AQUEOUS ORGANOMETALLIC CATALYSIS

by

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Preface

Aqueous organometallic catalysis is a rapidly developing field and there are several reasons for the widespread interest. Perhaps the most important is the possibility of using liquid-liquid two-phase systems for running catalytic reactions. Often termed liquid biphasic catalysis, these two-phase procedures allow recycling of the catalyst dissolved exclusively in one of the phases – of course, this book focuses on the aqueous phase. It is this catalyst recycling, together with the much simplified technology, where the interest of the chemical industry lies. Small scale laboratory procedures may also benefit from using organometallic catalysts in aqueous solutions due to the easier, cleaner isolation of the desired products of biphasic reactions. In addition, growing environmental concern forces industry and research laboratories to use less and less environmentally hazardous chemicals, and water –as opposed to most organics– is certainly an environmentally benign (green) solvent. A somewhat less obvious and less exploited possibility is in that several catalytic reactions which do take place in homogeneous aqueous solutions or in biphasic systems simply do not happen in dry organic solvents.

This book is devoted to a systematic description of the basic phenomena, principles and practice of aqueous organometallic catalysis in a relatively concise and organised way. Organisation of the material is not an easy task, since fundamental chemical questions, such as reactivity and selectivity of a catalyst in a given reaction should be treated together with the various synthetic applications and industrial or engineering aspects. Only those systems are described where the catalyst itself is a genuine organometallic compound or where such intermediates are formed along the reaction pathway. Accordingly, those organic syntheses in aqueous solutions where

an organometallic compound acts as a stoichiometric reagent are largely omitted. The field of liquid multiphase catalysis expands readily, nevertheless other multiphase techniques are just scarcely mentioned. Among them phase transfer assisted organometallic catalysis is a special approach because there are many cases when the catalyst resides and acts in the aqueous phase or at the aqueous/organic interface. Reactions, where the organometallic catalysis takes place entirely in the organic phase, and phase transfer catalysis is used merely to supply reagents from the aqueous phase are not discussed.

Numerous reviews, special journal editions and books have been already devoted to the topic of aqueous organometallic catalysis especially in the last 5-8 years. All these publications, however, comprise of detailed reviews or accounts on particular topics written by leading specialists. While this is certainly beneficial for those who themselves work in the same direction, non-specialists, students or those who are just to enter this field of research may be better served by a monograph of the style and size of the *Catalysis by Metal Complexes* series. In 1994, in Volume 15 of this series, a chapter was published on aqueous organometallic hydrogenations – with the aim of giving a *complete* description of what had been done before in that respect. After only seven years such an aim of all-inclusivity is irrealistic, and this had to bring with itself a selection of the literature used.

Writing of this book took much more time than originally expected. I owe a lot of thanks to D. J. Larner, E. M. C. Lutanie and J. W. Wijnen, Publishing Editors at Kluwer Academic Publishers who helped this long process by their advice and patience. Thanks are due to the American Chemical Society, the Royal Society, Elsevier Science B. V. and Wiley-VCH Verlag GmbH for permissions to use previously published material. All my family, colleagues and students had to survive the consequences of my preoccupation with this task – many thanks for their understanding. I am particularly indebted to Gábor Papp for preparing the artwork. Finally, and with utmost appreciation I thank the support and encouragement provided by my wife Dr. Ágnes Kathó. Without her understanding at home, and her invaluable help in literature search, proofreading and in discussions of the various versions of the manuscript this book could have never been completed.

Debrecen, September 2001

Ferenc Joó

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Chapter 1

Introduction

1.1 A personal look at the history of aqueous organometallic catalysis

"Organometallic chemistry deals with moisture sensitive compounds therefore all manipulations should be carried out under strictly anhydrous conditions" – this was the rule of thumb ever since the preparation of the first organometallic compounds. Not as if there were no isolated examples of water-stable organometallics from the very beginning, in fact Zeise`s salt, $[PtCl_3(C_2H_4)]^-$ was prepared as early as 1827. Nevertheless, it is true, that compounds having highly polarized M-C, M-H etc. bonds may be easily decomposed in water by protonation. In other cases, oxidative addition of or oxygen abstraction from water leads to formation of metal hydroxides or oxides, i.e. the redox stability of water may not be sufficient to dissolve without deterioration a compound having a highly reduced metal center. Still, there are the procedures for preparation of important compounds (such as e.g. $[HRh(PPh_3)_4]$) which call for washing the products with water in order to remove inorganics – these compounds cannot be highly sensitive to water.

Nowadays we look with other eyes at organometallic compounds the family of which has expanded enormously. Some members of this family are soluble in water due to their ionic nature; the legions of anionic carbonylmetallates (e.g. $[Ni(CN)(CO)_3]^-$) and cationic bisphosphine Rh-chelate complexes (e.g. $[Rh(BDPP)(COD)]^+$) just come to mind. Others obtain their solubility in water from the well soluble ligands they contain; these can be ionic (sulfonate, carboxylate, phosphonate, ammonium, phosphonium etc. derivatives) or neutral, such as the ligands with polyoxyethylene chains or with a modified urotropin structure.

One of the most important metal complex catalyzed processes is the hydroformylation of light alkenes. In the early years the catalyst was based on cobalt and this brought about an intense research into the chemistry of cobalt carbonyls. A key intermediate, $[CoH(CO)_4]$ is well soluble and stable in water and behaves like a strong acid [1] in aqueous solution:

$$[CoH(CO)_4] \rightleftharpoons [Co(CO)_4]^- + H^+ \qquad (1.1)$$

For a decade or so $[CoH(CN)_5]^{3-}$ was another acclaimed catalyst for the selective hydrogenation of dienes to monoenes [2] and due to the exclusive solubility of this cobalt complex in water the studies were made either in biphasic systems or in homogeneous aqueous solutions using water soluble substrates, such as salts of sorbic acid (2,4-hexadienoic acid). In the late nineteen-sixties olefin-metal and alkyl-metal complexes were observed in hydrogenation and hydration reactions of olefins and acetylenes with simple Rh(III)- and Ru(II)-chloride salts in aqueous hydrochloric acid [3,4]. No significance, however, was attributed to the water-solubility of these catalysts, and a new impetus had to come to trigger research specifically into water soluble organometallic catalysts.

New incentives came from two major sources, and it is tempting to categorize these as "academic" and "industrial" ones. In the early fifties the renaissance of inorganic chemistry brought about the need for water soluble, phosphorus-donor ligands in order to establish correlations between metal complex stability and structure and the characteristics of donor atoms in a given ligand set. By that time tertiary phosphines, introduced to organometallic chemistry by F. G. Mann, were widely recognized as capable of coordinating and stabilizing low oxidation state metal ions in organic solvents. For Ahrland, Chatt and co-workers it appeared straightforward to derivatise the well-known and conveniently handled triphenylphosphine (PPh_3) by sulfonation in fuming sulfuric acid in order to get the required P-donor ligand for complexation studies in aqueous solution [5]. The monosulfonated derivative, 3-sulfonatophenyldiphenylphosphine, nowadays widely known as TPPMS, was successfully used in complex stability measurements which later led to the categorization of ligands according to their donor atoms (ligands of *a* and *b* character and the Ahrland-Chatt triangle, forerunner of the *hard* and *soft* characterization). TPPMS was then investigated in extensive details by J. Bjerrum who established stability constants of complexes of a dozen of metal ions with this ligand [6]. In addition to TPPMS, another water soluble tertiary phosphine, *2*-hydroxyethyldiethylphosphine (abbreviated that time as dop) was prepared and its complex forming properties studied in Schwarzenbach`s laboratory [7]. All this had nothing to do with catalysis let alone catalysis with

organometallic complexes in aqueous solutions. However, the stage was already set, the ingredients of such catalytic systems were at hand. This was the situation in 1968 when I joined the Institute of Physical Chemistry at the (then) Lajos Kossuth University of Debrecen, Hungary, chaired by Professor M.T. Beck who later became my M.Sc. supervisor. Our work showed convincingly that complexes of ruthenium(II) and rhodium(I) with TPPMS as ligand could be successfully used for hydrogenation of water soluble olefins in aqueous solutions. My Thesis was submitted in 1972 and the first papers [8,9] appeared in 1973 (see also [10] for further recollections). All our catalytic work was carried out in strictly homogeneous aqueous solutions.

At about the same time it was already clear that homogeneous catalysis could not be widely practiced in industry without solving the inherent problem of separation of the catalysts from the product mixture applying relatively easy and economic methods. The first written record of the idea of metal complex catalysis in two immiscible liquid phases systems as a viable general solution to this problem can be traced back in the report [11] of a Working Group on Heterogenizing Catalysts, chaired by Manassen (then at the Weizmann Institute, Rehovot, Israel) at a NATO Science Committee Conference in late 1972. The proceedings of the conference were published in 1973 at the same time as our first publications, a clear evidence to that these ideas developed independently. The Group Report did not specifically mentioned aqueous/organic two-phase systems for organometallic catalysis, though later Manassen put this idea into practice [12] using a Rh(I)-TPPMS catalyst for hydrogenation of olefins in water/benzene mixtures (with a correct reference to our related earlier work on homogeneous catalysis).

In general, the first papers on catalysis by water soluble phosphine complexes did not draw much enthusiasm from the catalysis society. As one of the most reputed colleagues stated: "not *any* of the important processes of organometallic catalysis takes place in aqueous solutions". It needed the imagination of Kuntz [13-15] to develop the chemistry of (and file patents in 1975-1976 for Rhône-Poulenc on) two-phase hydroformylation, hydrocyanation and telomerization of olefins – three really important processes of organometallic catalysis. Not only the principle of aqueous/organic biphasic procedures was successfully realized for manufacturing important industrial products, but new sulfonated phosphine ligands were also prepared of which the highly water soluble trisulfonated triphenylphosphine (tris(3-sulfonatophenyl)phosphine, TPPTS) was later shown a key component of the rhodium(I) catalyst of large scale hydroformylation. However, even these results did not find their way into immediate industrial utilization.

Another important industrial process based on multiphase catalysis in immiscible organic solvents [16] was developed by Shell in the mid-1970-ies for oligomerization of higher olefins (SHOP). However, the wide significance of the technique as a *general means* for recycling soluble catalysts was apparently not widely publicized. During the late 1970-ies, early 1980-ies an extraordinarily important step was taken by Ruhrchemie: Cornils and coworkers realized the enormous potential dormant in the patents of Rhône Poulenc and a decision was made to develop a commercial two-phase process for hydroformylation of propene with the water soluble catalyst $[RhH(CO)(TPPTS)_3]$. The first plant of the capacity of 100.000 tons of butyraldehyde per year started production in 1984 in Oberhausen [17] and this industrial success changed the scene entirely for research into aqueous organometallic chemistry and catalysis. In addition to industry, dozens of academic laboratories worldwide initiated research projects on all aspects of this chemistry, and the number of available ligands and catalytically active metal complexes grew exponentially. It can be said with no exaggeration that a large part of classical "non-aqueous" organometallic catalysis can now be performed in water or in two-phase systems which largely widens the scope of organic synthesis.

Some like to point out that during the development of aqueous organometallic catalysis and specifically during that of two-phase aqueous/organic processes research within industry was far ahead of the contributions made by academic institutions. Looking back to the very beginnings, however, it seems to me, that aqueous organometallic catalysis and liquid multiphase catalysis developed independently at a few places both in academe and in industry when the scientific curiosity and/or practical need for such processes arose and when previous basic research could give a lead. No question, the clear interest, strategic vision and financial resources of industry coupled with an energetic and efficient conduct of chemical and engineering research decisively shaped the present state of the art. One takes no serious risk by stating that without the industrial success of the Ruhrchemie – Rhône-Poulenc (RCH-RP) hydroformylation process aqueous organometallic catalysis might have well remained in its infancy for many years more, with its great potential in synthesis undiscovered. It should be remembered, however, that all goes back to the purely "academic" question of stability and structure of metal complexes with ligands having various donor atoms.

In addition to the outstanding achievements in connection with the RCH-RP process other breakthroughs of aqueous organometallic catalysis deserve mentioning, too. The first attempts of enantioselective hydrogenation in water with soluble catalysts were described already in 1978 and today there are several examples of almost complete

enantioselectivity in hydrogenation of acylated dehydroaminoacids. Reactions with C-C bond formation (carbonylation, telomerization, polymerization, various kinds of C-C coupling, and new variants of hydroformylation) are in the focus of intensive studies and a few of such processes reached industrial application. Special effects observed in water due to variation in pH, concentration of dissolved inorganic salts or surfactants are being studied and exploited in order to increase reaction rates and selectivities. Selective hydrogenation of unsaturated lipids in cell membranes, first attempted in aqueous membrane dispersions in 1980, gives unique information on the effect of membrane composition and structure on the defense mechanism of cells against environmental stress. Activation of carbon dioxide in aqueous solution with several kinds of transition metal complexes may bring us closer to construction of systems of artificial photosynthesis or to the use of CO_2 as a C1 building block in synthesis.

The development of aquous organometallic catalysis has been indicated by appearance of several reviews, proceedings, monographs and special journal volumes [10, 18-42], almost evenly paced in the last two decades.

The exciting results of aqueous biphasic catalysis encouraged research in closely related fields. Such are the study of supported aqueous phase catalysts (SAPC) [43] and other techniques of heterogenization on solid supports [44]; the use of supercritical water [45] and carbon dioxide [46] as solvent; the revival of organic/organic two-phase processes including the ingenious concept of fluorous [47] biphase systems (FBS) and engineering aspects of conducting reactions in two immiscible phases. The advantages/disadvantages of multiphase procedures, either in organic/organic or in ionic liquid/organic systems [48] are often compared to those in aqueous/organic solvent mixtures i.e. the aqueous systems became the standard point of reference.

However fascinated by the achievements in catalysis, one has always to keep in mind, that all those successes were made possible by the extensive research into the synthesis of new ligands and metal complexes, their structural characterization, and the meticulous studies on reaction kinetics with the new catalysts in model systems and in the desired applications. Only the synthetic and catalytic work, hand in hand, can lead to development of new, efficient and clean laboratory and industrial processes.

1.2 General characteristics of aqueous organometallic catalysis

In the simplest form of aqueous organometallic catalysis (AOC) the reaction takes place in a homogeneous aqueous solution. This requires all

reactants, catalyst(s) and additives, if any, be soluble in water. In reactions with gases (hydrogenation, hydroformylation, etc.), this condition is met only with limitations. The catalytic reaction further depletes the concentration of H_2, CO, etc. below their low equilibrium solubility level and even to maintain a steady state requires a constant and fast supply from the gas phase. Although the chemical reaction itself happens only in one of the phases, technically this is a gas/liquid two-phase process. The partial pressure of the reacting gas and the efficiency of its dissolution into the aqueous phase (aided by rapid mixing of the gas into the solution) together with the temperature at which the reaction takes place govern the steady state concentration of this reactant available for the reaction. In some cases the low concentration of one of the reacting species due to solubility constraints may result in changes in the selectivity of the catalyzed reaction.

In a two-phase AOC process the catalyst is dissolved in the aqueous phase and several or all of the substrates and products are present in the organic phase. All these compounds may dissolve to an appreciable extent in the other phase, however, in a practical process the catalyst must not leave the aqueous phase in order to minimize catalyst loss. On the contrary, *limited* solubility of the organic reactants in water is an advantage, since it facilitates the reaction inside the bulk aqueous phase where most of the catalyst molecules are found. A specific example is the hydrogenation of aldehydes in biphasic systems. The solubility of benzaldehyde in water at room temperature is approximately 0.03 M and that of benzyl alcohol 0.37 M [49]. Such a partial dissolution of the substrate and product does not result in considerable losses, especially when the saturated aqueous catalyst phase is repeatedly or continously recycled. When the reaction takes place in the bulk aqueous phase, its rate increases according to a saturation curve with increasing speed of stirring and levels off when the dissolution rate of the reactant(s) become(s) much higher than the rate of the chemical reaction itself so that mass transfer no longer influences the overall kinetics of the process.

When the substrate of a catalytic conversion is practically insoluble in the aqueous phase (this is the case with higher olefins) the reaction still may proceed, this time at the aqueous/organic interface. However, the overall rate will be governed by the molar ratio of the catalyst present in the interphase layer related to the bulk aqueous phase. One possibility is to increase the volume ratio of this phase boundary layer itself as compared to the bulk of solution by applying high stirring rates. In such instances the rate of the chemical reaction increases continuously with stirring velocity, however, if no other effects operate this alone may not be sufficient to make a process practicably fast. Increase of the overall rate can be achieved by specifically directing the catalyst to the interface similar to the excess

concentration of surfactants in the interphase layers. Indeed, catalysts having ligands with surfactant properties (such as TPPMS) are more efficient with water-insoluble substrates than their analogs with no such features. Some long-chain ω-sulfoalkylphosphines and their Rh(I)-complexes form micelles above the critical micellar concentration and solubilize the water-insoluble substrate into the aqueous phase; by doing so the rate of hydroformylation is increased.

Compounds which selectively concentrate in the interphase layers (surfactants), display solubility -at least to some extent- in both phases (amphiphiles), or form microheterogeneous structures (micelles, bi- or multilayers, vesicles) have all been already applied either as additives or as substrates in AOC. Exceedingly diverse effects were observed which are hard to categorize into general terms and will be discussed at the specific reactions later. However, a hint of caution seems appropriate here: the more expressed is the amphiphilic nature of the additive the greater is the probability of the catalyst leaching into the organic phase. This may result in catalyst loss and hinder large-scale applications. Moreover, the catalyst in the organic phase may operate there in a different way than in the aqueous phase which may result in low selectivity and more side-products.

There is an attractive suggestion in the literature on how to speed up reactions of water-insoluble substrates in AOC. Supposedly, when two related phosphine ligands are applied, one strongly hydrophilic (such as TPPTS) the other strongly organophilic (PPh_3) the interaction of the metal center of the catalyst (such as $[RhH(CO)(TPPTS)_3]$) with both kinds of phosphine ligands will result of its positioning within the interphase layer. Although experiments really do show a substantial increase of the rate of hydroformylation of octene-1 in the presence of PPh_3 in the organic phase [50] one has to be very careful with the interpretation. First, in chemical terms the "interaction" referred to above should mean formation of mixed ligand complexes, e.g such as the one in (1.2), via phosphine exchange:

$$[RhH(CO)(TPPTS)_3]+PPh_3 \rightleftharpoons [RhH(CO)(TPPTS)_2(PPh_3)]+TPPTS \quad (1.2)$$

Due to the practical insolubility of TPPTS in apolar organic solvents and to that of PPh_3 in water, the concentration of the mixed ligand species must be negligibly small in both bulk phases, and indeed, no evidence on their presence under such conditions are found in the literature [51]. (Leaching of rhodium to the organic phase would not be welcome anyway.) Second, neither $[RhH(CO)(TPPTS)_3]$ nor $[RhH(CO)(PPh_3)_3]$ show surfactant properties therefore the mixed ligand species are not expected to concentrate at the interface *a priori.* However, nothing is known about the composition and solvent properties of the aqueous/organic mixture within the interphase

layer which may favour dissolution of rhodium complexes containing simultaneously TPPMS and PPh_3 ligands. Therefore, albeit the concept looks of general applicability its specific realization without leaching of the catalyst requires finely matched pairs of ligands and an organic phase with appropriate solvent properties.

