the β-cyclodextrin-modified catalyst was selective in favor of the phenyl-substituted olefin which interacts strongly with the cyclodextrin unit. Indeed, the substrate selectivity decreased drastically on addition of *p*-xylene, which competes for the β-cyclodextrin cavity [52].

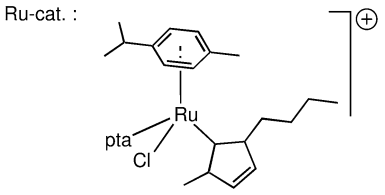
The hydrogenation of polymers results in improved thermal and oxidative stability, reduced gas permeability, and greater resistance to oils and fluids. Aqueous emulsions of acrylonitrile-butadiene-styrene (ABS) co-polymers (as obtained in the polymerization process) were hydrogenated at 70–100 °C and 15 bar (r.t.) H_2 with $[RhCl(PPh_3)_3]$, $[RhH(CO)(PPh_3)_3]$, or $[Rh(COD)(PPh_3)_2][BF_4]$ catalysts dissolved in acetone:toluene mixtures, and this resulted in the saturation of up to 70% of the double bonds. Neither the nitrile nor the aromatic functionalities were hydrogenated. The recovery of the catalyst in the organic phase was also claimed [56, 57]. Several carboxylatoalkyl-diphenylphosphines, Ph_2P-$(CH_2)_n$-CO_2Na (n=1, 2, 4, 5, 7) together with *p*- or *m*-Ph_2P-C_6H_4-CO_2Na and their rhodium complexes were synthetized and used for the hydrogenation of various polymers (polybutadiene, PBD; nitrile-butadiene rubber, NBR; and styrene-butadiene rubber, SBR) in water:toluene biphasic media. With $[\{RhCl[Ph_2P$-$(CH_2)_5$-$CO_2Na]_2\}_2]$ and $[\{RhCl[Ph_2P$-$(CH_2)_7$-$CO_2Na]_2\}_2]$ as catalysts, the pendant (terminal) vinyl units of the polymers were hydrogenated preferentially over the internal double bonds. At 100 °C and 15 bar H_2 total conversions as high as 84% (PBD), 62% (NBR), and 50% (SBR) were obtained [58, 59]. Exceptionally high catalytic activities (TOF >840 h^{-1}) were achieved in the hydrogenation of polybutadiene-1,4-*block*-poly(ethylene oxide) with an *in-situ*-prepared Rh/*m*tppts catalyst in the presence of the micelle-forming agent dodecyltrimethylammonium chloride [60]. In the presence of a non-ionic surfactant Triton X-305, NBR latexes were only slowly hydrogenated by $[RhCl(mtppms)_3]$ (TOF=4.0–9.3 h^{-1}) [61].

Aqueous two-phase hydrogenations are dominated by platinum group metal catalysts containing water-soluble tertiary phosphine ligands. The extremely stable and versatile N-heterocyclic carbene complexes attracted only limited interest, despite the fact that such complexes were described in the literature [62–65]. Recently, it was reported that the water-soluble [RuXY(1-butyl-3-methylimidazol-2-ylidene)(η^6-*p*-cymene)]$^{n+}$ (X=Cl^-, H_2O; Y=Cl^-, H_2O, pta) complexes preferentially hydrogenated cinnamaldehyde and benzylideneacetone at the C=C double bond (Scheme 38.5) with TOF values of 30 to 60 h^{-1} in water:substrate biphasic mixtures (80 °C, 10 bar H_2) [66].

The catalytic modification of lipid dispersions (liposomes) or the lipid membranes of living cells [4, 67] is a special application of the homogeneous hydrogenation of alkenes in aqueous biphasic (microheterogeneous) media. An ideal catalyst efficiently reduces the unsaturated fatty acid units in the polar lipids at low temperatures (0–40 °C) in an aqueous environment, does not effect transformations other than hydrogenation, can be totally removed from the cell after the reaction is completed, and has no "self-effect", such as toxicity. To date, the most investigated homogeneous catalyst for biomembrane hydrogenation is $[Pd(QS)_2]$, QS=1,2-dioxy-9,10-anthraquinone-3-sulfonic acid (Alizarin red) [68].



Scheme 38.5



The hydrogenation of alkynes in aqueous systems has been much less studied than that of alkenes. Interestingly, *mer*-[Ir(H)(H)Cl(PMe_3)$_3$] was found to be water-soluble and to catalyze the hydrogenation of various terminal and internal alkynes to alkanes (TOFs in the range of 1–2 h^{-1} at 60 °C, 28 bar H_2). However, this catalytic activity was displayed only in aqueous mixtures, there being no activity in organic solvents [69]. Although the detailed mechanism of the reaction was not elucidated, ^{1}H-NMR spectra showed – in addition to the neutral *mer*-[Ir(H)(H)Cl(PMe_3)$_3$] complex – the presence of the cationic *mer*-[Ir(H)(H)(H_2O)(PMe_3)$_3$]$^+$ species in which the H_2O ligand may be easily replaced by the substrate alkyne. In aqueous solutions, chloride dissociation from the neutral catalysts or their precursors is facilitated (compared to the dissociation of a phosphine ligand) by the strong solvation of the resulting ions, and may lead to the alteration of the catalytic properties [70].

Diphenylacetylene and 1-phenyl-1-propyne were hydrogenated to the corresponding 1,2-disubstituted alkenes in aqueous organic biphasic media using [{$RuCl_2$(*m*tppms)$_2$}$_2$] and an excess of *m*tppms (80 °C, 1 bar H_2, TOFs up to 25 h^{-1}). The stereoselectivity of the reaction depended heavily on the pH of the catalyst-containing aqueous phase (Fig. 38.1) and, under acidic conditions, *Z*-alkenes could be obtained with a selectivity close to 100% [71].