Early attempts to run metal complex catalyzed reactions in aqeous/organic two-phase systems included hydrogenation of butene-diol, dissolved in water, catalyzed by $[RhCl(PPh_3)_3]$ in a benzene phase. This is not a typical example of AOC, moreover, the scope of this variant of biphasic catalysis is limited to the case of water soluble substrates. However, it is also worth remembering, that 1% v/v of water in an organic solvent gives a 0.56 M H_2O concentration on the molar scale and this is much higher than the usual concentration of soluble catalysts (typically in the millimolar range). Consequently, there is enough H_2O in most of the water-saturated organic solvents to interact with the catalyst.

Deterioration of catalysts is an everyday experience from working with highly water-sensitive compounds in insufficiently dried solvents, but in the reactions within aqueous organometallic catalysis water is either innocuous (this is the case with $[RhCl(PPh_3)_3]$) or may even be advantageous, taking an active part in the formation of catalytically active species.

The example in the preceding paragraph takes us to phase transfer catalytic processes. In their classical form such systems comprise of an aqueous phase together with an immiscible organic phase. The desired chemical transformation takes place in the organic phase and one or more of the reactants are supplied from the aqueous phase with the aid of phase transfer catalysts (agents). The reaction may be catalyzed by an organometallic compound and in that case the catalyst should be stable to water. There are clearly advantageous features of such phase transfer assisted catalytic processes, comprising *inter alia* the easy supply of water-soluble reactants (halides, OH^-, CN^-, MnO_4^- etc.). However, the products and the catalyst are still found in the same phase and a separation (product purification) procedure is necessarry. In addition, in small scale laboratory processes catalyst recycling is usually not a priority. In several cases however, the active catalyst itself is formed in a phase transfer catalyzed process, e.g. $[Co(CO)_4]^-$ from $[Co_2(CO)_8]$ and OH^- [52].

It is often useful to keep some of the reactants or the products in separate phases (principle of chemical protection by phase separation [53]). For instance, when the reaction is inhibited by its own substrate having the latter in an other phase than the one in which the catalyst is dissolved helps to eliminate long induction periods or complete stop of the reaction. An example is the biphasic hydrogenation of aldehydes with the water-soluble

$[\{RuCl_2(TPPMS)_2\}_2]$ catalyst [54]. We shall cover such special cases as *extraction phenomena.*

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Chapter 2

Ligands used for aqueous organometallic catalysis

Solubility of the catalysts in water is determined by their overall hydrophilic nature which may arise either as a consequence of the charge of the complex ion as a whole, or may be due to the good solubility of the ligands. Although transition metal complexes with small ionic ligands, such as halides, pseudohalides or simple carboxylates can be useful for specific reactions the possibility of the variation of such ligands is very limited. As in organometallic catalysis in general, phosphines play a leading role in aqueous organometallic catalysis (AOC), too. There is a vast armoury of synthetic organic chemistry available for preparation and modification of various phosphine derivatives of which almost exclusively the tertiary phosphines are used for catalysis. The main reason for the ubiquity of tertiary phosphines in catalysis is in that most transformations in AOC involve the catalysts in a lower valent state at one or more stages along the catalytic cycle and phosphines are capable of stabilizing such low oxidation state ions, such way hindering metal precipitation. For the same reason, ligands posessing only hard donor atoms (e.g. N or O) are not common in AOC and used mainly for synthesizing catalysts for oxidations or other reactions where the oxidation state of the metal ion remains constant throughout the catalytic cycle (examples can be the heterolytic activation of dihydrogen or certain hydrogen transfer reactions).

Some of the neutral (that is non-ionic) ligands are water-soluble due to their ability of forming several strong hydrogen bonds to the surrounding water molecules. These ligands usually contain several N or O atoms, such as the 1,3,5-triaza-7-phosphaadamantane (PTA, the phosphorus analog of urotropin), tris(hydroxymethyl)phosphine, $P(CH_2OH)_3$ or several phosphines containing long polyether (e.g. polyethyleneglycol-, PEG-type) chains. Most of the ligands in AOC, however, are derived from water-insoluble tertiary phosphines by attaching onto them ionic or polar groups,

namely sulfonate, sulfate, phosphonate, carboxylate, phenolate, quaternary ammonium and phosphonium, hydroxylic, polyether, or polyamide (peptide) etc. substituents or a combination of those. This latter approach stems from the philosophy behind research into AOC in the early days when the aim was to "transfer" efficient catalytic processes, like hydroformylation, from the homogeneous organic phase into an aqueous/organic biphasic system simply by rendering the catalyst water soluble through proper modification (e.g. sulfonation) of its ligands. Although this approach is still useful, so much more is known today of the specific characteristics and requirements of the processes in AOC that tayloring the ligands (and by this way the catalysts) to the particular chemical transformation in aqueous or biphasic systems is not only a more and more manageable task but a drive at the same time for synthesis of new compounds for specific use in aqueous environment.

In the following few sections we shall now review the most important water-soluble ligands and the synthetic methods of general importance. It should be noted, that in many cases only a few examples of the numerous products available through a certain synthetic procedure are shown in the tables and the reader is referred to the literature for further details.

2.1 TERTIARY PHOSPHINE LIGANDS WITH SULFONATE OR ALKYLENE SULFATE SUBSTITUENTS

This class of compounds is comprised by far the most important ligands in aqueous organometallic chemistry. The main reasons for that are the following:

- sulfonated phosphines are generally well soluble in the entire pH-range available for AOC and in their ionized form they are insoluble in common non-polar organic solvents
- in many cases these ligands can be prepared with straightforward methods, for example by simple, direct sulfonation
- the sulfonate group is deprotonated in a wide pH-range, its coordination to the metal usually need not be considered i.e. the molecular state of the catalyst is not influenced by coordination of the $-SO_3^-$ substituent (important exceptions exist!)
- they are sufficiently stable under most catalytic conditions.

Due to these reasons both in the early attempts in academic research and in the first successful industrial process in AOC sulfonated phosphines were used as ligands (TPPMS and TPPTS, respectively). A detailed survey of the sulfonated ligands is contained in Table 1 and in Figures 1-5.

2.1.1 Direct sulfonation

Fuming sulfuric acid (oleum) of 20% SO_3 strength is suitable for preparation of monosulfonated products [1-3] while for multiple sulfonation 30% (or more) SO_3 is required [4-10]. The phosphine is dissolved in cold oleum with protonation of the phosphorus atom therefore in cases when the phenyl rings are directly attached to the phosphorus (e.g. triphenylphosphine or the bis(diphenylphosphino)alkanes) sulfonation takes place in the 3-position.

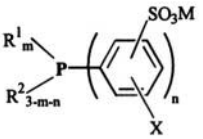


Figure 1. General structure of sulfonated tertiary phosphines

For monosulfonation of PPh_3 the reaction mixture can be heated for a limited time [1-3] while multiple sulfonation is achieved by letting the solution stand at room temperature for a few days [4-10]. In this simplest way of the preparation several problems may arise. Under the harsh conditions of sulfonation there is always some oxidation of the phosphine into phosphine oxide and phosphine sulfides are formed, too. Furthermore, selective preparation of TPPMS (**1**) or TPPDS (**2**) requires optimum reaction temperature and time and is best achieved by constantly monitoring the reaction by NMR [10] or HPLC [7]. Even then, the product can be contaminated with unreacted starting material. However, **1** can be freed of both the non-sulfonated and the multiply sulfonated contaminants by simple methods, and in the preparation of TPPTS (**3**) contamination with PPh_3, **1** or **2** is usually not the case. Direct sulfonation with fuming sulfuric acid was also used for the preparation of the chelating diphosphines **34-38**, **51**, **52**.

Table 1. Selected examples of sulfonated phosphine ligands for aqueous organometallic catalysis (see Figure 1 for general structure)

Nº	R^1	m	R^2	3-m-n	X	$-SO_3M$	n	Abbreviation	Ref.
1	Ph	2	-	0	H	$3\text{-}SO_3M$	1	TPPMS (mTPPMS)	[1-3]
2	Ph	1	-	0	H	$3\text{-}SO_3M$	2	TPPDS (mTPPDS)	[4,158]
3	-	0	-	0	H	$3\text{-}SO_3M$	3	TPPTS (mTPPTS)	[4-12,150]
4	Ph	2	-	0	H	$4\text{-}SO_3M$	1	pTPPMS	[13-15]
5	Ph	1	-	0	H	$4\text{-}SO_3M$	2	pTPPDS	[15]
6	-	0	-	0	H	$4\text{-}SO_3M$	3	pTPPTS	[15,16]
7	Ph	2	-	0	H	$2\text{-}SO_3M$	1	oTPPMS	[17]
8	Ph	2	-	0	$4\text{-}SO_3M$	$2\text{-}SO_3M$	1		[15.18]
9	Ph	1		0	$4\text{-}SO_3M$	$2\text{-}SO_3M$	2		[15]
10	Ph	1	Me	1	H	$4\text{-}SO_3M$	1		[18]
11	^nBu	1	-	0	$4\text{-}SO_3M$	$2\text{-}SO_3M$	2		[15]
12	Ph	1	H	0	$4\text{-}SO_3M$	$2\text{-}SO_3M$	1		[18]
13	$C_6H_4\text{-}3\text{-}SO_3M$	2	-	0	2-MeO	$5\text{-}SO_3M$	1	MOM-TPPTS	[19]
14	$C_6H_4\text{-}3\text{-}SO_3M$	1	-	0	2-MeO	$5\text{-}SO_3M$	2	BOM-TPPTS	[19]
15	-	0	-	0	2-MeO	$5\text{-}SO_3M$	3	TOM-TPPTS	[19]
16	$C_6H_4\text{-}4\text{-}F$	1	-	0	4-F	$3\text{-}SO_3M$	2	p-F-TPPDS	[19]
17	-	0	-	0	2-Me	$5\text{-}SO_3M$	3	TOT-TPPMS	[19]
18	Ph	2	$-(CH_2)_y\text{-}SO_3M$ y=2, 3, 4	1	-	-	0		[20-22]
19	Cy	2	$-CH_2CH_2SO_3M$	1	-	-	0		[23]
20	Menthyl	2	$-(CH_2)_4\text{-}SO_3M$	1	-	-	0		[20]

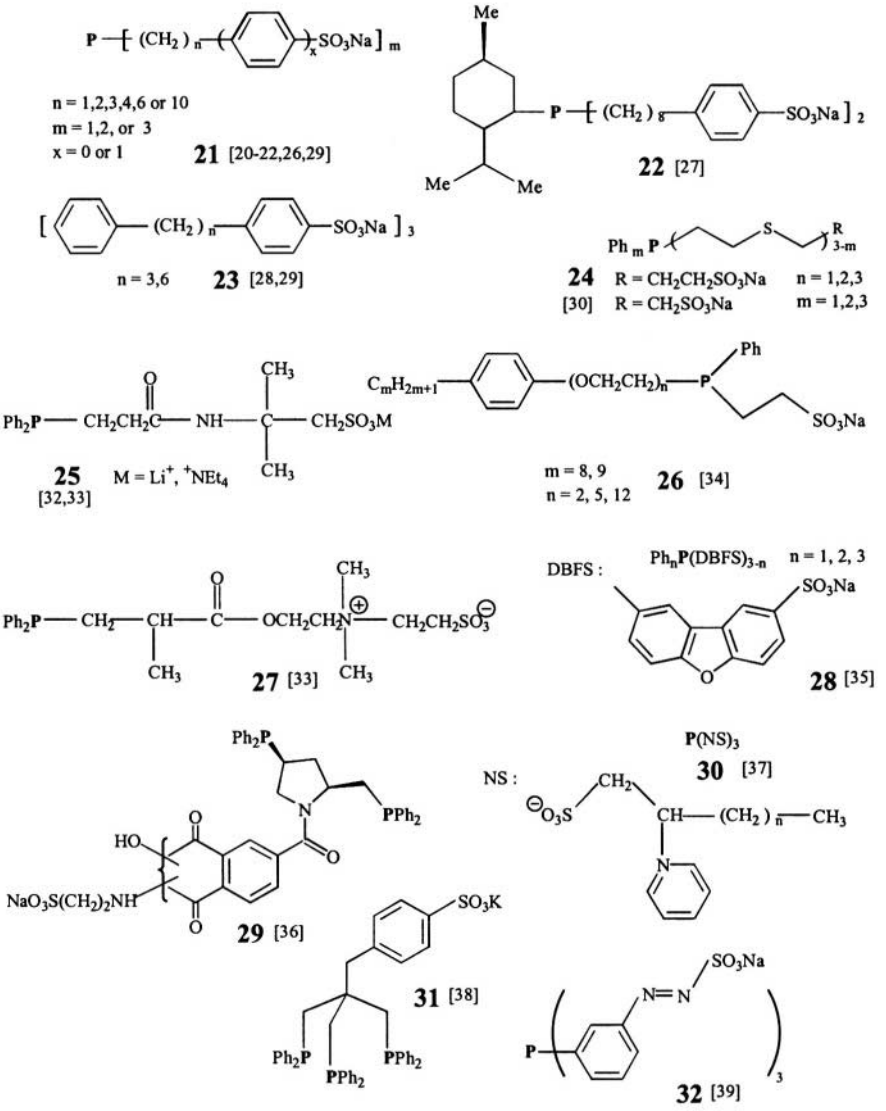


Figure 2. Water-soluble sulfonated phosphines

Most of the problems of side reactions can be circumvented by using a mixture of unhydrous sulfuric acid (containing no free SO_3, a powerful oxidant) and orthoboric acid [4,8]. The superacidic nature of this sulfonation mixture ensures complete protonation and the lack of free SO_3 excludes the possibility of oxidation. In addition, the number and position of the sulfonate groups can be more effectively controlled than by using oleum for

the sulfonation and this method is the procedure of choice for functionalization of more oxidation sensitive phosphines such as **13-17**, **42-46**.

In cases where the phenyl ring is not directly attached to a protonated phosphorus, sulfonation can be carried out in 95-100% H_2SO_4 i.e. with no dissolved free SO_3 (**28**, **31**, **42**, **47**, **49-51**).

In these syntheses based upon direct sulfonation, the reaction mixture should be neutralized at the appropriate reaction time; this is usually achieved with concentrated NaOH or KOH solutions [1-3] with the concomitant production of lots of inorganic sulfates. The less soluble monosulfonated products can be crystallized and the raw products contain Na_2SO_4 or K_2SO_4.

The highly soluble multiply sulfonated phosphines are usually extracted into an organic phase (toluene) from acidic aqueous solutions (at controlled pH) as their amine salts; triisooctylamine is an effective agent [4]. The pure sulfonates can then be rextracted to an aqueous phase of appropriate pH and isolated by evaporation of the solvent (in some instances by freeze drying). If necessary, purification of the phosphines can be achieved by recrystallization (**1**) or gel-permeation chromatography (**2,3**) the latter being a generally useful method for obtaining *pure ligands and complexes* [4,19]. Quaternary ammonium salts of the sulfonated phosphines can be prepared by extracting aqueous solutions of the Na- or K-salts with a toluene solution of the appropriate $R_4N^+X^-$ salt [24].

In a different approach [11] to access pure products, the use of strong oleum (65% SO_3) for sulfonation of PPh_3 resulted in quantitative formation of TPPTS oxide. This was converted to the ethyl sulfoester through the reaction of an intermediate silver sulfonate salt (isolated) with iodoethane. Reduction with $SiHCl_3$ in toluene/THF afforded tris(**3**-ethylsulfonatophenyl)phosphine which was finally converted to *pure* 3 with NaBr in wet acetone. In four steps the overall yield was 40% (for PPh_3) which compares fairly with other procedures to obtain pure TPPTS. Since phosphine oxides are readily available from easily formed quaternary phosphonium salts this method potentially allows preparation of a variety of sulfonated phosphines (e.g. $(CH_3)P(C_6H_4\text{-}3\text{-}SO_3Na)_2$).

2.1.2 Nucleophilic phosphinations, Grignard-reactions and catalytic cross-coupling for preparation of sulfonated phosphines

PH_3, primary and secondary phosphines can be deprotonated in the superbasic KOH(solid)/DMSO media [15,16,25]. Nucleophilic aromatic substitution of fluorine in substituted fluorobenzenes with the resulting

phosphide affords a wide range of primary, tertiary or secondary phosphines, including **4-12**, having the sulfonate group in the 2- or 4-position or in both. Such sulfonated phosphines are inaccessible by direct sulfonation.