The hydrogenation of benzene to cyclohexane is a large-scale industrial process applying heterogeneous ruthenium catalysts in the presence of water and zinc-based additives. Several attempts were made to develop homogeneous catalysts for the hydrogenation of arenes. It has been reported that benzene and monosubstituted benzenes can be efficiently hydrogenated in aqueous biphasic systems with hydridoareneruthenium cluster catalysts, such as [$Ru_3(\mu_2\text{-H})_2(\mu_2\text{-OH})(\mu_3\text{-O})(\eta^6\text{-}C_6H_6)(\eta^6\text{-}C_6Me_6)_2]^+$ [72–75] and with phosphine-containing areneruthenium compounds such as [$RuCl_2(\eta^6$-*p*-cymene)(pta)], [$RuCl_2(\eta^6$-*p*-cymene)(*m*tppts)] and related complexes [76, 77]. It was reported, that the well-known alkene hydrogenation catalyst, [$RuCl_2$(*m*tppts)$_2$], also catalyzed the hydrogenation of benzene to cyclohexane, whereas in the presence of $ZnCl_2$ the major product (91%) was cyclohexene [78]. Lignin phenols were hydrogenated to the corresponding cyclohexanols with Ru(II)/*m*tppms or *m*tppts catalysts, resulting

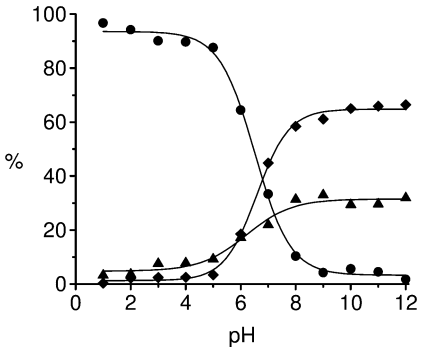


Fig. 38.1 Product distribution in the hydrogenation of diphenylacetylene as a function of the pH. [{$RuCl_2$(*m*tppms)$_2$}$_2$]=6.6 mg (6.79×10^{-3} mmol ruthenium), *m*tppms=8.1 mg (2.03×10^{-2} mmol), diphenylacetylene=89.1 mg (0.5 mmol), 1 bar H_2, 1 mL chlorobenzene, 2 mL phosphate buffer, 50 °C, 3 h. ●, *Z*-stilbene; ▲, *E*-stilbene; ◆, 1,2-diphenylethane. (Reproduced with permission from H. H. Horváth, F. Joó, *React. Kinet. Catal. Lett.* **2005**, *85*, 355–360.)

in inhibition of the light-induced yellowing of lignin and lignin-rich wood pulps [79]. While the mentioned catalysts can be useful for synthetic purposes, recent studies [80, 81] called attention to the possible formation of metal colloids in such aqueous arene hydrogenations. A very thorough analysis of the two-phase hydrogenation of benzene with $[Ru_3(\mu_2\text{-}H)_3(\eta^6\text{-}C_6H_6)(\eta^6\text{-}C_6Me_6)_2(\mu_3\text{-}O)]^+$ has revealed, that indeed the reduction was catalyzed by trace Ru(0) derived from the water-soluble cluster under the reaction conditions [82].

38.3 Enantioselective Hydrogenation of Alkenes in Two-Phase Aqueous Systems

Examples of enantioselective hydrogenations of alkenes in aqueous biphasic systems are listed in Table 38.2. Of course, the original references contain much more information; in order to compile Table 38.2, only those reactions with the highest enantiomeric excess were selected. In most of these investigations the activity and selectivity of the catalysts were characterized in reduction of the standard substrates of enantioselective hydrogenations (dehydroaminoacid derivatives, dimethyl itaconate; Scheme 38.6); however, in a few cases substrates of more practical significance (isobutylatropic acid, geraniol) were also used. Not surprisingly, this field of catalysis is dominated by rhodium complexes of the most diverse tertiary phosphine ligands (Scheme 38.7), although a few ruthenium and iridium complexes have also been studied. In the quest of catalysts with increasingly greater stereoselectivities, the catalytic activity was often of secondary significance. In most cases the reactions were run until complete hydrogenation, and the TOFs derived from the reaction times required (or greatly exceeding the time needed) for full conversions were not particularly well defined.

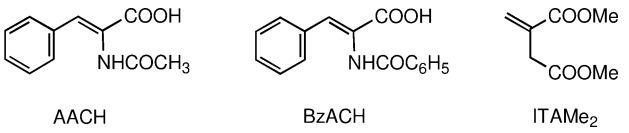
Table 38.2 Enantioselective hydrogenation of alkenes in aqueous-organic two-phase systems.

Entry	Catalyst	Substrate	ee [%]	TOF [h^{-1}]	Solvent	Conditions	Reference
1	[{RhCl(COD)}$_2$] + (*S*,*S*)-**A**	BzACH	86 (*R*)	≥8.3	H_2O/EtOAC (1/1)	25 °C, 10 bar	83
2	[{RhCl(COD)}$_2$] + (*S*,*S*)-**A**	AACMe	88 (*R*)	≥8.3	H_2O/EtOAC (1/1)	25 °C, 10 bar	84
3	[{RhCl(COD)}$_2$] + (*S*,*S*)-**C**	ITAMe$_2$	43 (*S*)	≥8.3	H_2O/EtOAC (1/1)	25 °C, 10 bar	84
4	[Rh(NBD)(B)]$^{5+}$	AACMe	77	50	H_2O/EtOAc/benzene (2/1/1)	20 °C, 14 bar	85
5	[Rh(NBD){(*S*,*S*)-**E**}]$^+$	AACMe	50	n.d.	H_2O/EtOAC + HBF_4	20 °C, 14 bar	86
6	[Rh(NBD){(*S*,*S*)-**E**}]$^+$	AACH	67 (*R*)	16.7	H_2O/EtOAc/benzene (2/1/1)	20 °C, 14 bar	87
7	[{RhCl(COD)}$_2$] + **G**	AACMe	69	67	H_2O/EtOAC (1/1)	25 °C, 1 bar	88
8	[Rh(NBD){(*R*,*R*-H}]	ITAMe$_2$	66	0.9	H_2O/MeOH/*n*-heptane (1/1/2)	r.t., 5 bar	89
9	[Ir(NBD){(*R*,*R*-**H**}]	ITAMe$_2$	76	0.9	H_2O/MeOH/*n*-heptane (1/1/2)	r.t., 5 bar	89
10	[{RhCl(COD)}$_2$] + **F** (*n* = 1)	AACH	87	≥12.5	H_2O/EtOAC (1/1)	r.t., 10 bar	90
11	[{RhCl(COD)}$_2$] + **F** (*n* = 1)	AACMe	74	≥12.5	H_2O/EtOAC (1/1)	r.t., 10 bar	90
12	[{RhCl(COD)}$_2$] + **F** (*n* = 1)	ITAMe$_2$	28	≥12.5	H_2O/EtOAC (1/1)	r.t., 10 bar	90
13	[Rh(COD)(I)][BF_4]	AACMe	22 (*R*)	115	H_2O/EtOAC (1/1)	25 °C, 1 bar	91
14	[Rh(NBD)(J)][CF_3SO_3]	AACH	74 (*R*)	≥97	H_2O/EtOAC (1/1) (pH = 7.0)	r.t., 1 bar, [P] = 4.0%	92
15	[Rh(NBD)(J)][CF_3SO_3]	AACH	89 (*R*)	20	H_2O/EtOAC (1/1)	r.t., 1 bar, [P] = 1.0%	93
16	[Rh(COD)(*α*,*α*-**K**)][BF_4]	AACMe	76 (*S*)	≥34	H_2O/MeOH/EtOAc (3/2/5)	r.t., 5 bar	94
17	[Rh(COD)(*β*,*β*-**K**)][BF_4]	AACMe	98 (*S*)	≥34	H_2O/MeOH/EtOAc (3/2/5)	r.t., 5 bar	94
18	[Rh(COD)(L)][BF_4]	AACMe	73 (*R*)	≥4.2	H_2O/EtOAC (1/1)	r.t., 50 bar	95
19	[{RhCl(COD)}$_2$] + **F** (mixt.)[a]	dehydropeptides	87	≥1.0	H_2O/CH_2Cl_2 (1/2)	25 °C, 10 bar	96
20	[Rh(NBD)$_2$][BF_4] + **M**	AAMe	79 (*R*)	77	H_2O/EtOAC (10/7)	25 °C, 1 bar	97
21	[{RhCl(COD)}$_2$] + (*R*,*R*)-**N**	AACA-Na	60–80	≥1.1	H_2O/toluene (AAC-Na in the aq. phase, catalyst in the toluene phase!)	r.t., 1 bar	98
22	[{$RuCl_2$(η^6-*p*-cymene)}$_2$] + **P**	isobutyl atropica.	64	51	H_2O/EtOAC, Et_3N	24–30 °C, 60 bar	99