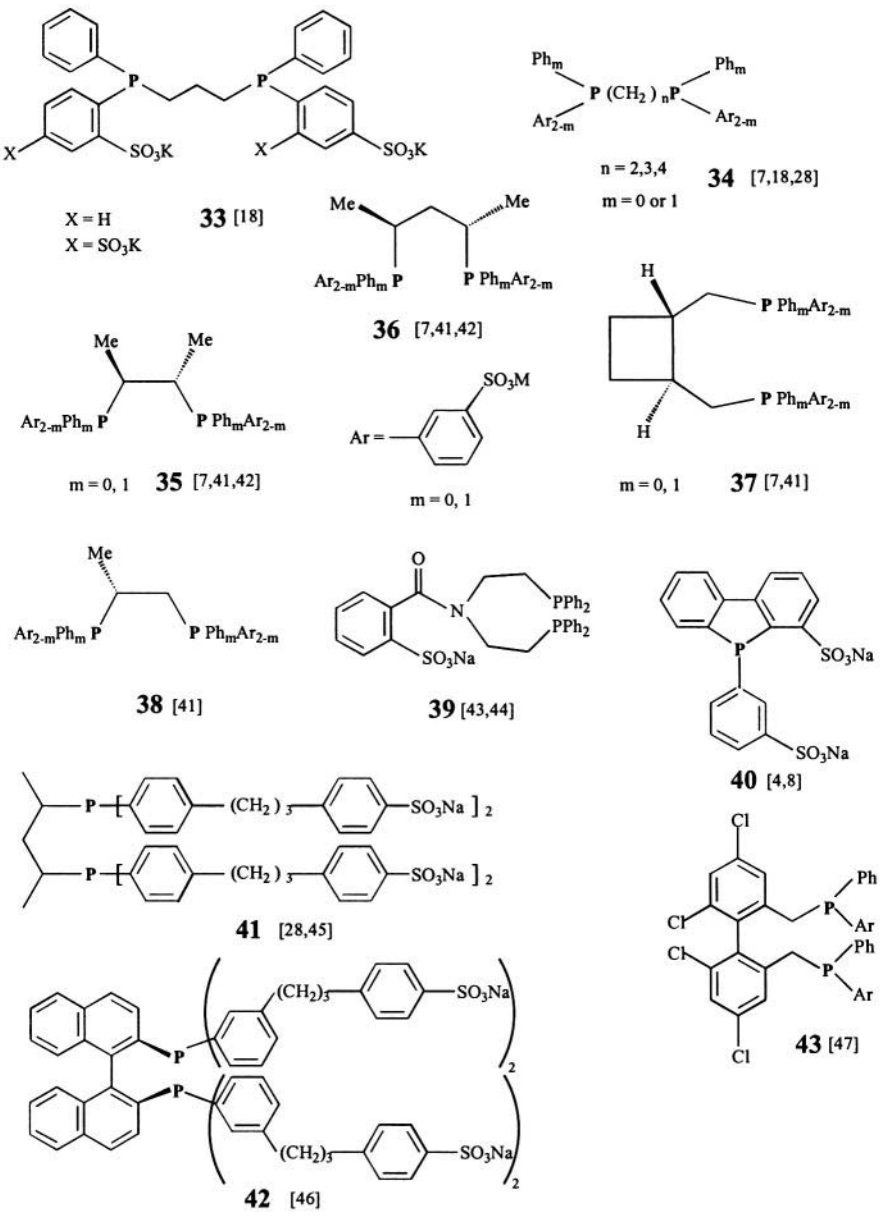


Figure 3. Water-soluble sulfonated phosphines (continued)

Note also, that **10** is chiral at the phosphorus; this compound and its analogs can easily be prepared starting, for example, from **12**.

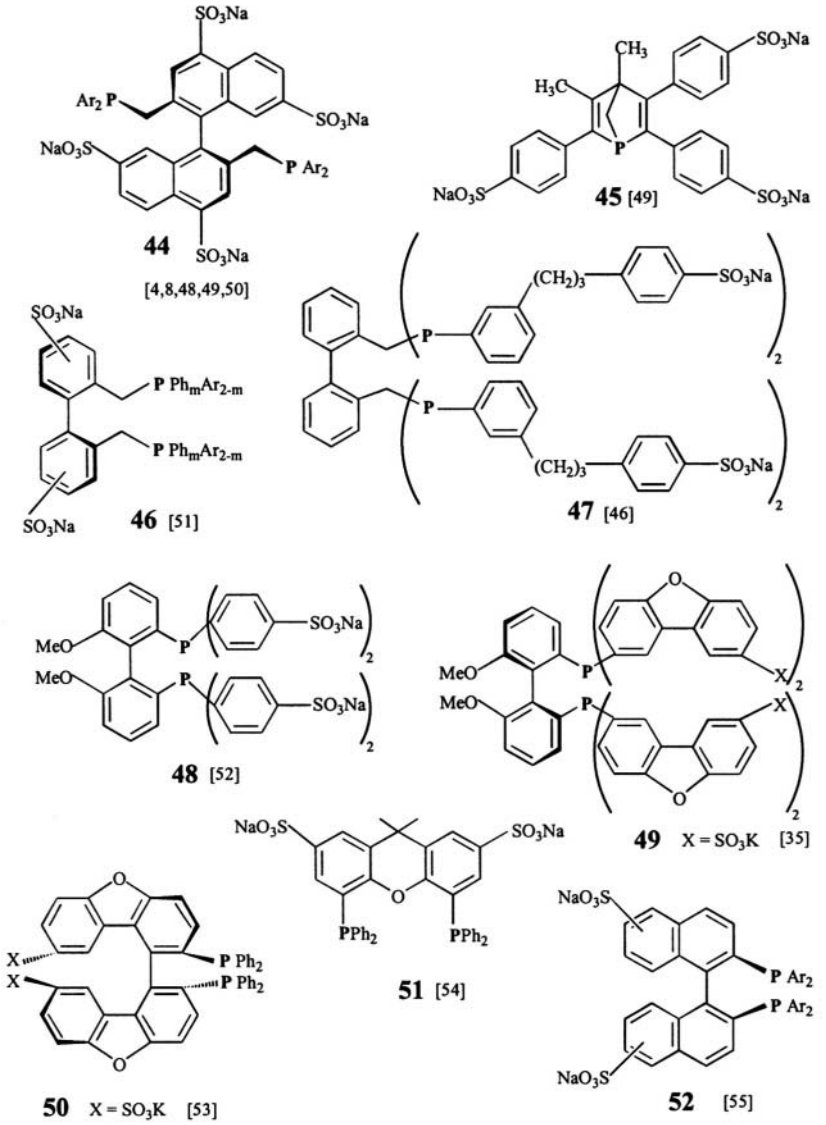


Figure 4. Water-soluble sulfonated phosphines (continued)

The reaction of alkali metal phosphides with appropriate halides, sultones or cyclic sulfates is a general method for preparation of a variety of tertiary phosphines useful in aqueous organometallic catalysis. These

phosphides can be generated in reactions of Li, K or Na with phosphorus halides (e.g. Ph_2PCl) in THF or from a suitable phosphine such as PPh_3 in dioxane, dimethoxyethane or in liquid ammonia.

pTPPMS (**4**) has long been known [13] as the side product of the preparation of 1,4-bis(diphenylphosphino)benzene. In addition to its synthesis from Ph_2PH with the KOH/DMSO method [15], it can also be obtained in the reaction of Ph_2PK (from $Ph_2PCl+2K$) and potassium p-F-benzenesulfonate in refluxing THF [14]. oTPPMS (**7**) and several **ω-sulfoalkyldiphenylphosphines** (**18**) were also obtained this way [20-22].

The borane adducts of phosphines having hydrogen, methyl or methylene groups adjacent to the phosphorus can be easily deprotonated by strong bases and the resulting anions react with various nucleophiles affording borane-protected tertiary phosphines as air stable, crystalline materials [23]. Quantitative deprotection of the phosphorus can be achieved by treatment with morpholine at 110 °C followed by evaporation to dryness. Dissolution of the solid residue and addition of THF results in precipitation of the products such as -among others- **19**.

Sultones are useful starting materials for the preparation of various sulfoalkyl- (**18, 20**) or sulfoarylphosphines (**7**) when reacted with the appropriate alkali metal phosphide [20]. Reaction of the homologous alkyl-1,2-sultones (C_3 to C_{14}) with tris(2-pyridylphosphine) afforded highly water soluble betains (**30**) [21].

Cyclic sulfates can be obtained from diols or polyols in the reaction of the latter with $SOCl_2$ followed by ruthenium catalyzed oxidation. These sulfates readily react with $LiPPh_2$ yielding mono- and di-tertiary diphenylphosphines having alkylene sulfate substituents (**54-57**). This is a highly versatile procedure, since the starting diols are readily available and the products are well soluble and fairly stable in neutral or slightly alkaline aqueous solutions [57,105].

Hydroxy-phosphines undergo benzoylation with o-sulfobenzoic anhydride in the presence of bases (Na_2CO_3 or BuLi) affording sulfobenzoylated phosphine products. In such a way several mono- and dihydroxy phosphines could be made soluble in water, exemplified by the chiral bisphosphines **53**. It should be noted, that this general method allows the preparation of water-soluble sulfonated derivatives of acid-sensitive phosphines, such as DIOP, too, which are not accessible *via* direct sulfonation [56].

The sulfonated atropisomeric bisphosphine MeOBIPHEP (**48**) was prepared in a Grignard reaction of the appropriate bisphosphonic dichloride and p-indolylsulfonamido-bromobenzene followed by reduction of the phosphine oxide with $HSiCl_3$ [52]. The indolylsulfonyl protecting group was

stable under the conditions of the Grignard reaction and the subsequent reduction and was finally removed by mild alkaline hydrolysis.

The cross coupling of various substituted iodobenzenes and $PhPH_2$ or Ph_2PH catalyzed by $[Pd(OAc)_2]$ or $[Pd(PPh_3)_4]$ in neat or aqueous organic solvents (DMA, CH_3CN, MeOH) is a versatile synthetic method for preparation of secondary and tertiary phosphines; reaction of $PhPH_2$ and 4-NaO_3S-C_6H_4I afforded (4-NaO_3S-C_6H_4)PPhH in 78% yield [58].

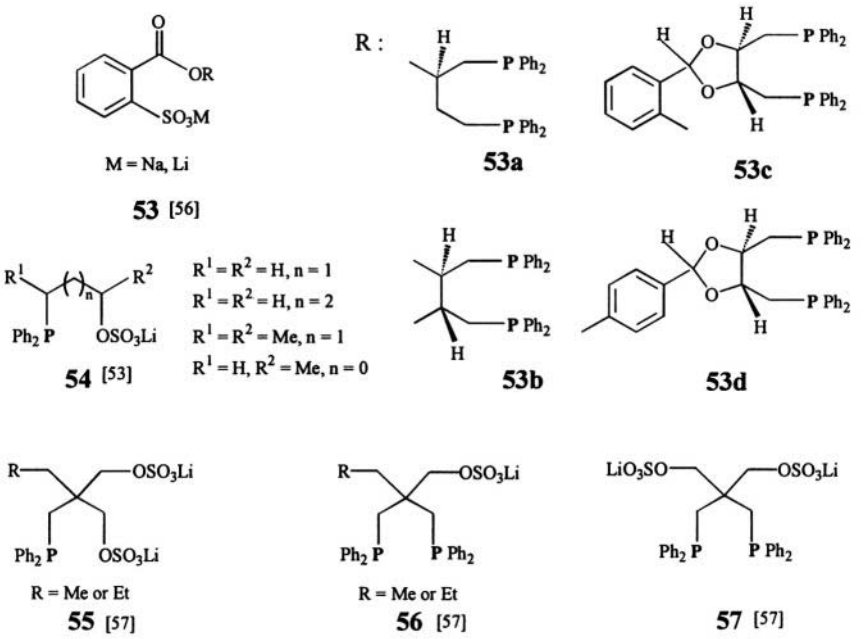


Figure 5. Water-soluble phosphines with sulfonate or alkyl sulfate substituents (continued)

2.1.3 Addition reactions

Michael addition of secondary phosphines on conjugated olefins is a well known reaction in organic synthesis. Accordingly, addition of diphenylphosphine on hydrophilic activated alkenes in CH_3CN or in CH_3CN/H_2O solution leads to various tertiary phosphines [33]; examples include **1**, **25**, **27**. In order to avoid the formation of phosphine oxides and/or the hydrolysis of some alkene derivatives (e.g. acryl esters) a small amount of $Et_4N^+OH^-$ was used as base, and a small quantity of ditertbutylphenol was

added to prevent polymerization. **25** was also prepared from Ph_2PLi and CH_2=CH-CONHC$(CH_3)_2CH_2SO_3H$ in THF[31].

In ethanol/water mixtures addition of sodium mercaptoalkane sulfonates on vinyldiphenylphosphine proceeds smoothly at room temperature and yields a variety of tertiary phosphines such as **24**. Interestingly, at the beginning of the reaction the ethanolic solution of the vinylphosphine and the aqueous solution of the educt comprise two separate phases and this is favourable for the high yields obtained (59-97%) [30].

2.2 TERTIARY PHOSPHINE LIGANDS WITH NITROGEN-CONTAINING SUBSTITUENTS

Phosphine ligands having an aliphatic, benzylic or aromatic nitrogen in the organic moiety attached to phosphorus are usually well soluble in water only under acidic conditions. Besides, coordination of the nitrogen donor atom may further decrease aqueous solubility. Nonetheless, this class of compounds offers an enormously wide choice of possible structures and further funcionalization so that amino- or ammonium-substituted phosphines proved their usefulness already at the dawn of aqueous organometallic catalysis. Protonation or alkylation of these ligands lead to much higher solubilities. In many cases, however, exclusive quaternization of the nitrogen atoms requires protection of the phosphorus by oxidation or complexation.

Synthetic procedures for the preparation of nitrogen-containing tertiary phosphines comprise the methods described in some detail in the preceeding sections **1.2** and **1.3**. Representative examples of these ligands are shown in Figures 6 and 7. Several of these compounds are nowadays available commercially. A detailed review on pyridylphosphines [59] appeared in 1993.

The first amino-phosphines used in AOC for studies of catalyst recovery by aqueous extraction, **59**, were prepared by radical addition of PH_3 on dialkylallilamines [61]. Similar addition of diphenylphosphine on activated alkenes [33] resulted in formation of a variety of phosphines including also **66**.

By far the most ubiquitous intermediates in synthesis of this class of phosphines are the alkali metal phosphides which can be prepared by either the KOH/DMSO method, by reaction of tertiary phosphines or chlorophosphines with alkali metals, or in the reaction of BuLi with appropriate secondary or tertiary phosphines. A number of the ligands in Figures 6 and 7 were prepared this way (**60-69**,**72-74**).

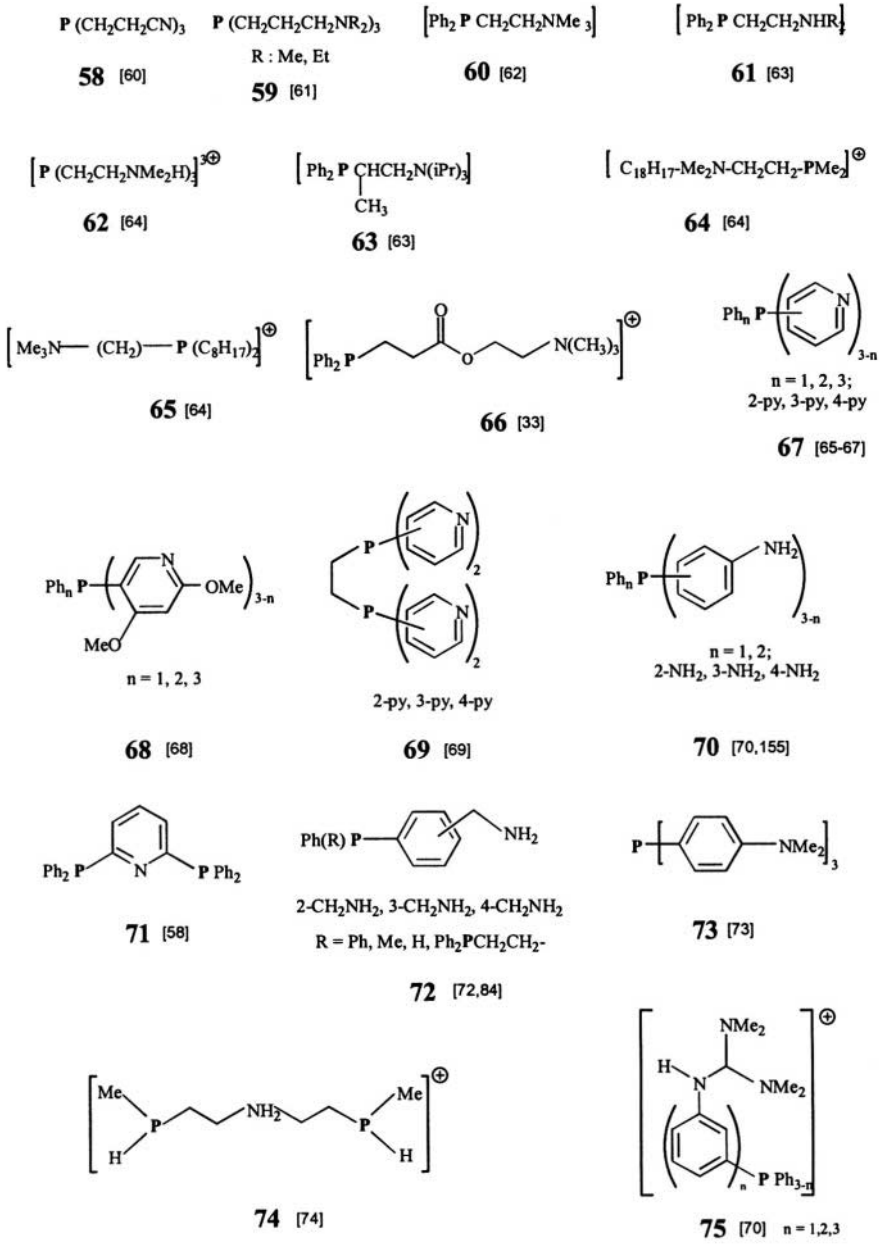


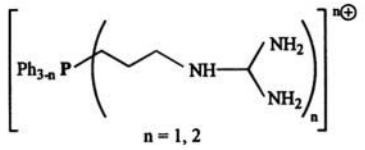
Figure 6. Nitrogen-containing phosphine ligands

Palladium catalyzed P-C cross coupling [58] between primary or secondary phosphines and appropriate aryl iodides made possible the preparation of several aminophenyl-phosphines with the general formula **70** and also the bisphosphine **71**.

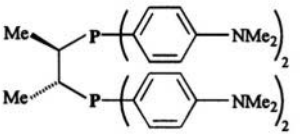
Strongly basic cationic phosphine ligands **75**, **76** containing guanidino functions were prepared either in the reaction of 3-aminopropyldiphenylphosphine with 1H-pyrazole-l-carboxamide under basic conditions in DMF [75] or by the addition of dimethylcyanamide to the amino groups of tertiary (3-aminophenyl)phosphines in acidic medium [70]. These phosphines (as acetate or chloride salts) are highly soluble in water; in some cases the solubility reaches that of TPPMS. Another noteworthy feature of these compounds that they are considerably less sensitive to air oxidation then the anionic (e.g. sulfonated) phosphines.