Table 38.2 (continued)

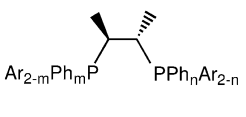
Entry	Catalyst	Substrate	ee [%]	TOF [h^{-1}]	Solvent	Conditions	Reference
23	[RuCl(η^6-C_6H_6){(*R*)-(+)-**R**}]Cl	AACH	72 (*R*)	0.3	H_2O/EtOAC (1/1)	r.t., 4 bar	100
24	Ru(II)/**Q**	geraniol	98	n.d.	H_2O/EtOAC	n.d.	101
25	[Ru(OAc)$_2$(tolBINAP)]	tiglic acid	92	2.2	H_2O/[bmim][PF_6]/$scCO_2$	25 °C, 5 bar	102
26	[Ru(OAc)$_2$(tolBINAP)]	isobutyl atropica.	"poor"	2.2	H_2O/[bmim][PF_6]/$scCO_2$	25 °C, 60 bar	102

For ligands **A**–**R**, see Scheme 38.7.
a) Mixture of mono- (25%), di- (70%), and trisulfonated (5%) BDPP.
n.d. = no data.

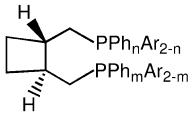


AACH BzACH $ITAMe_2$

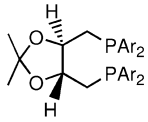
Scheme 38.6 Standard substrates for enantioselective hydrogenations.



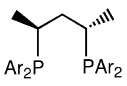
A: Ar = *m*-$C_6H_4SO_3Na$
B: Ar = [*p*-$C_6H_4NMe_3$][BF_4]



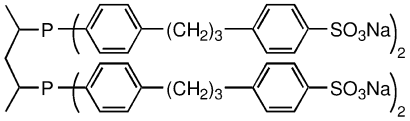
C: Ar = *m*-$C_6H_4SO_3Na$



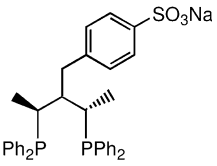
D: Ar = [*p*-$C_6H_4NMe_3$][BF_4]



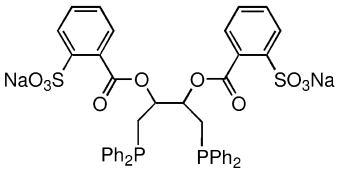
E: Ar = [*p*-$C_6H_4NMe_3$][BF_4]
F: Ar = *m*-$C_6H_4SO_3Na$



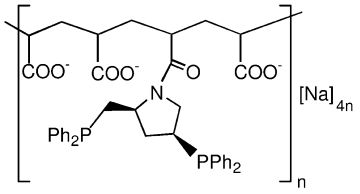
G



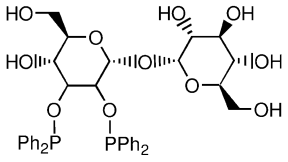
H; BDPBzPSO_3Na



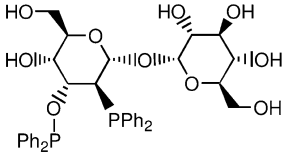
I



J; PAA-PPM

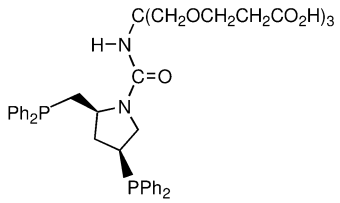


K

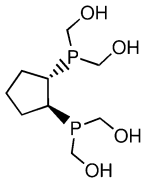


L

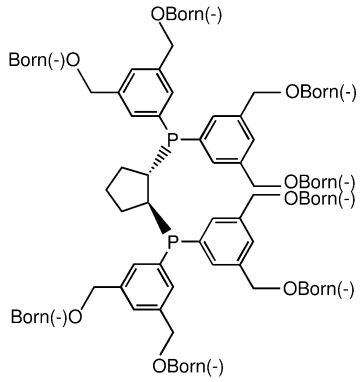
Scheme 38.7



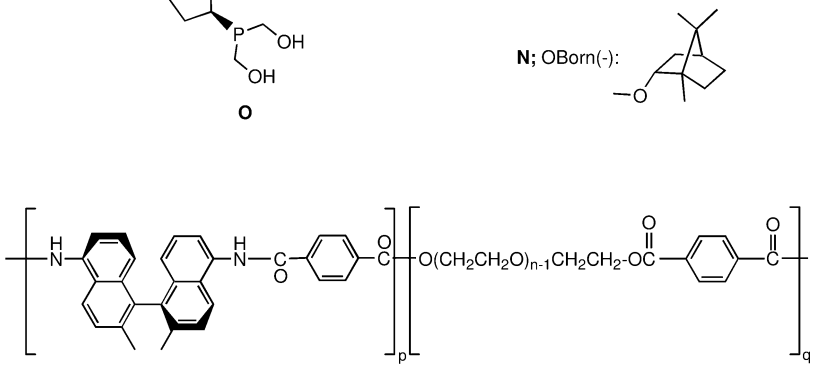
M



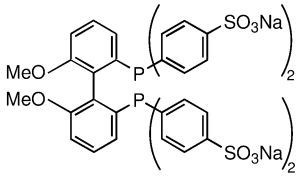
O



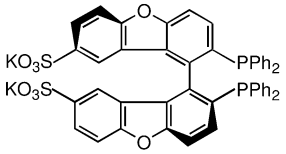
N; OBorn(-):



P; PEG-BINAP



Q; MeOBIPHEP-TS



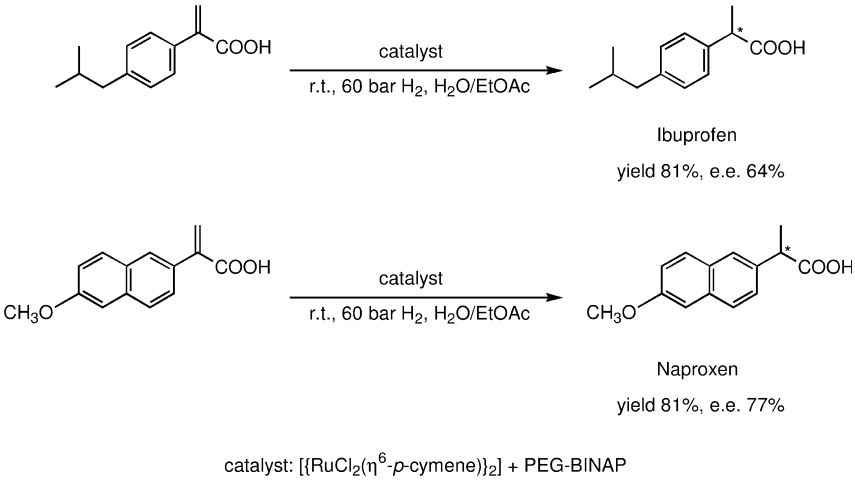
R; BIFAPS

Scheme 38.7 (continued)

In general, the chiral ligands are water-soluble variants of those already studied in purely organic solvents (e.g., the sulfonated chiraphos, A, cyclobutanediop, C, BDPP, F, MeOBIPHEP-TS, Q, BIFAPS, R and the quaternary ammonium derivatives of diop, D, BDPP, E). Solubility in water could also be achieved by attaching the parent phosphine molecule to a water-soluble polymer (J, M, P). The chiral phosphinites and phosphines derived from carbohydrates (e.g., K and L) have intrinsic solubility in water. During studies of one-phase

systems it was found that in several cases the catalytic activity and selectivity of an asymmetric hydrogenation was substantially decreased when it was performed in water instead of an organic solvent [4]; however, both the activity and selectivity could be restored by the addition of surfactants [103–106]. Based on these observations, a chiral *and* surfactant phosphine, G was synthetized and used as ligand in the Rh(I) complex-catalyzed hydrogenation of methyl *α*-acetamidocinnamate in MeOH and in H_2O:EtOAc. Indeed, with this ligand only a slight decrease in the catalytic activity and in the enantioselectivity was observed in the aqueous two-phase system compared to the reactions in methanol (69% versus 75% ee), while with the tetrasulfonated BDPP (F) the reaction was slowed considerably and the enantioselectivity fell from 72% to 20% upon the same solvent change [88]. Similar observations were made in water:ethyl acetate biphasic systems with the Ru(II)-catalysts containing the surfactant PEG-BINAP ligand (Scheme 38.7) – that is, the catalytic activity was found to be higher than in homogeneous solutions made either with ethyl acetate or with methanol:-water (1:1) mixtures [99]. The latter catalyst was used for the synthesis of the anti-inflammatory drugs ibuprofen and naproxen by hydrogenation of the corresponding 2-arylacrylic acids (Scheme 38.8) [99].

Whether asymmetric hydrogenations in aqueous two-phase systems will develop into practically significant procedures remains to be seen. Nevertheless, it is clear from the above investigations, that aqueous biphases are suitable media for asymmetric hydrogenations, and with the proper choice of the catalyst and the reaction conditions, very high selectivities and good catalytic activities can be achieved (see for example entry 17 in Table 38.2). High-throughput screening of catalysts and conditions with specifically designed microdevices [107] may also accelerate the advancement of this area of catalysis.



Scheme 38.8

38.4
Aqueous Two-Phase Hydrogenation of Aldehydes and Ketones

Hydrogenation of the carbonyl function can be achieved in aqueous biphasic systems (Table 38.3) using catalysts with water-soluble chiral ligands (Scheme 38.9). Most of these catalysts contain ruthenium [108, 109], although a few rhodium, iridium, osmium, and palladium complexes have also been found useful for this type of catalytic conversion. By far the greatest attention was devoted to the selective hydrogenation of *α,β*-unsaturated aldehydes, since the resulting allylic alcohols are important fine chemicals and synthetic intermediates for the flavor and fragrance industries.

Details of the hydrogenation of cinnamaldehyde (Scheme 38.10) and other *α,β*-unsaturated aldehydes were very thoroughly studied by several groups [10, 11, 110–120]. The general conclusion was that Ru(II)-phosphine complexes are suitable for the synthesis of allylic alcohols (selective C=O hydrogenation), while Rh(I)–phosphine complexes catalyze the selective hydrogenation of C=C bonds and yield saturated aldehydes. The reaction mechanisms behind this plain statement are certainly more complex, since it has been reported that, with the proper choice of pH of the aqueous phase, *either* cinnamyl alcohol ($pH \geq 8$) *or* 3-phenylpropionaldehyde ($pH \leq 5$) can be *selectively* obtained by hydrogenation of cinnamaldehyde with the same catalyst precursor, $[\{RuCl_2(m\text{tppms})_2\}_2]$, in the presence of excess *m*tppms (Fig. 38.2) [10, 11].

This finding is the consequence of the distribution of various ruthenium(II) hydrides in aqueous solutions as a function of pH; $[RuHCl(m\text{tppms})_3]$ is stable in acidic solutions, while under basic conditions the dominant species is $[RuH_2(m\text{tppms})_4]$ [10, 11]. A similar distribution of the Ru(II) hydrido-species as a function of the pH was observed with complexes of the related *p*-monosulfonated triphenylphosphine, *p*tppms, too [116]. Nevertheless, the picture is even more complicated, since the unsaturated alcohol : saturated aldehyde ratio depends also on the hydrogen pressure, and selective formation of the allylic alcohol product can be observed in acidic solutions (e.g., at pH 3) at elevated pressures of H_2 (10–40 bar; [117, 120]). (The effects of pH on the reaction rate of C=O hydrogenation were also studied in detail with the $[IrCp^*(H_2O)_3]^{2+}$ and $[RuCpH(pta)_2]$ catalyst precursors [118, 128].)