$KP(C_6H_4\text{-}4\text{-}NMe_2)_2$ reacts with the appropriate diol ditosylates yielding the chiral phosphines **77-79**. These analogs of the well known Chiraphos, BDPP (Skewphos) and DIOP can be made water soluble by protonation or quaternization. Quaternization can be achieved with $(CH_3)_3OBF_4$ with the phosphorus atoms protected by complexation to Rh(I) [76]. This method of quaternization was originally introduced [77] to prepare **81** in its rhodium complex. It is remarkable, that DIOP which is known to be acid sensitive survives all these manipulations.

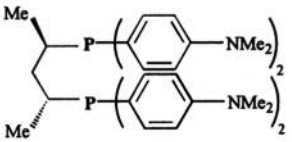
The aliphatic phosphine 1,3,5-triaza-7-phosphatricyclo[3.3.1.$1^{3,7}$]decane (l,3,5-triaza-7-phosphaadamantane, PTA, **82**) can be easily prepared from tris(hydroxymethyl)phosphine, formaldehyde and hexamethylenetetramine [78,79]. This is an air-stable, small-size ligand similar in electronic and steric properties to PMe_3. It is well soluble in water, probably due to extensive hydrogen bonding to surrounding H_2O molecules. Protonation (pK_a=5.7 at 25°C [71]) and quaternization (e.g. with CH_3I) takes place exclusively on the nitrogen atoms. Unlike most phosphine ligands used in aqueous organometallic catalysis, PTA and its derivatives, including also its metal complexes, usually crystallize well from aqueous solutions and this property allowed the determination of a large number of structures by X-ray crystallography.



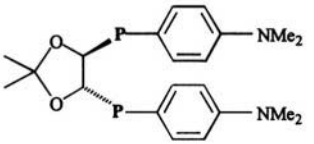
76 [70,75]



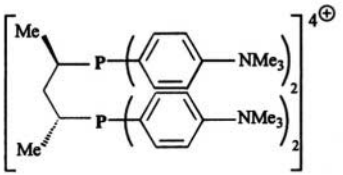
77 [76]



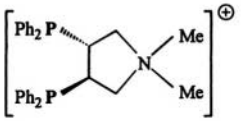
78 [76]



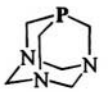
79 [76]



80 [76]



81 [77]



82 [78,79]

Figure 7. Nitrogen-containing phosphine ligands (continued)

2.3 PHOSPHINE LIGANDS WITH CARBOXYL SUBSTITUENTS

Tertiary phosphine ligands containing carboxyl substituents are somewhat less investigated in aqueous organometallic chemistry than those with $-SO_3H$ or $-NH_2$ functions. There can be several reasons for this relatively low-key performance. First, these compounds are usually weak or only medium strong acids and therefore show appreciable water solubility only above a certain pH (approx. 4-5). However, when dissolved in their deprotonated form their carboxylate group is ready to coordinate transition metals - a process which again leads to the decrease of solubility. Nevertheless, several representatives of this large group of phosphines were used as ligands in AOC and there are numerous general methods for their preparation. The carboxylic acid substituent also allows further functionalization.

Reaction of metallated tertiary or secondary phosphines either with halogen-substituted carboxylic acid esters or with the unhydrous salts of halocarboxylic acids leads to the corresponding phosphinocarboxylic acid esters or salts (**83-91**). The phosphide ions for these reactions can be obtained also by deprotonation of primary or secondary phosphines with KOH either in water or in DMSO. The *meta*- and *para*-isomers of 87, as well as **89** and **90** were obtained in palladium catalyzed cross-coupling of the corresponding aryl iodides with Ph_2PH [58]. Free radical addition of activated alkenes including acrylic acid esters and itaconic acid resulted in formation of **85** and **86**, respectively. Such free radical addition of acrylonitrile to PH_3, primary or secondary phosphines gives cyanoethylphosphines which by alkaline hydrolysis yield carboxyethylphosphines. Similarly, phosphinobenzoic acids, **87**, can be prepared by acid hydrolysis of phosphinobenzonitriles obtained by nucleophilic phosphination of bromobenzonitriles. The chelating phosphine, **92**, was prepared with hydrolysis of 1,2-bis(diphenylphosphino)maleic anhydride obtained in the reaction of 2,3-dichloromaleic anhydride with Ph_2PSiMe_3 [83]. Chiral tertiary phosphines (**93**, **94**) were prepared from 2- and 4-fluorophenylglycine and -alanine with Ph(R)PK [84]. In these compounds there are several possibilities for coordination to metal ions, the e.g. the *ortho*-phosphinophenyl derivatives may coordinate as P~N chelates (so called hybride ligands). The known chiral chelating bisphosphine 2-[diphenylphosphino)methyl]-4-(diphenylphosphino)pyrrolidone was made water soluble (**95**) by acylation with trimellitic anhydride acid chloride [36].

2.4 HYDROXYL-SUBSTITUTED WATER-SOLUBLE TERTIARY PHOSPHINES

Several members of this large family of ligands have been known for long (Figure 9) although only a few of them gained application in aqueous catalysis. Historically, the first such ligand used for complexation studies was **97** (dop) [88], and the first in catalysis was $P(CH_2OH)_3$, **98** [91]. Dop can be prepared in the reaction of $(Et)_2PMe$ with ethylene oxide; other cyclic ethers react similarly [25] giving rise to a number of hydroxyalkylphosphines. PH_3, primary and secondary phosphines react with substituted alkynes [97] yielding e.g. **102**, or with allyl acetate or allyl alcohol - **100** and **108** were prepared by this route. Formylation of phosphorus(**III**) hydrides with formaldehyde allows the preparation of a very wide array of hydroxymethylphosphines. Of the many compounds obtained so far in this reaction only a few examples are shown: **98**, **104-107**, **109.**

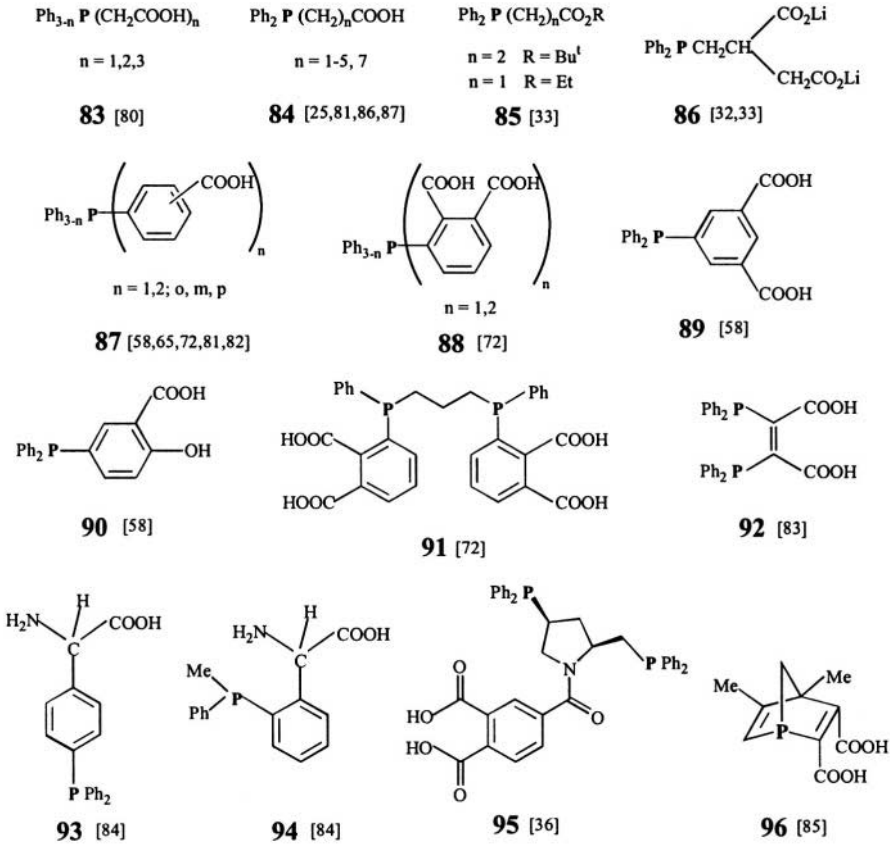


Figure 8. Tertiary phosphines with carboxyl substituents

It is established by solubility measurements, that a medium sized ligand should have at least two **-CH_2OH** substituents in order to achieve good aqueous solubility [91]. However, through the flexible synthesis of these tertiary phosphines the number and the chain length of the hydroxyalkyl substituents built into the target molecule can be varied easily and this way the balance of hydrophilicity and lipophilicity can be finely tuned. Incorporation of other donor atoms, such as S in **109**, and a pendant arm with an other reactive substituent (-COOH in **109**) makes these compounds even more versatile.

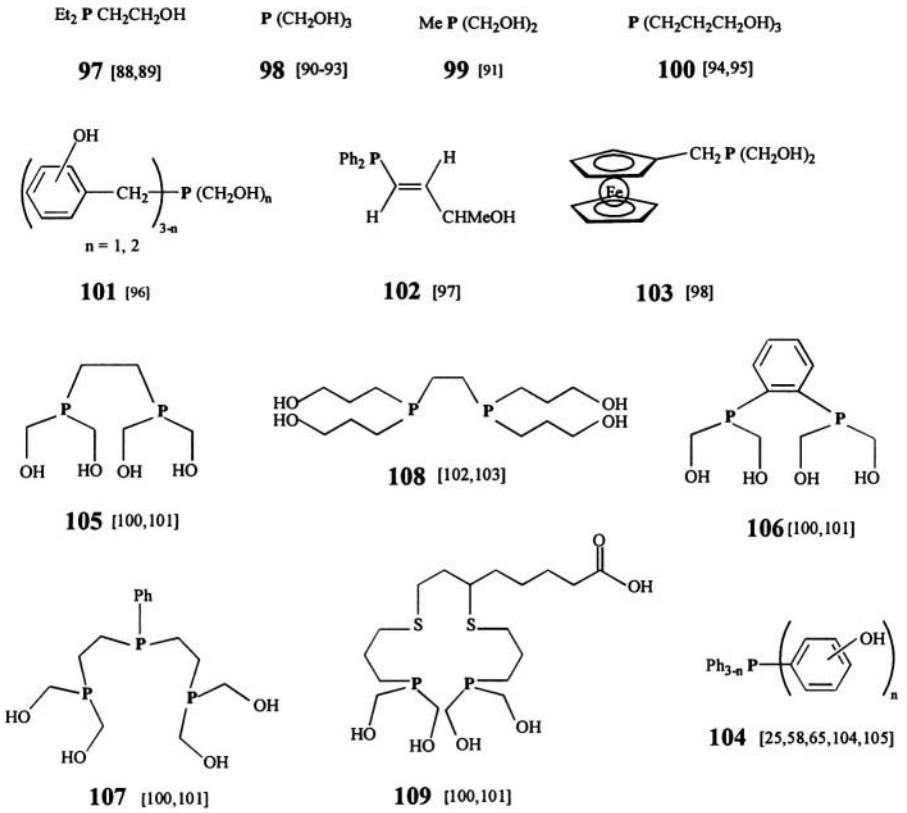


Figure 9. Water-soluble hydroxyphosphines

2.5 MACROLIGANDS IN AQUEOUS ORGANOMETALLIC CATALYSIS

In the previous sections we have reviewed the pool of ligands, mostly tertiary (or in a small part: secondary) phosphines which found their application in aqueous organometallic catalysis. Almost with no exception these ligands were of small or medium size monomeric molecules. There is an interesting and potentially very useful category of ligands, not necessarily phosphines, based on oligomeric or polymeric substances carrying suitable donor atoms. Such ligands are of interest for the following reasons:

- They can serve as soluble or insoluble carriers for catalytically active metal complexes. Separation of catalysts of this kind can be effected by dialysis, ultrafiltration, simple filtration or sedimentation.
- Well-known important ligands (e.g. DIOP) can be made water soluble by functionalization with oligo- or polyoxyalkylenic groups.
- Easily available, large, synthetic or natural molecules offer themselves for further functionalization with donor atoms or groups. Among the natural substances carbohydrates make an obvious choice, not the least because of their chirality.
- In cases of macroligands of appropriate structure, exemplified by cyclodextrins, molecular recognition may increase the aqueous solubility of the substrate and may contribute to the rate and selectivity of its catalytic transformation.

Olygo- or polyoxyalkylenic substituted tertiary phosphines, such as **110** were prepared by Grignard reaction of PCl_3 and the appropriate alkyl halide; by reaction of oxirane with hydroxyalkyl or hydroxyaryl compounds (**112**) or by addition of glycerin allyl ether on primary or secondary phosphines (**111**). N-acylation of amines with chlorocarbonic acid esters afforded **117** and **118** while **115** and **116** were prepared from the parent tosylates with $LiPPh_2$. 1-*O*-glycosides of hydroxytriarylphosphines **121-123** are available by two-phase glycosidation reactions aided by $Bu_4N^+HSO_4^-$ as phase transfer agent. In the presence of DCC, poly(4-pentenoic) acid can be reacted with (2-bisdiphenylphosphinoethyl)amine to obtain **130**; the commercially available resin, *Gantrez*, containing maleic anhydride functionalities reacts with the same phosphine derivative yielding **131**. Polyacrylic acid and polyethyleneimine both can serves as backbones for polymeric phosphines (**134-136**). Combination of a polystyrene backbone with polyethylene glycol spacer chains gives a flexible, well swelling polymer which can be further functionalized to yield a macromolecular chelating phosphine ligand **140** [138]. Finally, it should be emphasized, that phosphines are not *the* exclusive ligands for aqueous organometallic catalysis, as exemplified by the macromolecular ligands **137-139**.

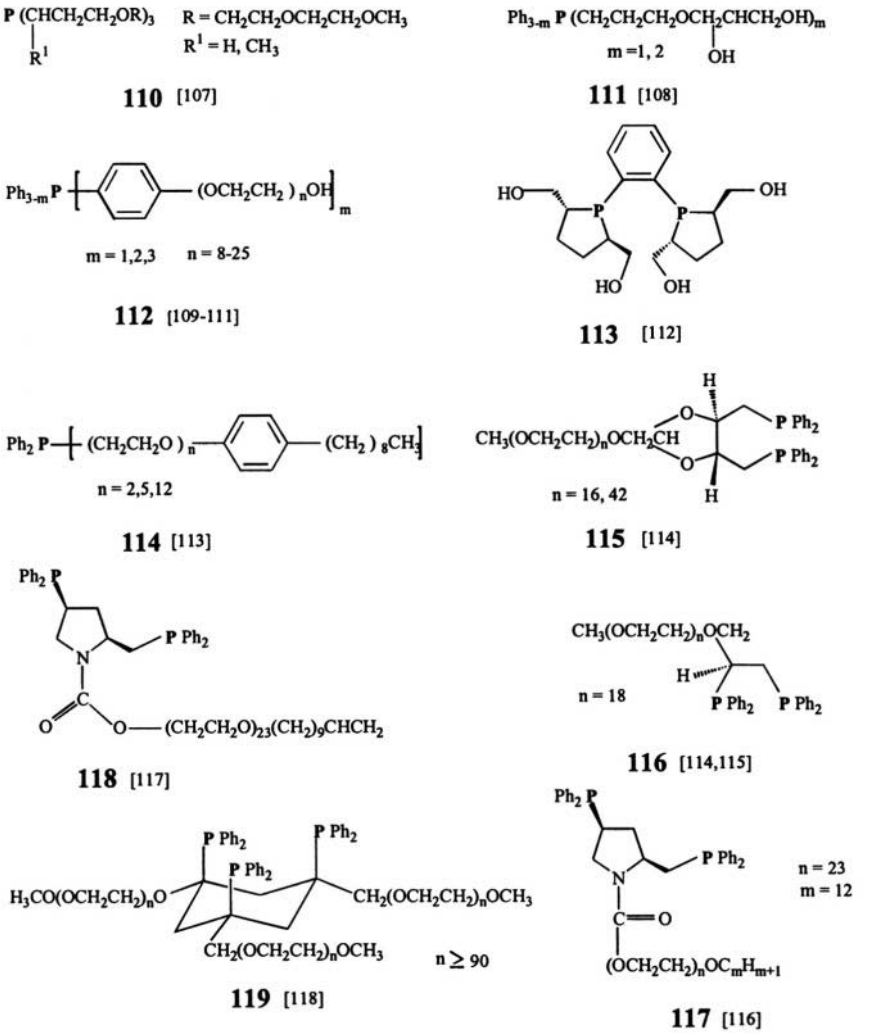
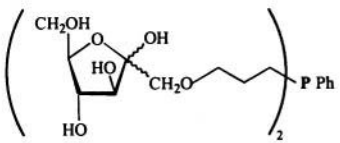
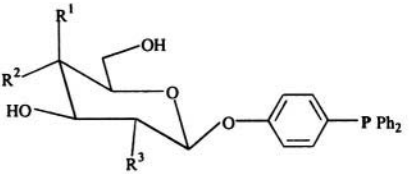


Figure 10. Macromolecular and carbohydrate-derived phosphine ligands

It may be appropriate to mention here, that since water soluble oligomeric and polymeric ligands necessarily contain a large number of ionic groups or atoms capable of hydrogen bonding (usually O or N), in many cases coordination of these groups or donor atoms is observed, the result of which sometimes being beneficial and in other cases detrimental to the catalytic properties of the particular complexes.

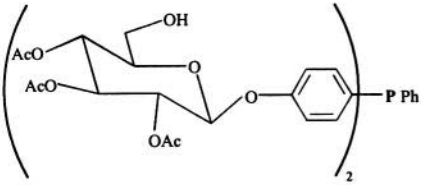


120 [108]

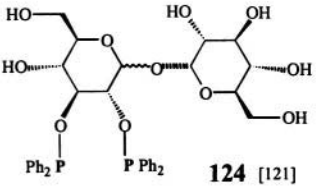


R^1 = H, R^2 = OH, R^3 = NHAc
R^1 = H, R^2 = H, R^3 = OH
R^1 = H, R^2 = OH, R^3 = OH

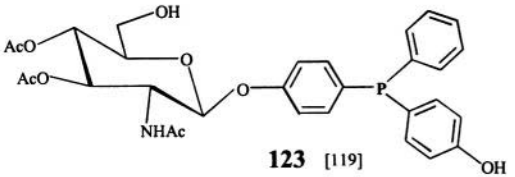
121 [119,120]



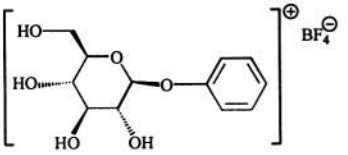
122 [119]



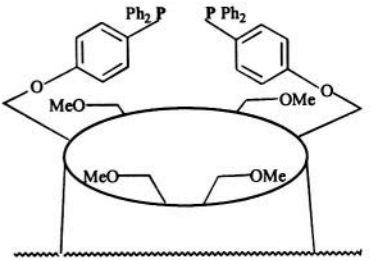
124 [121]



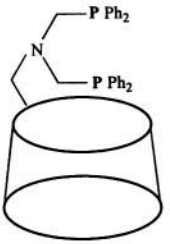
123 [119]



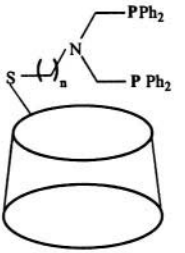
125 [122]



128 [126]



126 [123-125]



n = 2,3,4

127 [124]

Figure 11. Macromolecular and carbohydrate-derived phosphine ligands (continued)

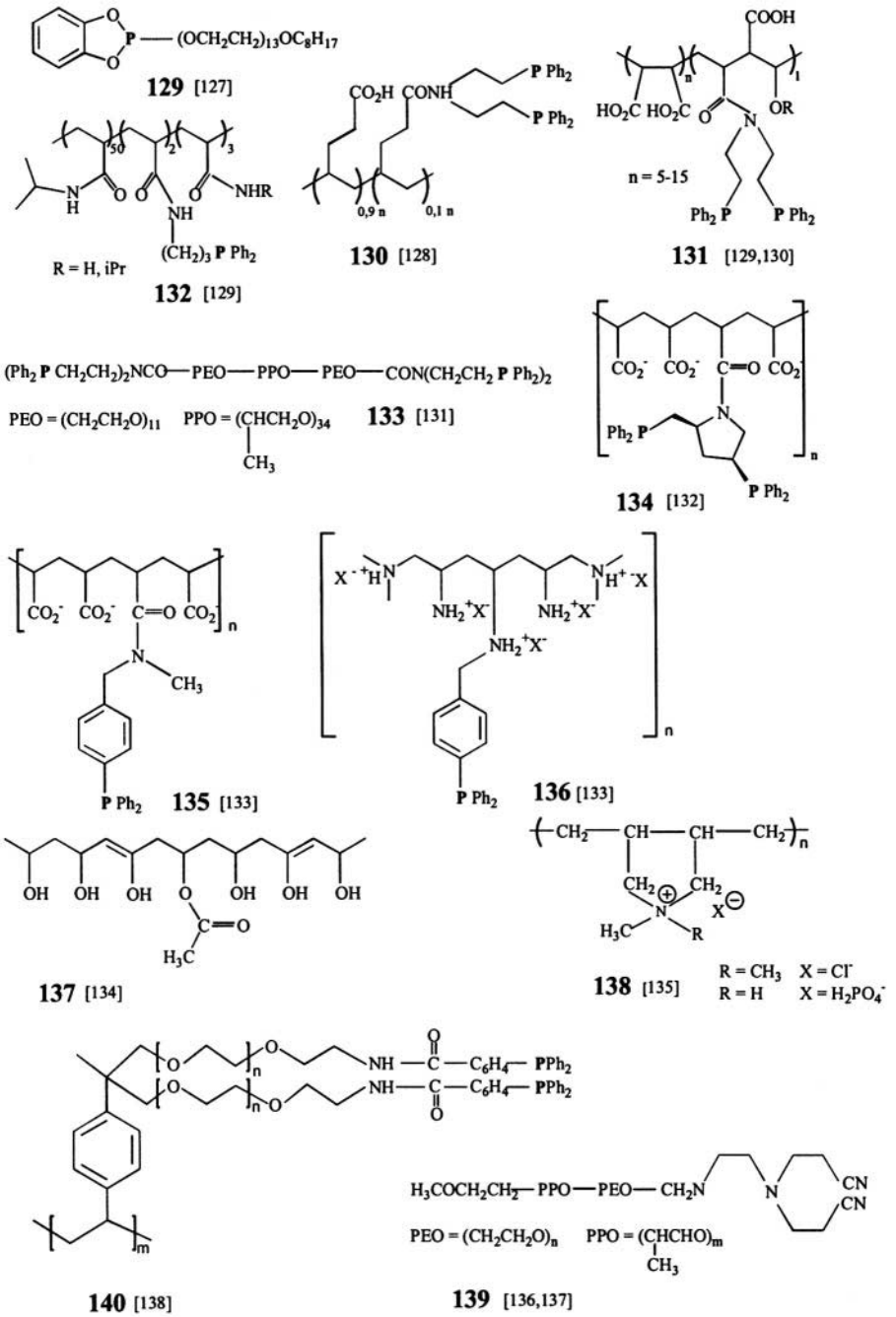


Figure 12. Macromolecular and carbohydrate-derived phosphine ligands (continued)

2.6 BIS[2-(DIPHENYLPHOSPHINO)ETHYL]AMINE – A VERSATILE STARTING MATERIAL FOR CHELATING BISPHOSPHINES

Bis[2-(diphenylphosphino)ethyl]amine can be prepared in high yield from the commercially available diphenylphosphine and bis(2-chloroethyl)-amine - usually it is isolated as the air stable, crystalline hydrochloride. This compound is cleanly acylated at nitrogen without competing reaction at phosphorus. Several acylating agents proved useful, including anhydrides, acid chlorides, alkyl chlorocarbonates, N-hydroxysuccinimide active esters, and others [44,139,140]. Some of the resulting chelating bisphosphines are water-soluble and, indeed, their rhodium complexes have been used in hydrogenation and catalysis of H/D isotope exchange [139,140]. A selection of phosphines prepared by this method is shown in Figure 13.

2.7 TERTIARY PHOSPHINES WITH PHOSPHONATE AND PHOSPHONIUM SUBSTITUENTS

Alkylene phosphonates are obtained from alkali metal-phosphides and the appropriate bromo- or iodoalkylphosphonate ester [141,143]. Alternatively, lithiated arylphosphines react with diethylchlorophosphate yielding phosphinoaryldiethylphosphonates [144]. Palladium-catalyzed P-C coupling [145] and the reaction of fluoroarylphosphonic acid bis(dialkyl)amides [146] with lithiumphenylphosphide proved convenient, high-yield syntheses. The resulting compounds can be easily hydrolyzed to the corresponding sodium salts which may have extremely high solubility in water [142,145]. Examples of such ligands can be found on Figure 14.

The synthetic procedures are relatively simple and productive, the phosphonate group is chemically stable and non-coordinating, so in the future these compounds can be expected to play a more significant role in aqueous organometallic chemistry.

2.8 WATER-SOLUBLE LIGANDS FOR AQUEOUS ORGANOMETALLIC CATALYSIS - LATEST DEVELOPMENTS

Research into aqueous organometallic catalysis did not cease during the writing of this book and many new ligands have been synthetized according

to the needs of new directions of catalytic syntheses. For example, a few years ago the preparation of well-defined transition metal-carbenes, stable in aqueous solutions, could have sound a weird idea. Now we have them, stabilized by ionic derivatives of dicyclohexylphosphine (e.g. **173**), and they are most useful for catalysis of ring opening metathesis polymerization of olefins in water [23]. Such latest developments are represented by the compounds in the following Figures.

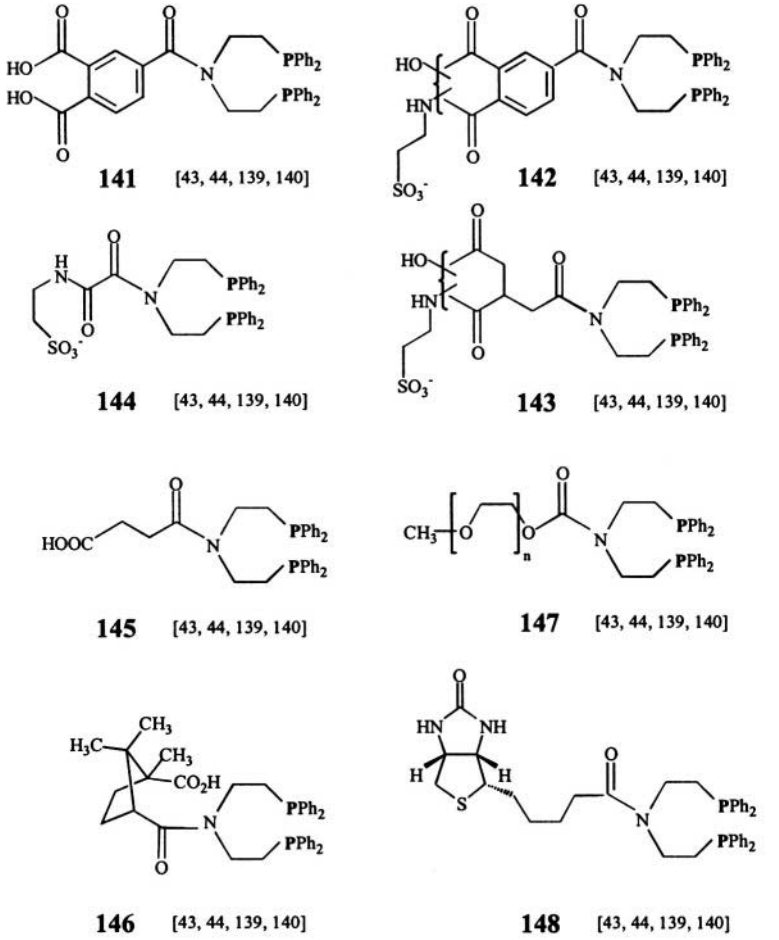


Figure 13. Ligands prepared from bis[2-(diphenylphosphino)ethyl]amine

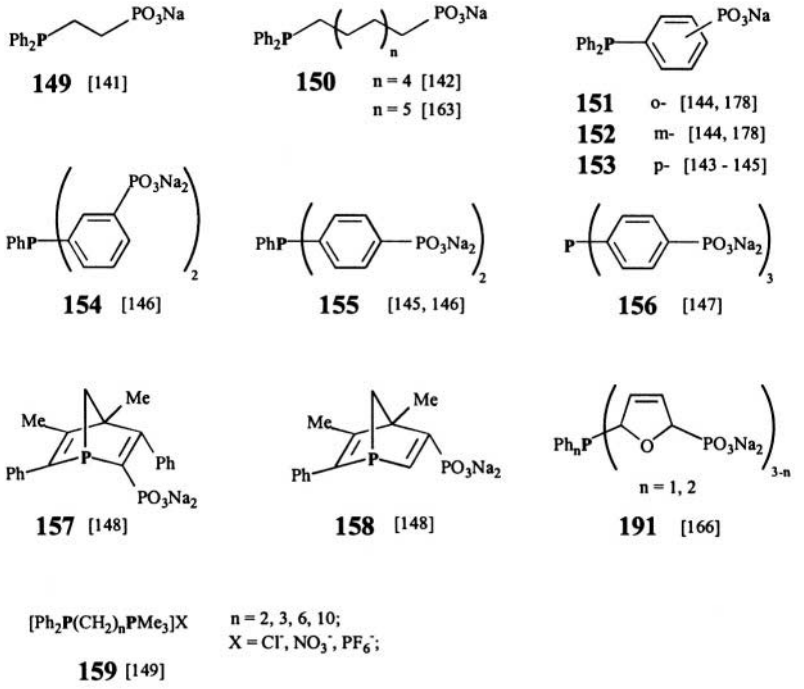


Figure 14. Tertiary phosphines with phosphonate and phosphonium substituents

Nitrogen-containing phosphines (Figure 15) remain in the center of ligand synthesis. One reason for this may be in the solubility of the (unprotonated) amines in common organic solvents which allows the use of the methods of conventional organic synthesis. An additional aspect is in that amines can be further functionalized by several ways, for example as seen in 2.6 above. Another example is the reaction of **160** (*diam*-BINAP) with 2,6-tolylene diisocyanate affording an enantiopure polymeric phosphine ligand [153].

Condensation of tris(hydroxymethyl)phosphine with easily available water soluble secondary amines yielded the hydrophilic aminomethylphosphines **164-168** [154]. Some of these compounds have surprisingly high solubility in water (**6 M** L^{-1} in case of **167**).

The two N-containing phosphines, **N_3P 206** [179] and PAA-pyrphos **207** [180] served as useful components of hydroformylation and hydrogenation catalysts.

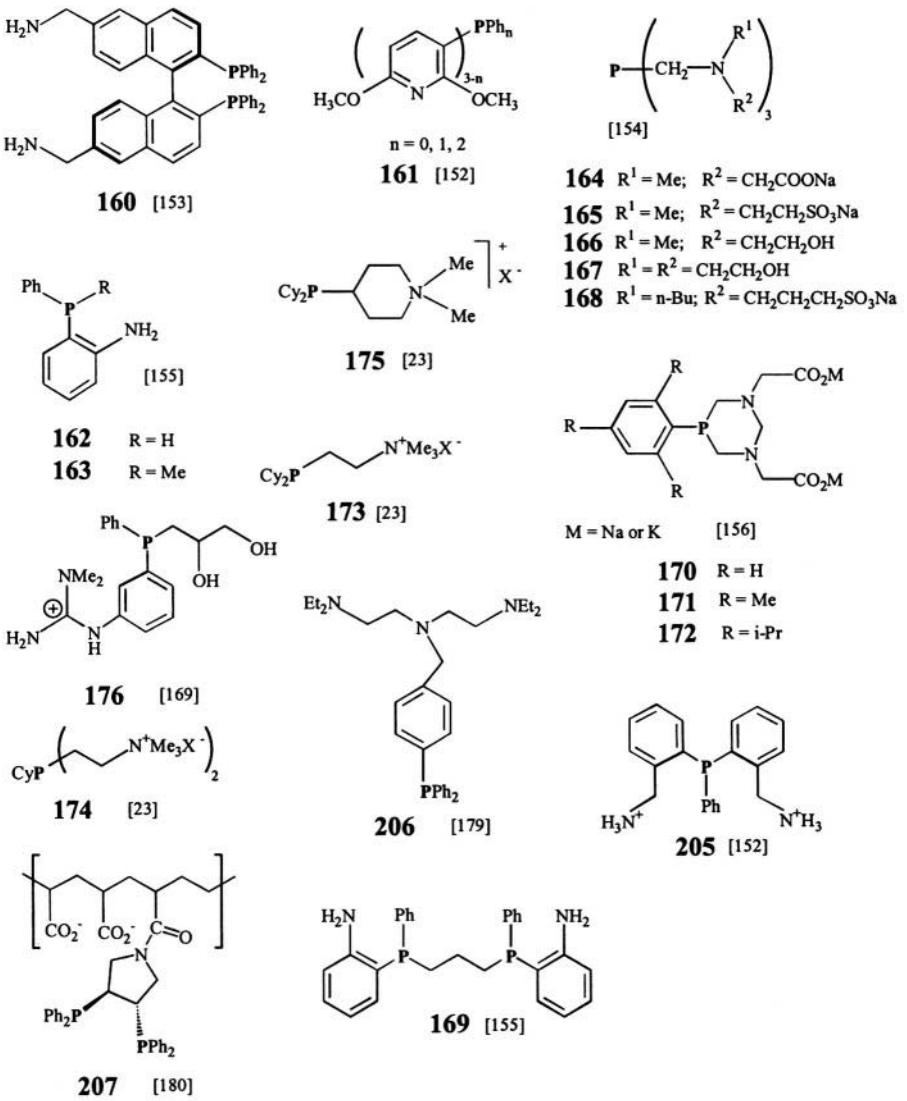


Figure 15. Nitrogen-containing water-soluble phosphines

The number of new *sulfonated phosphines* (Figure 16) is not very high, however their performance is really outstanding. Compounds **178-181** [159] and **182** [160] gave extremely active and stable Pd-catalysts for the alternating copolymerization of ethene and CO (details of the catalytic reactions are found in Chapter 7). Rhodium complexes of the surfactant **184** and **185** form stable vesicles in aqueous media and show good catalytic

properties in the hydroformylation of higher alkenes [161]. It may be appropriate to mention here, that the amphiphilic phosphonate-phosphine, **150 (n=4)** similarly gives a highly active and selective Rh-catalyst for the hydroformylation long-chain -olefins [163].

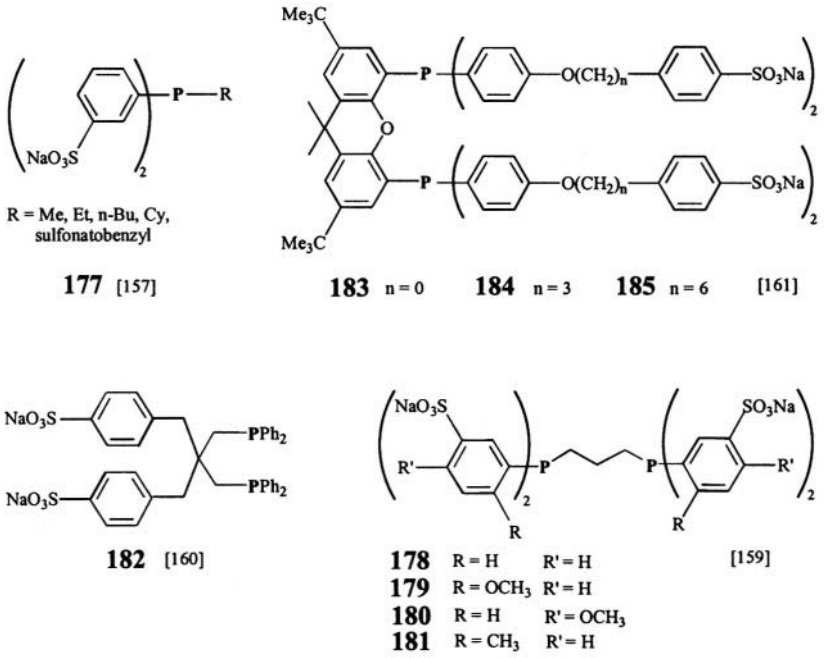


Figure 16. New sulfonated phosphines

Addition of diphenylphosphine or phenylphosphine to methyl 1-cyclohexanecarboxylate under base catalysis yielded **186** and **187** [164] (Figure 17). The Pd-catalyzed Heck reaction of substituted olefins with (p-bromophenyl)diphenylphosphine oxide in dimethylformamide afforded substituted phosphine oxides which could be reduced with trichlorosilane to yiled the corresponding *carboxylated phosphines* - **188**, too, was prepared this way [165].