As elsewhere in the various fields of hydrogenation, the number of catalysts with ligands other than tertiary phosphines is rather limited. Bis-phosphonic acid derivatives of 2,2′-bipyridine and 1,2-cyclohexanediamines were used as ligands in iridium complexes which catalyzed the hydrogenation of acetophenone and several substituted acetophenones [130]. $[Ru(6,6'\text{-}Cl_2bipy)_2(H_2O)_2][CF_3SO_3]_2$ was also active in the biphasic hydrogenation of aldehydes and ketones [43]. The Ru(II)-N-heterocyclic carbene complex (see Scheme 38.5) catalyzed the hydrogenation of aldehydes and ketones; besides, in addition, the redox isomerization of allylic alcohol was also observed and part of this substrate was hydrogenated to propanol via prior isomerization to propionaldehyde [66].

Table 38.3 Hydrogenation of aldehydes and ketones in aqueous-organic two-phase systems.

Entry	Catalyst	Substrate	TOF [h^{-1}]	Selectivity [%][a)]	Solvent and conditions	Reference
1	$RuCl_3$/3–5 *m*tppts	crotonaldehyde	48	99	H_2O/toluene 1/1, 35–50 °C, 20–50 bar H_2	110
		prenal	400	97		111
		cinnamaldehyde	66	98		112
		citral	13	98		113
2	$[\{RhCl(COD)\}_2]$/5 *m*tppts	crotonaldehyde	625	99[b)]	H_2O/toluene 1/1, or H_2O/hexane 1/1, 30–80 °C, 20–40 bar H_2	111
		prenal	600	95[b)]		114
		cinnamaldehyde	124	96[b)]		
		citral	13	95[b)]		
3	$[RhCl(m\text{tppts})_3]$	cinnamaldehyde	140	95	H_2O/toluene 1/1, 50–90 °C, 10–40 bar H_2	115
4	$[\{RuCl_2(m\text{tppms})_2\}_2]$/*m*tppms	cinnamaldehyde	≤15	93 (pH 8) varies with pH	aq. buffer of various pH/chlorobenzene 3/5, 80 °C, 1 bar H_2	10, 11
5	$[\{RuCl_2(p\text{tppms})_2\}_2]$/*p*tppms	cinnamaldehyde	≤13	95 (pH 13) varies with pH	aq. buffer of various pH/chlorobenzene 3/5, 80 °C, 1 bar H_2	116
6	$[\{RuCl_2(m\text{tppms})_2\}_2]$/*m*tppms	cinnamaldehyde	≤14	93 (pH 3) varies with H_2 pressure	aq. buffer of various pH/chlorobenzene 3/3, 80 °C, 1–11 bar H_2	117

Table 38.3 (continued)

Entry	Catalyst	Substrate	TOF [h^{-1}]	Selectivity [%] [a]	Solvent and conditions	Reference
7	$RuCl_3$/6 *m*tppms, $RuCl_3$/6 *m*tppts $[\{RuCl_2(mtppms)_2\}_2]$, $[\{RuHCl(mtppms)_2\}_2]$	cinnamaldehyde	≤25	≤95	H_2O/toluene 1/1, 100 °C, 30 bar H_2	119
	$OsCl_3$/6 *m*tppms, $OsCl_3$/6 *m*tppts $[OsH_4(mtppms)_3]$, $[OsHCl(CO)(mtppms)_2]$		≤20	≤90		
	$[\{OsCl_2(mtppms)_2\}_2]$		0.4	100		
8	$RuCl_3$/ 5 *m*tppts $[\{RuCl_2(mtppts)_2\}_2]$, $[RuH_2(mtppts)_4]$ $[RuH(OAc)(mtppts)_3]$, $[RuHCl(mtppts)_3]$	cinnamaldehyde	≤95	≤96	H_2O/toluene 1/1, 40 °C, 20 bar H_2	120
	$[RuH(\eta^6\text{-}C_6H_5CH_3)(mtppts)_2]Cl$		0		H_2O/Et_2O, 40 °C, 20 bar H_2	
	$RuCl_3$/5 *m*tppts	crotonaldehyde	116	99	H_2O/toluene 1/1, 40 °C, 20 bar H_2	
	$[RuHCl(mtppts)_3]$		342	93		
	$[RuH_2(mtppts)_4]$		140	93		
	$[\{RuCl_2(mtppts)_2\}_2]$		13	32		
	$[\{RuCl_2(mtppts)_2\}_2]$		16	46	H_2O/Et_2O, 40 °C, 20 bar H_2	
	$[RuHCl(mtppts)_3]$	prenal	400	100	H_2O/toluene 1/1, 20 °C, 20 bar H_2, 23% over-reduction to 3-methyl-butanol	
9	$[\{RhCl(COD)\}_2]$/*m*tppts	benzaldehyde	33		aq. buffer (pH 7)/EtOAc 1/1, 65 °C, 20 bar (r.t.) H_2	121
	$[\{RhCl(COD)\}_2]$/T(p-A)PTS	benzaldehyde	16			
	$[\{RhCl(COD)\}_2]$/T(p-A)PTS	hexanal	19			
	$[\{Ir(COD)Cl\}_2]$/*m*tppts	benzaldehyde	3			
	$[\{Ir(COD)Cl\}_2]$/T(p-A)PTS	benzaldehyde	3			
	$[\{Ir(COD)Cl\}_2]$/T(2,4-X)PTS	benzaldehyde	40			

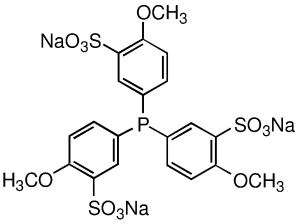
10	$[RuCl_2(pta)_4]$	benzaldehyde	7.2		aq. buffer (pH 8)/chlorobenzene 1/1	122
11	$[Ir(COD)\{P(CH_2OH)_3\}_3]Cl$	cinnamaldehyde	20	≤97	H_2O/benzene 1/1, 100–125 °C, 30–100 bar H_2	123
12	$[RhI_4(mtpa)_2]I$ [d]	cinnamaldehyde	190	88 [b]	H_2O/toluene 1/1, 60 °C, 35 bar H_2	124
	$[RuI_4(mtpa)_2] \cdot 2H_2O$		40	94		
	$[RuI_2(mpta)_3(H_2O)]I_3 \cdot 2H_2O$		183	80		
13	$[RhI(CO)(mpta)_3]I_3 \cdot 4H_2O$	pentanal	108	80 [c]	H_2O/substrate, 80 °C, 80 bar H_2	125
		hexanal	108	84 [c]		
		heptanal	106	78 [c]		
14	$[PdCl_2(m\text{tppts})_2]$	crotonaldehyde	3750	100 [b]	H_2O/benzene 30/5, 10–60 °C, 1–50 bar H_2	126
		cinnamaldehyde	1250	≤58		
		citral	307	≤97 [b]	main product: citronellal	127
15	$[RuCpCl(pta)_2]$	benzylideneacetone	10–35	75–89 [b]	H_2O/*n*-octane 1/2, 130 °C, 31.5 bar H_2	44
	$RuCp^*Cl(pta)_2]$		6–11	81–94		
16	$[RuCpH(pta)_2]$	benzylideneacetone	3.3	99 (pH 4.5) [b]	aq. phosphate buffer/substrate, 25 °C, 4 bar H_2	128
17	$[\{Ir(COD)Cl\}_2]$/**L1**, **L2** or **L3**	various ketones	1	100 [c]	H_2O/substrate, or H_2O/EtOAc, r.t., 40 bar H_2	129
	$[\{RhCl(COD)\}_2]$/**L1**, **L2** or **L3**					
18	$[Ru(\eta^6\text{-}C_6H_6)(CH_3CN)_3]^{2+}$	cyclohexen-2-one	178	96 [b]	H_2O/benzene, 90–110 °C, 40 bar H_2	42
		mesityl oxide	118	100 [b]		
		benzylideneacetone	245	98 [b]		

Table 38.3 (continued)

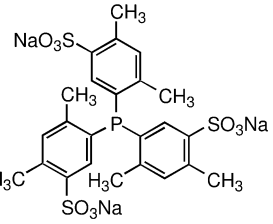
Entry	Catalyst	Substrate	TOF [h^{-1}]	Selectivity [%] [a]	Solvent and conditions	Reference
19	[Ru(6,6′-Cl_2bipy)$_2$(H_2O)$_2$][CF_3SO_3]$_2$	cinnamaldehyde	120	71	H_2O/toluene 8/5, or H_2O/cyclohexane 8/5, 130 °C, 40 bar H_2	43
		mesityl oxide	233	100 [b]		
		benzylideneacetone	220	98 [b]		
		acetophenone	213			
20	[{$RuCl_2$(*m*tppts)$_2$}$_2$]	benzylideneacetone	3	98 [b]	H_2O/benzene 5/2, 80 °C, 35 bar H_2	120
	[{$RuCl_2$(*m*tppts)$_2$}$_2$]	benzylideneacetone	5	95 [b]	H_2O/CH_2Cl_2 5/2, 80 °C, 35 bar H_2	
	[RuH_2(*m*tppts)$_4$]	benzylideneacetone	9	78 [b]	H_2O/benzene 5/2, 80 °C, 35 bar H_2	
21	[Ir(COD)$_2$][BF_4]/ **L4**	acetophenone	18	52 (ee)	H_2O/MeOH/substrate, 50 °C, 45 bar H_2	130
		4-MeO-acetophenone	≥9.5	50 (ee)		
		2-MeO-acetophenone	≥9.5	70 (ee)		
		t-butylphenylketone	≥9.5	72 (ee)		
22	[$RuBr_2$(6,6′-diamBINAP.2HBr)]	ethyl acetoacetate	≥63	94 (ee)	H_2O/substrate, 50 °C, 40 bar H_2	131
	[$RuBr_2$(4,4′-diamBINAP.2HBr)]	ethyl acetoacetate	≥67	99 (ee)	H_2O/substrate, 50 °C, 40 bar H_2	132
	[$RuBr_2$(5,5′-diamBINAP.2HBr)]	ethyl acetoacetate	≥67	99 (ee)	H_2O/substrate, 50 °C, 40 bar H_2	132
23	[$RuCl_2$(η^6-*p*-cymene)(**L5**)]	cinnamaldehyde	39 [b]		aq. phosphate buffer (pH 6.9)/ substrate, 80 °C, 10 bar H_2	66
		acetophenone	40			
		benzylideneacetone	29 [b]			
	[RuCl(η^6-*p*-cymene)(pta)(**L5**)]$^+$	cinnamaldehyde	59 [b]			
		acetophenone	65			
		benzylideneacetone	60 [b]			

24	[{RhCl(COD)}$_2$]/chiral diphenyl-phosphinoacetamides	acetophenone	7	22 (ee)	H_2O/benzene 1/4, 50 °C, 1 bar H_2	133
25	$RuCl_3$/8 *m*tppts	cinnamaldehyde	36	92	H_2O/toluene 1/50, 40 °C, 40 bar H_2	135
	$RuCl_3$/8 *m*tppts	cinnamaldehyde	124	99	H_2O/sc CO_2 (140 bar), 40 °C, 40 bar H_2	
	$RhCl_3$/8 *m*tppts	cinnamaldehyde	114	100[b)]	H_2O/sc CO_2 (140 bar), 40 °C, 40 bar H_2	
	$Pd(OAc)_2$/8 *m*tppts	cinnamaldehyde	72	100[b)]	H_2O/sc CO_2 (140 bar), 40 °C, 40 bar H_2	

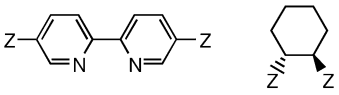
a) Unsaturated alcohol.
b) Saturated aldehyde or ketone.
c) Alkanol.
d) mpta = N-methyl-pta.
For the ligands *m*tppms, *m*tppts and pta, see Scheme 38.2; for T(p-A)PTS, T(2,4-X)PTS, diamBINAP.2HBr, and **L1–L5**, see Scheme 38.9.