Carbohydrates remain an attractive source of chirality in preparation of ligands for asymmetric catalysis. Functionalized phospholanes, **192** [167], and chiral bisphosphinites **193** [168] with an attached crown ether unit were obtained recently from D-mannitol and from phenyl 2,3-di-*O*-allyl-4,6-*O*-benzylidene-β-D-glucopyranoside, respectively (Figure 18). Compounds **194** and **195** were obtained in the photochemical addition of $H_2P(CH_2)_3PPH_2$ onto the crresponding alkenes - Pd-complexes of these new bisphosphines were successfully applied as catalysts in the copolymerization of CO and

ethene [170]. Although an indium complex of the *poly(ethylene glycol)* derivative **196** was active in hydrogenation of allylbenzene, the ligand severly hindered phase-separation in aqueous/organic biphasic systems [171].

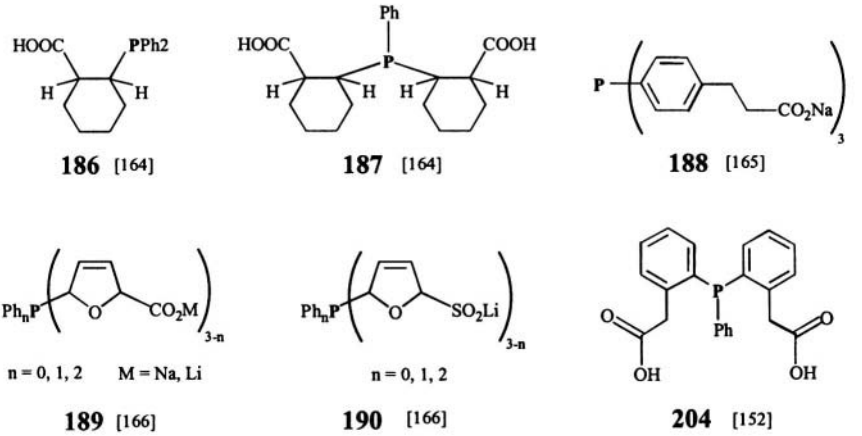


Figure 17. New carboxylated phosphines

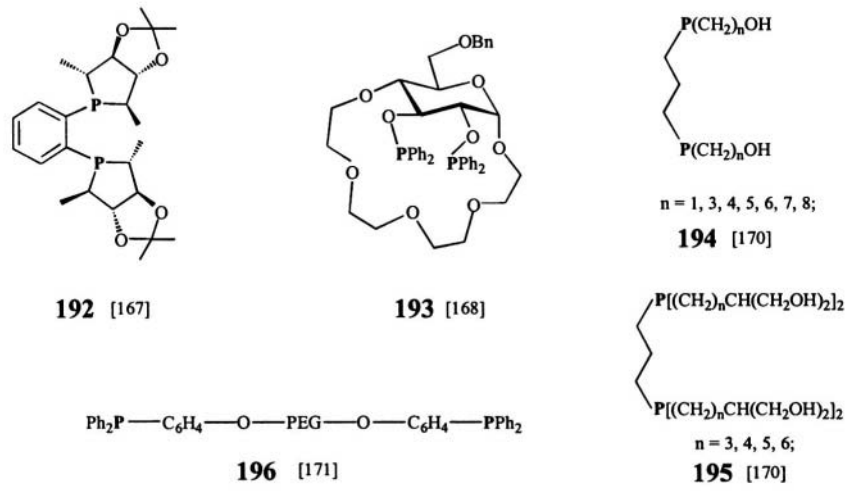


Figure 18. New oxygen-containing water-soluble phosphines

Water-soluble *calixarenes* are more and more investigated in order to make use of their ability to host other molecules, and the first examples of the use of phosphine-modified calixarenes in organometallic catalysis appeared just recently. Rhodium complexes prepared with **197** (Figure 19)

were found active and selective in the hydroformylation of 1-octene [172]. The preparation of **199** via straightforward steps has been published but no catalytic use of this ligand is known presently [174].

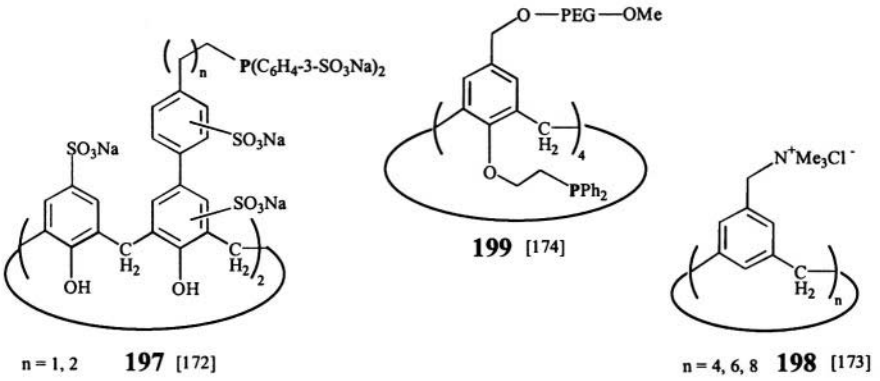


Figure 19. Water-soluble calixarenes

Non-phosphine type ligands are studied time by time with the aim to obtain water-soluble transition metal complexes with catalytic properties. However, with the exception of a few specific reaction types (e.g. oxidations) these catalysts cannot cope with tertiary phosphines - with the ligands on Figure 20 this has been found once again.

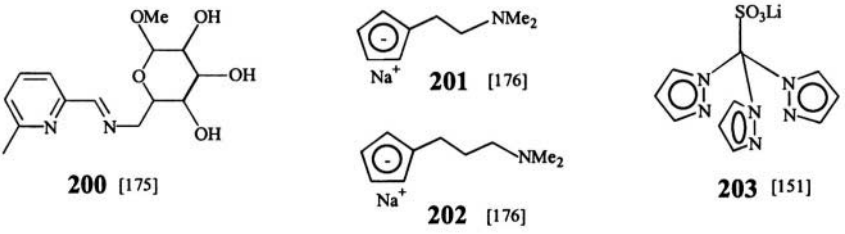


Figure 20. Non-phosphine ligands for aqueous organometallic catalysis

2.9 SOLUBILITIES OF TERTIARY PHOSPHINES AND THEIR COMPLEXES IN WATER

Water-soluble phosphines most often used to be prepared for the purposes of aqueous organometallic chemistry and catalysis. Especially for catalytic applications it is usually sufficient to know whether the complexes dissolve in water in "catalytic" (i.e. low) concentrations and whether they stay in the aqueous phase or tend to distribute between the aqueous and organic phases. At the other extreme, sometimes very high concentrations of the free ligand are needed in order to keep a catalyst protected against decomposition or to ascertain high selectivity towards the formation of one of the products, as is the case in the rhodium-catalyzed hydroformylation of propene. In such cases "high" solubility is required, but how much is that in actual quantities is not strictly defined. All this resulted in rather vague reports on aqueous solubility of phosphine ligands in the relevant literature. Another complication originates from the fact that polar or ionic substituents often make the phosphine amphiphilic or surfactant which may result in difficulties in the determination of true solubilities. Furthermore, the temperature of the measurements is not always stated and in those cases one may wonder whether the determinations were made at room temperature or in its vicinity. Therefore the following table does not contain a critical compilation of solubility data, instead the figures are taken over from the publications as they originally appeared.

Table 2. Solubility of tertiary phosphine ligands in water

Entry	Compound	Solubility[a]	T/°C	Ref.
1	**1** - Na	12[b]	r.t.	[178]
2	**1** - K	4	r.t.	[178]
3	**4** - K	100	r.t.	[16]
4	**3** - Na	1100-1400	r.t.	[16,177]
5	**6** - Na	900	r.t.	[16]
6	**6** - K	800	r.t.	[16]
7	**5** - K	400	r.t.	[16]
8	**8** - K	85	r.t.	[15]
9	**9** - K	1300	r.t.	[15]
10	**46** - Na	> 1500	r.t.	[51]
11	**151**	20	20	[144]
12	**152**	240	20	[144]
13	**153**	300-400	20	[145]
14	**155**	1000-1100	20	[145]
15	**88**, n=1, K	800	20	[72]
16	**88**, n=2, K	1300	20	[72]
17	**91** - K	1000	r.t.	[72]
18	**110**, R^1=CH_3, R=CH_3	65[c]	30	[107]
19	**110**, R^1=H	> 2000[c]	30	[107]

Entry	Compound	Solubility[a]	T/°C	Ref.
20	**110**, R^1=CH_3	> 2000[c]	30	[107]
21	**157**	20	r.t.	[148]
22	**164**	1130	r.t.	[154]
23	**165**	3550	r.t.	[154]
24	**166**	760	r.t.	[154]
25	**167**	2320	r.t.	[154]
26	**168**	1020	r.t.	[154]
27	**27**	≈ 200	r.t.	[31]
28	**72**, R=Ph, *ortho-*	27	20	[142]
29	**72**, R=Ph, *ortho-*	182	70	[142]
30	**96** - Na_2	> 300	r.t.	[85]
31	**24**, R=$CH_2CH_2SO_3Na$, m=2	250	r.t.	[30]
32	**24**, R=$CH_2CH_2SO_3Na$, m=1	440	r.t.	[30]
33	**24**, R=$CH_2CH_2SO_3Na$, m=0	1860	r.t.	[30]
34	**24**, R=CH_2SO_3Na, m=2	325	r.t.	[30]
35	**24**, R=CH_2SO_3Na, m=1	540	r.t.	[30]
36	**24**, R=CH_2SO_3Na, m=0	2500	r.t.	[30]
37	$Ph_2PCH_2CHS(CH_2CH_2SO_3Na)_2$	360	r.t.	[30]

[a] solubilities are given in g solute L^{-1} aqueous solution if not indicated otherwise

[b] in 1 M KNO_3

[c] g solute L^{-1} water

Almost no data can be found in the literature on the solubility of metal complexes with water-soluble phosphine ligands. It is mentioned that 5 kg(!) of the highly charged Pd-complexes, $[PdX_2\{P(CH_2CH_2NMe_2H)_3\}_2]^{6+}$ (X = Cl, Br) dissolved in 1 kg water at 25 °C [64].

At the end of this Chapter, looking at the exceptional variety of water-soluble ligands and the pace with which newer and newer compounds are synthetized it is safe to state that every aqueous reaction may find its perfect catalyst - at least the ligands are out there already. It seems that high-throughput screening could benefit aqueous organometallic catalysis, too.

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Chapter 3

Hydrogenation

Hydrogenation is one of the most intensively studied fields of metal complex catalyzed homogeneous transformations. There are several reasons for such a strong interest in this reaction. First of all, there are numerous important compounds which can be produced through hydrogenation, such as pharmaceuticals, herbicides, flavors, fragrances, etc [1-3]. Activation of H_2 is involved in other important industrial processes, such as hydroformylation, therefore the mechanistic conclusions drawn from hydrogenation studies can be relevant in those fields, as well. H_2 is a rather reactive molecule and its reactions can be followed relatively easily with a number of widely available techniques spanning the range from simple gas uptake measurements to gas and liquid chromatography and ^{1}H, ^{13}C etc. nuclear magnetic resonance spectroscopy for product identification and quantification. From this aspect, hydrogenation of simple olefinic substrates is a straightforward choice to check the catalytic activity of new complexes. Of course, the analysis of complicated product mixtures or the detection and characterization of catalytically active intermediates formed from catalyst precursors often requires the use of sophisticated instrumental techniques such as various mass spectrometric methods and multinuclear, multidimensional NMR spectroscopy (a very useful development for the investigation of metal hydrides uses *para*-hydrogen induced polarization [4]). Historically, hydrogenations were the first homogeneous metal complex catalyzed reactions where the reaction mechanisms could be studied in fine details [3] and later the hydrogenation of prochiral olefins served as the standard reaction for the development of enantioselective catalysts. It is not surprising that aqueous organometallic catalysis also started with studies on hydrogenation of water-soluble substrates such as maleic and fumaric acids with simple chlorocomplexes of platinum group metals, $[RhCl_n(H_2O)_{6-n}]^{3-n}$ [5] and $[RuCl_n(H_2O)_{6-n}]^{3-n}$ [6].

In many respects, aqueous organometallic hydrogenations do not differ from the analogous reactions in organic solvents. There are, however, three important points to consider. One of them concerns the activation of the hydrogen molecule [3]. The basic steps are the same in both kinds of solvents, i.e. H_2 can be split either by homolysis or heterolysis, equations (3.1) and (3.2), respectively.

$$H_2 \rightleftharpoons H^{\bullet} + H^{\bullet} \quad (3.1)$$

$$H_2 \rightleftharpoons H^{+} + H^{-} \quad (3.2)$$

In the gas phase homolytic splitting requires 436 kJ mol^{-1} and therefore reaction (3.1) is much more probable than heterolytic splitting which is accompanied by an enthalpy change of 1674 kJ mol^{-1}. However, hydration of both H^+ and H^- is strongly exothermic (-1090 kJ mol^{-1} and -435 kJ mol^{-1}, respectively) in contrast to the hydration of $H^{\bullet}$ (-4 kJ mol^{-1}). As a result, heterolytic activation becomes more favourable in water than homolytic splitting of H_2, requiring 156 kJ mol^{-1} and 423 kJ mol^{-1}, respectively. Although this simple calculation is not strictly applicable to activation of H_2 in its reaction with transition metal *complexes*, it shows the potential effect of solvation by a polar solvent such as water on the mode of dihydrogen activation.

Another major difference between aqueous and most organic solvent systems is in the low solubility of H_2 in water (Table 3.1). Consequently, in aqueous systems 2-5 times higher pressure is needed in order to run a hydrogenation at the same concentration of *dissolved* hydrogen as in the organic solvents of Table 3.1 under atmospheric pressure. In addition, in a fast reaction the stationary concentration of dissolved hydrogen can be even lower than the equilibrium solubility. However, not only the rate but the selectivity of a catalytic hydrogenation can also be decisively influenced by the concentration of H_2 in the solution [7] so that comparison of analogous aqueous and non-aqueous systems should be made with care.

Table 3.1. Solubility of H_2 in water and in organic solvents [8]

Solvent	$10^3[H_2]$/M	Temperature/°C
Water	0.81	20.0
Methanol	3.75	20.0
Ethanol	2.98	20.0
Ethyl acetate	3.40	21.0
Dimethylformamide	1.78	25.0
Benzene	2.94	20.0
Toluene	3.50	20.0
Chlorobenzene	2.46	21.2

Finally, dissociation of water always results in a certain concentration of H^+ conveniently expressed as the pH of the solution. Some of the catalysts and substrates also show acid-base behaviour themselves and their state of protonation/deprotonation may largely influence the catalyzed reactions. This is obviously important in hydrogenations involving heterolytic activation of H_2.

Research into homogeneous hydrogenation and its applications prior to 1973 are comprehensively described in the now classic book of James [3]. More recent books on hydrogenation [1] and on aqueous organometallic catalysis [2] contain special chapters on hydrogenation reactions in water. In adition, all reviews on aqueous organometallic catalysis devote considerable space to this topic, see e.g. references [9-12].

In this Chapter we shall look at hydrogenations both in one-phase and in two-phase systems organized according to the various reducible functional groups. However, early work, described adequately in [3] will be mentioned only briefly.

3.1 HYDROGENATION OF OLEFINS

3.1.1 Catalysts with simple ions as ligands

3.1.1.1 Ruthenium salts as hydrogenation catalysts

In the early nineteen-sixties Halpern, James and co-workers studied the hydrogenation of water-soluble substrates in aqueous solutions catalyzed by ruthenium salts [6]. $RuCl_3$ in 3 M HCl catalyzed the hydrogenation of Fe(III) to Fe(II) at 80 °C and 0.6 bar H_2. Similarly, Ru(IV) was autocatalytically reduced to Ru(III) which, however, did not react further. An extensive study of the effect of HC1 concentration on the rate of such hydrogenations revealed, that the hydrolysis product, $[RuCl_n(OH)(H_2O)_{5-n}]^{3-n}$ was a catalyst of lower activity. It was also established, that the mechanism involved a heterolytic splitting of H_2. In accordance with this suggestion, in the absence of reducible substrates, such as Fe(III) there was an extensive isotope exchange between the solvent H_2O and D_2 in the gas phase.

In aqueous hydrochloric acid solutions, ruthenium(II) chloride catalyzed the hydrogenation of water-soluble olefins such as maleic and fumaric acids [6]. After learning so much of so many catalytic hydrogenation reactions, the kinetics of these simple Ru(II)-catalyzed systems still seem quite fascinating since they display many features which later became established as standard steps in the mechanisms of hydrogenation. The catalyst itself does not react with hydrogen, however, the ruthenium(II)-olefin complex

formed from the Ru(II)-chloride and the substrate heterolytically activates H_2. With a later terminology, hydrogenation proceeds on the "unsaturate pathway". The reaction can be described with the simple rate law: $d(H_2)/dt = k[H_2][Ru(II)(alkene)]$. It is the *trans*-olefin, fumaric acid which reacts faster ($k = 3.6 \pm 0.6\ M^{-1}s^{-1}$) than the *cis*-isomer, maleic acid ($k = 2.3 \pm 0.1\ M^{-1}s^{-1}$). The activation energies were found to be $71\ kJ\ mol^{-1}$ and $59\ kJ\ mol^{-1}$, respectively. When the reactions were run in H_2O under D_2 there was no deuterium incorporation into the hydrogenated products, conversely, in D_2O under H_2 exclusive formation of dideuterated succinic acid was observed. This shows, that the isotope exchange between the solvent D_2O and the monohydrido Ru(II) complex formed in the heterolytic H_2 activation step is much faster than the hydride transfer to the olefin within the same intermediate.

These meticulous kinetic studies laid the foundations of our understanding of hydrogen activation. For more details the reader is referred to [3].

3.1.1.2 Hydridopentacyanocobaltate(III)

Addition of cyanide to Co(II)-salts under hydrogen produces an active hydrogenation catalyst which was subject of very intensive studies during the nineteen-sixties [13,14]. The catalytically active species is hydridopentacyanocobaltate formed according to eq. (3.3).

$$2[Co(CN)_5]^{3-} + H_2 \rightleftharpoons 2\ [CoH(CN)_5]^{3-} \qquad (3.3)$$

As seen from the equation, this reaction is a homolytic splitting of H_2 producing organometallic radicals. Water is an ideal solvent for harbouring such reactive species since itself hardly takes part in radical reactions. Although $[CoH(CN)_5]^{3-}$ has the valuable ability to reduce conjugated dienes selectively to monoenes (in most cases with 1,4-addition of hydrogen), it has not become a widely used catalyst due to the following limitations:

a) solutions of the catalyst "age" rapidly, which prevents or at least makes quantitative applications difficult and leads to gradual loss of activity

b) an excess of the substrate inhibits the reaction so continuous addition of the substrate is needed in larger scale applications

c) solutions of the catalyst are highly basic which excludes their use in case of base-sensitive substrates

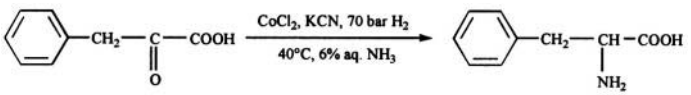
d) environmental concerns do not allow large scale use of concentrated cyanide solutions.