t(*p*-A)pts



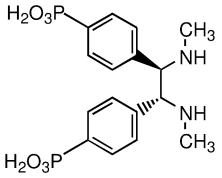
t(2,4-X)pts



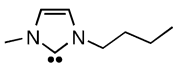
L1 : Z = -C(O)NHC$_3$H$_6$PO$_3$H$_2$

L2 : Z = -PO$_3$H$_2$

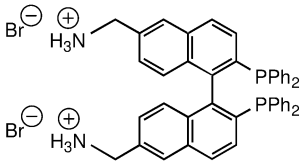
L3 : Z = -NHC(O)NHC$_6$H$_4$PO$_3$H$_2$



L4

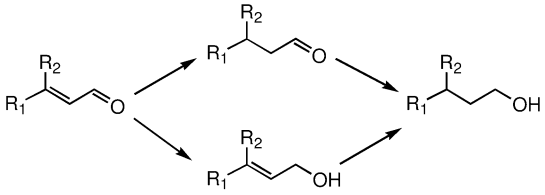


L5



6'6'-diamBINAP

Scheme 38.9



R_1 = Ph, R_2 = H : cinnamaldehyde
R_1 = CH_3, R_2 = H : crotonaldehyde
R_1 = R_2 = CH_3 : prenal

Scheme 38.10

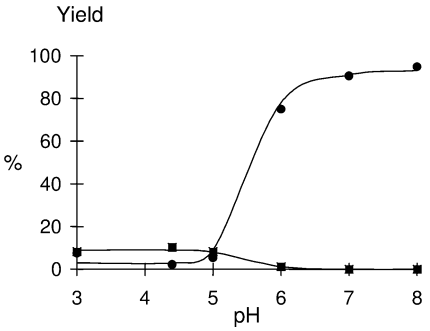


Fig. 38.2 Effect of pH on the yield of products in hydrogenation of *trans*-cinnamaldehyde with [{$RuCl_2$(*m*tppms)$_2$}$_2$] and *m*tppms as catalyst precursors. ●, cinnamyl alcohol; ■, dihydrocinnamaldehyde. [cinnamaldehyde]=80 mM in chlorobenzene (5 mL); [Ru]=3.4 mM; [*m*tppms]=10.3 mM; [KCl]=0.2 M in 0.2 M phosphate buffer (3 mL), 80 °C, H_2, P_{total}=1 bar. (Reproduced with permission from F. Joó, J. Kovács, A. Cs. Bényei, Á. Kathó, *Catal. Today* **1998**, *42*, 441–448.)

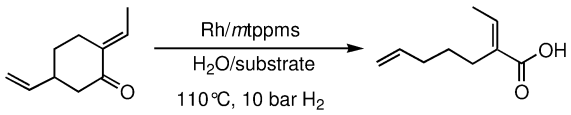
Enantioselective hydrogenation of prochiral ketones has rarely been studied in aqueous biphasic media. In addition to the chiral bisphosphonic acid derivatives of 1,2-cyclohexanediamine [130], the protonated 4,4′-, 5,5′-, and 6,6′-aminomethyl-substituted BINAP (diamBINAP · 2HBr) ligands (Scheme 38.7) served as constituents of the Ru(II)-based catalysts in the biphasic hydrogenations of ethyl acetoacetate [131, 132]. These catalysts were recovered in the aqueous phase and used in at least four cycles, with only a marginal loss of activity and enantioselectivity.

Besides the "conventional" aqueous : organic two-phase systems making use of hydrosoluble catalysts (i.e., version A in Scheme 38.1), reports have also been made on other approaches. Acetophenone dissolved in the benzene phase was hydrogenated with the unmodified Wilkinson's catalyst, [$RhCl(PPh_3)_3$] or its analogs containing chiral diphenylphosphinoacetamides (prepared from α-amino-acids) in the presence of an aqueous phase (and triethylamine) [133]. In this case, the role of the two phases is not in the separation of the catalyst and the substrate (products), but rather in facilitating the formation of the catalytically active Rh(I)-monohydride species by extracting the HCl byproduct into the aqueous phase [Eq. (4)].

$$[RhCl(P)_3 + H_2 \rightleftharpoons [RhH_2Cl(P)_3] \quad (3)$$

$$[RhH_2Cl(P)_3] \rightleftharpoons [RhH(P)_3] + H^+ + Cl^- \quad (4)$$

In another example, undecanal was hydrogenated to undecanol with a water-soluble catalyst in the presence of chemically modified β-cyclodextrins, which facilitated the mass transfer between the aqueous and the organic phase [134]. Hydrogenation of cinnamaldehyde with very high (99%) selectivity to cinnamyl alcohol was also performed in water : $scCO_2$ biphasic systems [135] which al-



Scheme 38.11

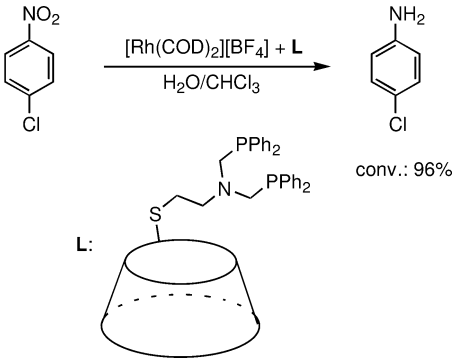
lowed an efficient mass transfer between the substrate-containing and the catalyst-containing phases.

The δ-lactone (Scheme 38.11) can be efficiently obtained by the telomerization of butadiene and CO_2. Its biphasic hydrogenation with an *in-situ*-prepared Rh/*m*tppts catalyst yields 2-ethylidene-6-heptenoic acid (and its isomers) [136]. Note, that the catalyst is selective for the hydrogenolysis of the lactone in the presence of two olefinic double bonds; this is probably due to the relatively large [P]:[Rh] ratio (10:1) which is known to inhibit C=C hydrogenations with [RhCl(*m*tppms)$_3$]. The mixture of heptenoic acids can further be hydrogenated on Pd/C and Mo/Rh catalysts to 2-ethylheptanol which finds several applications in lubricants, solvents, and plasticizers. This is one of the rare examples of using CO_2 as a C1 building block in a transition metal-catalyzed synthetic process.

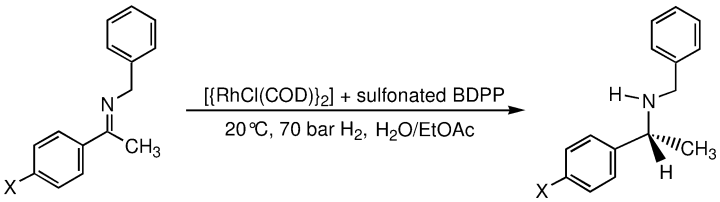
38.5 Aqueous Two-Phase Hydrogenations of Nitro-Compounds, Imines, Nitriles, Oximes, and Heteroaromatics

Although amines are very important intermediates or targets of synthesis, relatively few studies have been conducted on their catalytic production in aqueous-organic biphasic systems. It has long been known that $[CoH(CN)_5]^{3-}$ is capable of hydrogenating nitro-, azoxy- and azo-compounds under mild conditions [49]. Both the C=C and -NO_2 groups in 2-nitro-(2,5-dimethoxyphenyl)nitroethene were hydrogenated with an *in-situ*-prepared $RuCl_3$/*m*tppms catalyst in a two-phase reaction (90 °C, 40 bar H_2) to yield 2-(2,5-dimethoxyphenyl)ethylamine [137].

The catalytic hydrogenation of chloro-nitroaromatics is usually accompanied by dehalogenation. However, choloranilines could be obtained with very high selectivities (Scheme 38.12) on the catalytic action of rhodium(I) catalysts having β-cyclodextrin-modified chelating bisphosphine ligands [138, 139]. Nitrobenzene and several substituted nitroaromatics were selectively hydrogenated to the corresponding anilines in biphasic systems composed of water and the substrates with a water-soluble catalyst *in situ* prepared from $FeSO_4 \cdot 7H_2O$ and $EDTANa_2$ (Fe:ligand=1:5) [140]. Chloronitrobenzenes were hydrogenated to chloroanilines with ≥99.0% selectivity. Although somewhat harsh conditions had to be used (150 °C, 28 bar H_2), the TOF values were very high (430 to 1300 h^{-1}) and the catalyst could be recycled with no loss of activity or selectivity (tested in five cycles). Traditionally, Fe(0) is used in the stoichiometric (Béchamp-) reduction of nitrobenzene and in the heterogeneous catalytic hydrogenation of nitro compounds; however, this method is a rare example of the efficient use of soluble Fe-complexes in homogeneous catalytic hydrogenations.



Scheme 38.12

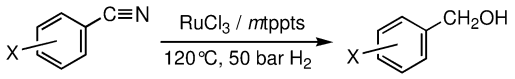


X = H, OMe, Cl

e.e. ≤ 94%

Scheme 38.13

Certain benzylimines are sufficiently resistant to hydrolysis, and their hydrogenation can also be studied in aqueous biphasic systems. The hydrogenation of acetophenone benzylimines (Scheme 38.13), catalyzed by [{RhCl(COD)}$_2$] + sulfonated BDPP (Scheme 38.7, F) afforded the corresponding amines with enantioselectivities up to 96%, provided that the degree of sulfonation of BDPP was close to 1 (in fact it was 1.41–1.65) [141]. When more than one of the BDPP phenyl rings was sulfonated the enantioselectivity decreased sharply. The "monosulfonation effect" was studied in detail with well-characterized complexes of sulfonated BDPP with N = 1, 2, 3, or 4 sulfonate groups [142]. Indeed, it was confirmed that by far the highest enantioselectivity was obtained with the monosulfonated ligand (N = 1, ee 94%; N = 2, ee 2%; N = 3, ee 3%; N = 4, ee 63%). With the monosulfonated BDPP ligand, the resulting rhodium(I) complex is very soluble in ethyl acetate and moves completely to the organic phase during hydrogenation. It is assumed, that the sulfonate group of the ligand coordinates to the cationic rhodium center and the resulting zwitterionic product dissolves in the organic solvent. In a related study, acetophenone benzylimine was hydrogenated with a [Rh{(–)-BDPP}(NBD)][ClO_4] catalyst in reverse micellar systems [143]. In the presence of the bis(2-ethylhexyl)sulfosuccinate (AOT) surfactant, as well as with various RSO_3Na salts, the enantioselectivity was appreciably



Scheme 38.14

X = H, 3-Me, 4-Me, 4-Br

higher then in their absence, showing again the selectivity-promoting effect of the possible coordination of the sulfonate anion to the cationic catalyst.

The hydrogenation of aliphatic and aromatic nitriles was catalyzed by *in-situ*-prepared Ru/*m*tppts catalysts in two-phase systems with close to quantitative conversion to the corresponding benzylalcohols (Scheme 38.14) [144]. Interestingly, the reactions were facilitated at high [P]:[Ru] ratios, and benzonitrile was completely converted to benzyl alcohol at [P]:[Ru] $\geq$20. It is assumed that, in the first step of the reaction, the nitriles are hydrogenated to imines, which undergo rapid hydrolysis to aldehydes at the reaction temperature (120 °C), after which the aldehydes are further hydrogenated to alcohols (this latter reaction is indeed promoted by high phosphine concentrations [145]).

Ketoximes and oximes of 2-oxo-acids are hydrogenated to amines by $[CoH(CN)_5]^{3-}$. The latter reaction allows the preparation of *α*-amino-acids by reductive amination of 2-oxo-acids in aqueous ammonia. At 40–50 °C and 70 bar H_2 the yields are ca. 90% [146].

The removal of sulfur and nitrogen from petroleum has enormous significance. Industrially, this is carried out by heterogeneous hydrogenation (hydrotreating). Several attempts were made to hydrogenate thiophene, benzo[*b*]thiophene, and quinoline in aqueous biphases using rhodium(I) and ruthenium(II) complexes of sulfonated phosphines and nitrogen-containing ligands [147–150], not only in model systems but also with naphthas of various origin. Indeed, 78% of the benzo[*b*]thiophene in a naphtha containing 4500 ppm sulfur was hydrogenated (TOF = 6.5 h^{-1}) to dihydrobenzo[*b*]thiophene at 130 °C and 70 bar H_2 with a catalyst prepared *in situ* from $RuCl_3$ and *m*tppms [151–153]. The same catalyst was even more active in the hydrogenation of quinoline to tetrahydroquinoline, while linear or cyclic olefins were reduced only to a small extent and other aromatics (e.g., benzene, toluene, naphthalene) were not hydrogenated at all.

38.6 Conclusions

Aqueous two-phase hydrogenation may be a method of choice for synthetic purposes when no incompatibility problems between water and the substrates, products, or catalyst arise. It has already been proven by the success of the Ruhrchemie-Rhône-Poulenc hydroformylation process, that the catalyst can be retained in the aqueous phase with very high efficiency, and that aqueous-organic biphasic processes using organometallic catalysts are suitable for indus-

trial applications. Whether a new, large-scale biphasic hydrogenation process will emerge remains to be seen. The many interesting synthetic examples of aqueous biphasic hydrogenations discussed in this chapter serve as a solid ground for such developments, and the combination of water with suitable supercritical fluids or ionic liquids may further widen the synthetic possibilities offered by aqueous two-phase hydrogenations.

Abbreviations

ABS acrylonitrile-butadiene-styrene
IL ionic liquid
NBR nitrile-butadiene rubber
PBD polybutadiene
SBR styrene-butadiene rubber
SCF supercritical fluid
TOF turnover frequency

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