Several efforts were made in order to circumvent these difficulties. In the preparatively interesting reduction of organic compounds such as dienes,

unsaturated ketones and aldehydes biphasic reactions were studied with toluene as the organic phase. Addition of a phase transfer agent [15], such as tetramethylammonium bromide or triethylbenzylammonium bromide not only accelerated the reaction but at the same time stabilized the catalyst. In case of unsaturated ketones and aldehydes selective C=C hydrogenation was observed, however, aldehyde reduction was accompanied by severe losses due to condensation and polymerization side reactions. In an other approach, neutral (Brij 35) or ionic (SDS, CTAB) surfactants were used to speed up the hydrogenation of cinnamic acid and its esters in a water/ dichloroethane two-phase system [16]. The substrates were solubilized into the catalyst-containing aqueous phase within the micelles formed by these surfactants and the increased local concentration resulted in higher rates of hydrogenation.

Interesting other additives used in the pentacyanocobaltate(III)–catalyzed hydrogenations are the various cyclodextrins [17] - these reactions will be discussed in Chapter 10.

$[CoH(CN)_5]^{3-}$ catalyses the hydrogenation of nitro compounds either to amines (aliphatic substrates) or to products of reductive dimerization, i.e. to azo and hydrazo derivatives. Ketoximes and oximes of 2-oxo-acids are hydrogenated to amines. This latter reaction gives a possibility to directly produce α-amino-acids in the reductive amination of 2-oxo-acids in aqueous ammonia at a temperature of 40-50 °C and 70 bar H_2 (Scheme 3.1). Yields are usually high (approximately 90%) [18].



Scheme 3.1

3.1.2 Water-soluble hydrogenation catalysts other than simple complex ions

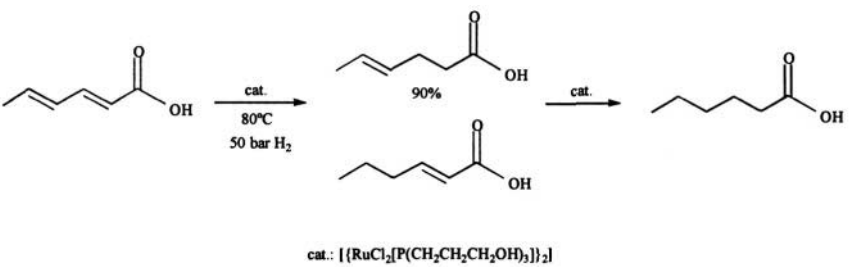
3.1.2.1 Catalysts containing phosphine ligands

In most cases the catalysts of homogeneous hydrogenation contain a metal ion from the platinum group and a certain number of tertiary phosphine ligands. Several papers describe such systems, a compilation of which is found in Table 3.2. Hydrogenation catalysts with no phosphine

ligands or with no platinum group metal ion are less abundant and a few of them are also shown in Table 3.3 (In general, the papers discussed in detail in the text are not included in these and similar Tables.)

Several of the studies listed in Table 3.2 served exploratory purposes in order to establish the stability of the catalysts in aqueous solution and their catalytic activity in hydrogenation of simple olefins. These investigations also helped to clarify the similarities and differences in the mechanism of hydrogenations in aqueous systems in relation to those well-known in organic solutions. Very detailed kinetic studies were conducted on the hydrogenation of water soluble C=C and C=O unsaturated acids in homogeneous sulutions using the ruthenium complexes with mono-sulfonated triphenylphosphine, $[\{RuCl_2(TPPMS)_2\}_2]$, $[RuClH(TPPMS)_3]$, and $[Ru(CH_3COO)H(TPPMS)_3]$ [47-53] as well as the water soluble analogue of Wilkinson`s catalyst, $[RhCl(TPPMS)_3]$ [48,54,55]. The results of these investigations will be discussed in Section 1.2.3.

For preparative purposes selective partial hydrogenation of sorbic acid (2,4-hexadienoic acid) would be valuable since the product unsaturated acids are useful starting materials in industrial syntheses of fine chemicals. However, in most reactions sorbic acid is fully hydrogenated to hexanoic acid. In this case the principle of "protection by phase separation" could be applied with considerable success. Using hydroxyalkylphosphine complexes of ruthenium(II) as catalysts, Drießen-Hölscher and co-workers [40] achieved selective hydrogenalion of sorbic acid to *trans-3*-hexenoic acid or to 4-hexenoic acid (Scheme 3.2). The rationale behind this selectivity is in the formation of the fully saturated product, hexanoic acid in *two successive* hydrogenation steps. In homogeneous solutions, such as those with $[CoH(CN)_5]^{3-}$, the intermediate hexenoic acids are easily available for the catalyst for further reduction. However, in biphasic systems these products of the first hydrogenation step move to the organic phase and thus become prevented from being hydrogenated further.



Scheme 3.2

Table 3.2. Hydrogenation of olefins with water-soluble catalysts in homogeneous solution and in aqueous-organic two phase systems

Catalyst	Substrates	Solvent	Conditions and remarks	Ref.
$[\{RhCl(cyclohexene)_2\}_2]$ + $P(CH_2OH)_3$	1-octene	EtOH	Isomerization	[19]
$[RhCl(TPPMS)_3]$	hexenes, cyclohexene	H_2O	25 °C, 3 bar H_2	[20]
$RhCl_3$ + TPPMS, 1:3	maleic, fumaric, crotonic acids	H_2O	35 °C, P_{tot}=1 bar	[21]
	1-octene	H_2O/MeOH	Bu_4NBr added	
		H_2O/benzene		
$RhCl_3$ + TPPMS, 1:6	cyclohexene	H_2O	35 °C, P_{tot}=1 bar Co-solvents: MeOH, EtOH, DMA, ($MeOCH_2$)	[22]
$[RhCl(COD)]_2$ + DSPrPE, 1:1.5	1-hexene	H_2O/THF 6:1	60 °C	[23]
$[RhCl(COD)]_2$ + DHPrPE, 1:1.5	crotonaldehyde		3.5 bar H_2	
$[RhCl(COD)]_2$ + PNS	1-hexene	H_2O	40-80 °C,	[24]
$[Rh(acac)(CO)_2]$ + PNS	1-buten-3-ol		1-5 bar H_2	[25]
$[RhH(CO)(PPh_3)_3]$ + PNS	2-buten-1-ol		pH effects	
	2-methyl-2-propen-1-ol		Isomerization to ketone	
[Rh(SULPHOS)(COD)]	styrene	methanol/n-heptane	65 °C, 30 bar H_2	[26]
$[Rh(SULPHOS)(CO)_2]$		1/1	Addn. of H_2O gives two-phase product mixture	
$[RhCl(PTA)_3]$	cinnamaldehyde	H_2O	50 °C, P_{tot}=1 bar	[27]
	allylbenzene		Selective C=C hydrogenation	[28]
			Isomerization	[29]
$[Rh(acac)(CO)PR_3]$	1-hexene cyclohexene	H_2O	30 °C, 1 bar H_2	[30]

Catalyst	Substrates	Solvent	Conditions and remarks	Ref.
PR_3 = PTA, TPPTS, Cyep	allyl alcohol		Isomerization	
$[RhH(MePTA^+I^-)_4]$	allyl alcohol	H_2O	20 °C, 1 bar H_2	[31]
$[RhH(EtPTA^+I^-)_4]$	maleic, fumaric, itaconic acid, acrylamide cinnamaldehyde		Selective C=C reduction Isomerization Strong effect of Co^{2+}	[32]
$[Rh(amphos)_2(MeOH)_2]^{3+}$	maleic acid fumaric acid styrene, 1-hexene	H_2O	r.t., P_{tot}=1 bar Co-solvents: CH_2Cl_2, Et_2O, pentane	[33] [34]
$[Rh(NBD)(n\text{-phophos})]^{3+}$ n=2,3,6,10	1-hexene maleic acid	H_2O	r.t., P_{tot}=1 bar	[35]
$[Rh(COD)_2]BF_4$ + DPDP, 1:3	1-hexene cyclohexene	H_2O	r.t., P_{tot}=1 bar	[36]
$[RhCl(DPUP)_3]$	unsaturated phospholipids	H_2O, buffered to pH 6.9	37 °C, P_{tot}=1.2 bar	[37]
$[Rh(COD)_2]PF_6$ + NORBOP, 1:2	α-acetamidocinnamic acid	H_2O/MeOH 1/4	r.t., 3 bar H_2	[38]
$[RuClH(TPPMS)_3]$	hexenes, cyclohexene	H_2O	80 °C, 3 bar H_2	[20]
$[RuH(CO)(TPPMS)_3]$	styrene, cyclohexene	H_2O/decalin		[39]
$[RuCl(CO)(Cp^*)(PR_3)]$ $[Ru(CO)(Cp^*)(PR_3)]CF_3SO_3$ R=CH_2OH, $(CH_2)_3OH$, C_6H_4-3-SO_3Na	sorbic acid	H_2O/n-heptane	80 °C, 50 bar H_2 Max. 86 % selectivity to *cis*- and *trans*-3-hexenoic acids	[40]
$[\{RuCl_2(PR_3)\}_2]$ R = $(CH_2)_3OH$	sorbic acid	H_2O /ethyl-acetate (buffered aq. phase, pH 7)	80 °C, 50 bar H_2 Max. 90 % selectivity to 4-hexenoic acid	[41]
$[Ru_3(CO)_{12-x}(TPPTS)_x]$	1-octene, 1-decene	H_2O	60 °C, 60 bar H_2	[42]

Catalyst	Substrates	Solvent	Conditions and remarks	Ref.
x = 1, 2, 3 $[Ru_4H_4(CO)_{11}(TPPTS)]$	cyclohexene, styrene benzene		Styrene to ethylbenzene Benzene to cyclohexane	
$[Ru\{HB(pz)_3\}(PPh_3)_2(CH_3CN)]^+$ $[Ru\{HB(pz)_3\}(PPh_3)(CH_3CN)_2]^+$	1-octene, 1-decene, styrene, 1-dodecene, cyclohexene, norbornene, cyclohex-1-ene-2-one, dimethylmaleate, benzylideneacetone	H_2O/THF	110 °C, 40 bar H_2	[43]
$[Pd(OH)(CH_3COO)(TPPMS)]$	allyl alcohol	H_2O	20 °C, P_{tot}=1 bar	[44]
$[Pd(OH)_2(TPPMS)_2]$	propargyl alcohol 1,3-pentadiene		Selective reduction of alkynes and dienes to olefins	[45]
$[Rh(acac)(CO)_2]$ + $Ph_2P(CH_2)_3PO_3Na_2$ 1:2.5	2,5-dimethoxy-2,5-dihydrofuran	H_2O	70 °C, 30 bar syngas Selective C=C hydrogenation	[46]

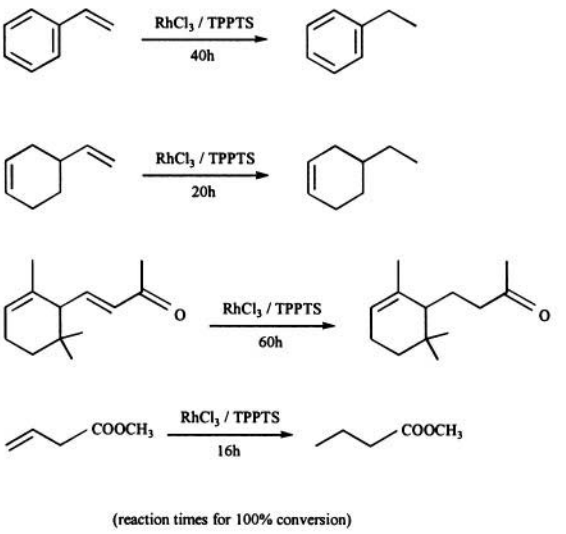
Another important practical problem is the hydrogenation of the residual double bonds in polymers, such as the acrylonitrile-butadiene-styrene (ABS) co-polymer. This was attempted in aqueous emulsion with a cationic rhodium complex catalyst, $[Rh(COD)(PPh_3)_2]^+[BF_4]^-$ which proved superior to $[RhCl(PPh_3)_3]$ due to its water-solubility [56]. No hydrogenation of the nitrile or the aromatic groups was observed and the catalyst could be recovered in the aqueous phase. Hydrogenation of polybutadiene (PBD), styrene-butadiene (SBR) and nitrile-butadiene (NBR) polymers was catalyzed by the water-soluble $[RhCl(HEXNa)_2]_2$ and related catalysts $(HEXNa = Ph_2P\text{-}(CH_2)_5\text{-}CO_2Na)$ in aqueous/organic biphasic systems at 100 °C and 55 bar H_2. These catalysts showed selectivity for the 1,2 (vinyl) addition units over 1,4 (internal) addition units in all the polymers studied [57,58].

In addition to the catalysts listed in Table 2, several rhodium(I) complexes of the various diphosphines prepared by acylation of *bis*(2-diphenylphosphinoethyl)amine were used for the hydrogenation of unsaturated acids as well as for that of pyruvic acid, allyl alcohol and flavin mononucleotide [59,60]. Reactions were run in 0.1 M phosphate buffer (pH = 7.0) at 25 °C under 2.5 bar H_2 pressure. Initial rates were in the range of 1.6-200 mol H_2/molRh.h.

Even in an excess of ligands capable of stabilizing low oxidation state transition metal ions in aqueous systems, one may often observe the reduction of the central ion of a catalyst complex to the metallic state. In many cases this leads to a loss of catalytic activity, however, in certain systems an active and selective catalyst mixture is formed. Such is the case when a solution of $RhCl_3$ in water:methanol = 1:1 is refluxed in the presence of three equivalents of TPPTS. Evaporation to dryness gives a brown solid which is an active catalyst for the hydrogenation of a wide range of olefins in aqueous solution or in two-phase reaction systems. This solid contains a mixture of Rh(I)-phosphine complexes, TPPTS oxide and colloidal rhodium. Patin and co-workers developed a preparative scale method for biphasic hydrogenation of olefins [61], some of the substrates and products are shown on Scheme 3.3. The reaction is strongly influenced by steric effects.

Despite their catalytic (preparative) efficiency similar colloidal systems will be only occasionally included into the present description of aqueous organometallic catalysis although it should be kept in mind that in aqueous systems they can be formed easily. Catalysis by *colloids* is a fast growing, important field in its own right, and special interest is turned recently to nanosized colloidal catalysts [62-64]. This, however, is outside the scope of this book.

In most aqueous/organic biphasic systems, the catalyst resides in the aqueous phase and the substrates and products are dissolved in (or constitute) the organic phase. In a few cases a reverse setup was applied i.e. the catalyst was dissolved in the organic phase and the substrates and products in the aqueous one. This way, in one of the earliest attempts of liquid-liquid biphasic catalysis an aqueous solution of butane-diol was hydrogenated with a $[RhCl(PPh_3)_3]$ catalyst dissolved in benzene [22].



Scheme 3.3

Although this arrangement obviates the need for modifications of organometallic catalysts in order to make them water soluble, the number of interesting water soluble substrates is rather limited. Nevertheless a few such efforts are worth mentioning.

When alkadienoic acids were hydrogenated with $[RhCl(PPh_3)_3]$ or $[RhCl\{P(p\text{-tolyl})_3\}_3]$ catalysts an unusual effect of water was observed [65]. In dry benzene, hydrogenation of 3,8-nonadienoic acid afforded mostly 3-nonenoic acid. In sharp contrast, when a benzene-water 1:1 mixture was used for the same reaction the major product was 8-nonenoic acid with only a few % of 3-nonenoic acid formed. Similar sharp changes in the selectivity of hydrogenations upon addition of an aqueous phase were observed with other alkadienoic acids (e.g.3,6-octadienoic acid) as well.

Several phosphines with crown ether substituents were synthetized in order to accelerate reactions catalyzed by their (water-insoluble) Rh(I) complexes by taking advantage of a "built-in" phase-transfer function [66,67]. Indeed, hydrogenation of Li-, Na-, K- and Cs-cinnamates in water-

benzene solvent mixtures, using a $[RhClL_2]$ catalyst prepared *in situ* was 50-times faster with L = crown-phosphine than with $(PPh_3$ + benzo-18-crown-6). The phase transfer properties of the crown-phosphines were determined separately by measurements on the extraction of Li-, Na-, K- and Cs-picrates in the same solvent system, and the rate of hydrogenation of cinnamate salts correlated well with the distribution of alkali metal picrates within the two phases. This finding refers to a catalytic hydrogenation taking place in the organic phase. However, there are indications that *interfacial* concentration of the substrate from one of the phases and the catalyst from the other may considerably accelerate biphasic catalytic reactions - the above observation may also be a manifestation of such effects.

3.1.2.2 Hydrogenation of olefins with miscellaneous water-soluble catalysts without phosphine ligands

Although the most versatile hydrogenation catalysts are based on tertiary phosphines there is a continuous effort to use transition metal complexes with other type of ligands as catalysts in aqueous systems; some of these are listed in Table 3.3.

3.1.2.3 Mechanistic features of hydrogenation of olefins in aqueous systems

It is very instructive to compare the kinetics and plausible mechanisms of reactions catalyzed by the same or related catalyst(s) in aqueous and non-aqueous systems. A catalyst which is sufficiently soluble both in aqueous and in organic solvents (a rather rare situation) can be used in both environments without chemical modifications which could alter its catalytic properties. Even then there may be important differences in the rate and selectivity of a catalytic reaction on going from an organic to an aqueous phase. The most important characteristics of water in this context are the following: polarity, capability of hydrogen bonding, and self-ionization (amphoteric acid-base nature).

It is often suggested that the activation of molecular hydrogen may take place via the formation of a molecular hydrogen complex $[M(H_2)]^{n+}$ [75-77] which may further undergo either oxidative addition giving a metal dihydride, $[M(H)(H)]^{n+}$, or acid dissociation to $[M(H)]^{(n-1)+} + H^+$. Both pathways are influenced by water.

Table 3.3 Hydrogenation of olefins in aqueous solution and in biphasic systems with catalysts containing no phosphine ligands

Catalyst	Substrate	Solvent	Conditions, remarks	Ref.
$[Ru_2(CO)_4(CH_3COO)(N\text{-}N)_2]X$	1-hexene	H_2O/THF	100 °C , 100 bar H_2 (r.t.)	[68]
$[Ru_2(CO)_2(CH_3COO)(N\text{-}N)_2]$	benzylideneacetone	H_2O/MeOH	Selective C=C hydrogenation	
	cyclohex-2-ene-1-one	H_2O	Faster reduction in H_2O than in H_2O/THF	
$[RuCl_2(DMSO)_4]$	1-hexene	H_2O	80 °C,P_{tot}=3 bar Isomerization. Catalyst decomp.	[69]
$[Ru_4(\eta^6\text{-}C_6H_6)_4H_6]^{2+}$	fumaric acid	H_2O	50 °C, 55 bar H_2	[70]
$[Ru(\eta^6\text{-}C_6H_6)(CH_3CN)_3](BF_4)_2$	1-octene, 1-decene, styrene, 1-dodecene, cyclohexene, norbornene,dimethylmaleate, cyclohex-1-ene-2-one, benzylideneacetone	H_2O/benzene	90-110 °C, 40 bar H_2 Slow hydrogenation of ketones and aldehydes, too.	[71]
[Pd(1M*)(fdn)]	acrylonitrile	H_2O	r.t., P_{tot}=1 bar	[72]
[Pd(3*)(fdn)]	methacrylonitrile α-ethyl-acrylonitrile crotonitrile	(0.25 M KOH)	Nitrile is not hydrolyzed. No enantioselection Catalyst decomposition	
$[Pd(QS)_2]$	unsaturated acids	H_2O	3-37 °C, P_{tot}=1 bar	[73]
QS = Alizarin red			Hydrogenation of nitro function	[74]

The kinetics of hydrogenation of *trans*-[IrCl(CO)(PPh_3)$_2$] in toluene and other organic solvents as well as that of the hydrogenation of *trans*-[IrCl(CO)(TPPMS)$_2$] [78, 79] in water were studied in detail by Atwood and co-workers [80,81]. The rate of both reactions could be described by an overall second-order rate law:

$$r_{toluene} = k_{toluene}[trans\text{-}IrCl(CO)(PPh_3)_2][H_2] \quad (3.4)$$

$$r_{water} = k_{water}[trans\text{-}IrCl(CO)(TPPMS)_2][H_2] \quad (3.5)$$

Strikingly, k_{water} was found approximately 40 times larger than $k_{toluene}$ (12 ± 3 M^{-1} s^{-1} and 0.26 ± 0.07 M^{-1} s^{-1}, respectively). However, when these complexes were hydrogenated in dimethyl sulfoxide in which both are sufficiently soluble, the rate constants were identical within experimental error (1.2 ± 0.2 M^{-1} s^{-1} for *trans*-[IrCl(CO)(PPh_3)$_2$] and 1.3 ± 0.2 M^{-1} s^{-1} for *trans*-[IrCl(CO)(TPPMS)$_2$]). *trans*-[IrCl(CO)(TPPTS)$_2$] behaves the same way [81]. These data show that sulfonation of the PPh_3 ligand did notchange the reactivity of the iridium complex and, consequently, changes in the reaction rate should be attributed to the change of the solvent solely. In fact, a good linear correlation was found between log *k* and the solvent effect parameter E_T from the toluene through DMF and DMSO to water, indicating a common mechanism of dihydrogen activation. It was speculated [80], that formation of a pseudo-five-coordinate molecular hydrogen complex (an appropriate model for the transition state on way to [IrCl(H)$_2$(CO)(TPPMS)$_2$]) builds up positive charge on the hydrogen atoms and therefore it is facilitated by a polar solvent environment. Somewhat unexpectedly, the rate of hydrogenation of *trans*-[IrCl(CO)(TPPMS)$_2$] and *trans*-[IrCl(CO)(TPPTS)$_2$] increased by a factor of approximately 3-5 on lowering the pH of the aqueous solution from 7 to 4. The origin of this rate increase is unclear. Based on IR spectroscopic investigations it was suggested that in acidic solutions the iridium center of the square planar complexes was protonated or involved in hydrogen bonding [81].

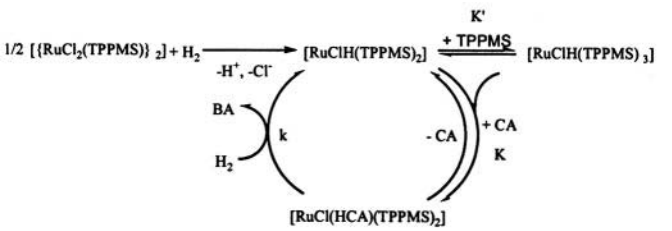
Some of the *dihydrogen complexes* are quite acidic, e.g. the pseudo aqueous acid dissociation constant, pK_a of [Os(H$_2$)(CO)(DPPP)$_2$]$^{2+}$ is -5.7 (CD_2Cl_2 solution, r.t) [76]. Nevertheless, in solutions this acid dissociation always means a proton exchange between the metal dihydrogen complex and a proton acceptor which may be the solvent itself or an external base (B). In aqueous solutions, deprotonation of a molecular hydrogen complex can obviously be influenced by the solution pH. Intermediate formation of molecular hydrogen complexes and their deprotonation was indeed established as important steps in the aqueous/organic biphasic hydrogenation of several olefins with [Ru(η^6-C_6H_6)(CH_3CN)$_3$](BF_4)$_2$ [71]

and in the hydrogenation of styrene with $[RuCl(HB(pz)_3)(PPh_3)_2]$ ($HB(pz)_3$ = tris(1-pyrazolyl)borate) in THF in the presence of H_2O or NEt_3 [43]. Although a clear-cut evidence for the role of a molecular hydrogen complex in hydrogenations in *purely aqueous* homogeneous solutions has not been obtained so far, the above examples allow the conclusion that this may only be a matter of time.

Kinetic investigations on the hydrogenation of simple water-soluble substrates [47-55] gave a general example of the differences and similarities of catalysis in analogous aqueous and non-aqueous hydrogenation reactions. In 0.1 M HC1 solutions $[\{RuCl_2(TPPMS)_2\}_2]$, $[Ru(CH_3COO)H(TPPMS)_3]$ and $[RuClH(TPPMS)_3]$ catalyze the hydrogenation of olefinic acids, such as maleic, fumaric, crotonic, cinnamic, itaconic acids and that of 1,3-butadiene-1-carboxylic acid [49]. The reactions can be conveniently run at 60 °C under 1 bar total pressure with initial turnover frequencies of approximately 100-700 h^{-1}. Under these conditions and in the presence of excess TPPMS, $[\{RuCl_2(TPPMS)_2\}_2]$ is converted to $[RuClH(TPPMS)_3]$. The kinetics of crotonic acid hydrogenation with these ruthenium catalysts could be described by the following rate law:

$$-\frac{d[H_2]}{dt} = \frac{kK[Ru]_0[H_2][CA]_0}{1+K[CA]_0+K'([TPPMS]_t-2[Ru]_0)} \qquad (3.6)$$

The kinetic findings can be rationalized by assuming that these catalytic hydrogenations involve a heterolytic activation of H_2 and proceed on the "hydride route" (Scheme 3.4).



Scheme 3.4

This mechanism is identical to that of olefin hydrogenation catalyzed by $[RuClH(PPh_3)_3]$ in benzene and in polar organic solvents such as dimethylacetamide [3]. It can be concluded therefore, that replacement of PPh_3 with its mono-sulfonated derivative, TPPMS, brings about no substantial changes in the reaction mechanism, neither does the change from

an apolar or polar organic solvent to 0.1 M aqueous HC1 solution. That this is not always so will be seen in the next example.

The water-soluble analogue of Wilkinson`s catalyst, $[RhCl(TPPMS)_3]$ was thoroughly studied in hydrogenations for obvious reasons. The complex catalyzes hydrogenation of several C=C and C=O unsaturated acids in their aqueous solution under mild conditions (Table 3.4), however, some kinetic peculiarities were found.

Table 3.4. Initial turnover frequency (TOF_0) and half-time ($t_{1/2}$) of hydrogenations[a] catalyzed by $[RhCl(TPPMS)_3]$ [54]

Substrate (S)	10^2[S]/M	TOF_0/h^{-1}	$t_{1/2}$/min
Fumaric acid[b]	3	1270	6.5
Maleic acid	3	53	13.5
Crotonic acid	3	180	7.0
Cinnamic acid	0.7	46	8.5
Allyl alcohol	5	111	82.0
Na pyruvate	3	35	16.5
α-Ketoglutaric acid	3	18	42.0

[a] Conditions: 0.01 mmol $[RhCl(TPPMS)_3]$, 0.8 bar H_2, 60 °C, 10 ml aqueous solution
[b] Same as a) but 0.001 mmol $[RhCl(TPPMS)_3]$

As seen from Table 3.4, fumaric acid is hydrogenated much faster than maleic acid. This is in contrast to the general findings with Wilkinson`s catalyst i.e. the higher reactivity of *cis*-olefins as compared to their *trans*-isomers. Another interesting observation is in that excess phosphine does not influence the rate of hydrogenation of maleic acid at all, while the rate of fumaric acid hydrogenation is decreased slightly. However, with crotonic acid there is a sharp decrease of the rate of hydrogenation catalyzed by $[RhCl(TPPMS)_3]$ with increasing concentration of free TPPMS which is in agreement with the general observations on the effect of ligand excess on the hydrogenations catalyzed by $[RhCl(PPh_3)_3]$. Interestingly, when the hydrogenation of maleic and fumaric acids was carried out in diglyme-water mixtures [55] of varying composition, the *cis*-olefin (maleic acid) was hydrogenated faster in anhydrous diglyme, while the reverse was true in mixtures with more than 50 % water content (Fig. 3.1). Obviously, in this case there must be some special effects operating in aqueous systems compared to the benzene or toluene solutions routinely used with $[RhCl(PPh_3)_3]$.

Part of the discrepancies can be removed by considering a reaction which becomes important only in water. It was found that in acidic aqueous solutions water soluble phosphines react with activated olefins yielding alkylphosphonium salts [83-85] (Scheme 3.5). The drive for this reaction is in the fast and practically irreversible protonation of the intermediate carbanion formed in the addition of TPPMS across the olefinic bond. Under

hydrogenation conditions, maleic acid reacts instantaneously while the reaction of fumaric acid is much slower and that of crotonic acid does not take place at all in the time frame of catalytic hydrogenations. When an excess of TPPMS is applied over the **[RhCl(TPPMS)$_3$]** catalyst the excess phosphine is readily consumed by maleic acid and therefore it cannot influence the rate of hydrogenation. Fumaric acid reacts slowly so there is a slight inhibition by excess TPPMS, while in case of crotonic acid phosphonium salt formation will not decrease the concentration of the free phosphine ligand, so the expected inhibition will be observed to a full extent. This explains the unusual effect of ligand excess on the rate of hydrogenation.

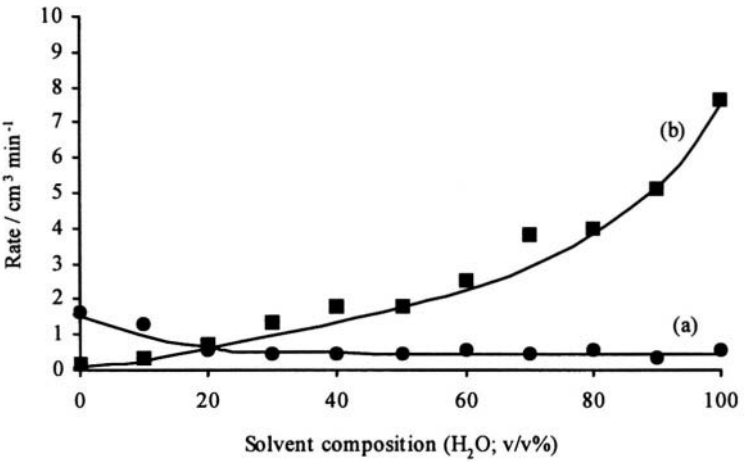
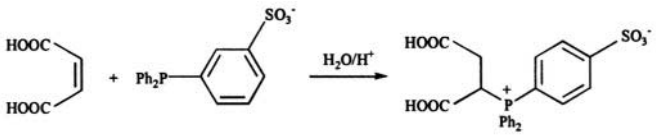


Figure 3.1. Variation of the hydrogenation rate of maleic (a) and fumaric (b) acids in water-diglyme mixtures as a function of the solvent composition. 0.001 M [RhCl(TPPMS)$_3$], 0.05 M substrate, 60 °C, H_2, 1 bar total pressure. Reprinted with permission from *J. Chem. Soc., Chem. Commun.* **1993**, 1602. Copyright (1993) American Chemical Society.

It should be added, though, that phosphonium salt formation *per se* is not necessarily detrimental to catalysis. It was found [85] that in a mixture of **[RhCl(TPPMS)$_3$]** and maleic acid under hydrogen approximately 20 % of all TPPMS was removed from the coordination sphere of rhodium(I) by this reaction, leaving behind a coordinatively unsaturated complex with the average composition of **[RhCl(TPPMS)$_{2.4}$]**. Classical studies on Wilkinson`s catalyst had shown that the highest activity in olefin hydrogenation was achieved at an average ratio of **[PPh$_3$]/[Rh]=2.2** so the opening of the

coordination sphere by phosphonium salt formation undoubtedly contributes to higher reaction rates.



Scheme 3.5

Let us consider now the origin of the effect of varying solvent composition on the hydrogenation rate in diglyme-water mixtures. The key to the explanation comes from the study of the effect of pH on the rate of hydrogenation of maleic and fumaric acids in homogeneous aqueous solutions. Fig. 3.2.a and 3.2.b show these rates as a function of pH together with the concentration distribution of the undissociated (H_2A), half dissociated (HA^-) and fully dissociated (A^{2-}) forms of the substrates [86].

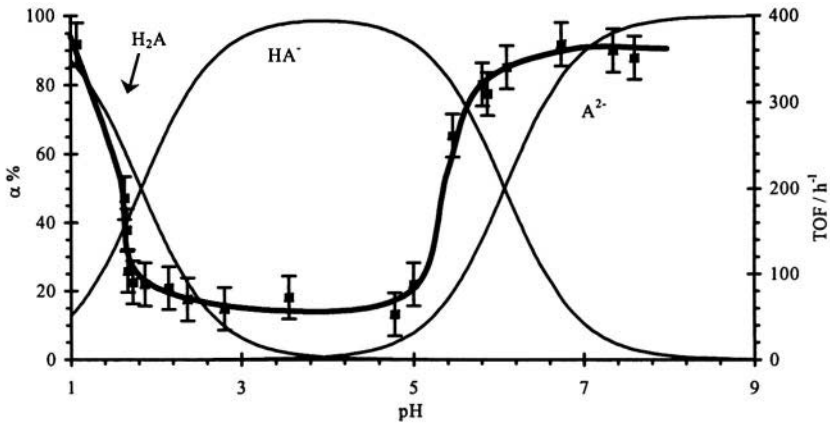


Figure 3.2a. The effect of pH on the initial rate of hydrogenation of maleic acid (MA) catalyzed by [$RhCl(TPPMS)_3$] in aqueous solution. [Rh]=0.001 M, [MA]=0.05 M, 60 °C, H_2, 1 bar total pressure. The calculated distribution (α%) of nondissociated (H_2A) and dissociated (HA^-, A^{2-}) maleic acid is also shown. Reprinted with permission from *Chem. Eur. J.* **2001**, *7*, 193. Copyright (2001) Wiley-VCH Verlag GmbH.

It is seen from these graphs that in case of maleic acid the monoanion, HA^- is the least reactive while with fumaric acid it is just the opposite. Although the extent of dissociation of these acids in diglyme-water mixtures of varying composition are not known, it is reasonable to assume, that both

maleic and fumaric acid are undissociated in anhydrous diglyme. In this case the usual order of reactivity is observed, i.e. the *cis*-olefin reacts faster than the *trans*-isomer. With increasing water content of the solvent partial dissociation of the acids take place replacing maleic acid with its less reactive monoanion while fumaric acid is replaced with its more reactive half-dissociated form. All this results in the reversed order of reactivity observed at higher water concentrations and in pure aqueous solutions.

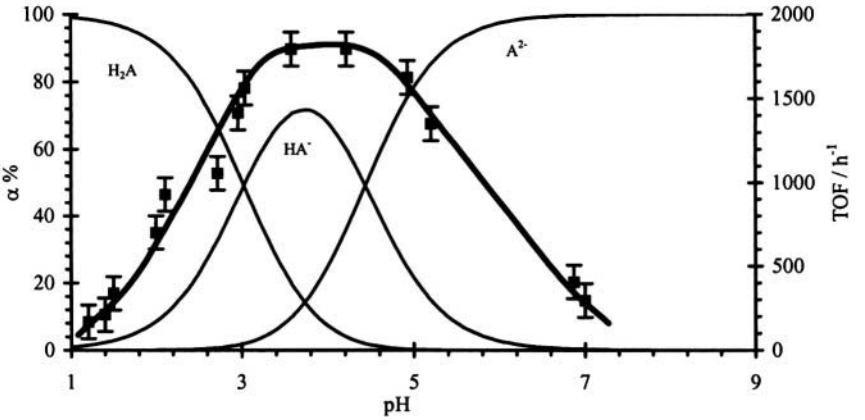


Figure 3.2b. The effect of pH on the initial rate of hydrogenation of fumaric acid (FA) catalyzed by [RhCl(TPPMS)$_3$] in aqueous solution. [Rh]=5.2 x 10^{-4} M, [FA]=0.05 M, 60 °C, H_2, 1 bar total pressure. The calculated distribution (α%) of nondissociated (H_2A) and dissociated (HA^-, A^{2-}) fumaric acid is also shown. Reprinted with permission from *Chem. Eur. J.* **2001**, *7*, 193. Copyright (2001) Wiley-VCH Verlag GmbH.

Hydrogenation of α-acetamidoacrylic acid with a $[Rh(DPPTS)(NBD)]^+$ catalyst [87] in aqueous solutions was found to proceed according to the same mechanism which was, established earlier for cationic rhodium complexes with chelating bisphosphine ligands. Hydrogenation of this complex both at pH 2.9 and at pH 4.2 produced $[Rh(DPPTS)(H_2O)_2]^+$ which did not react further with H_2. Addition of the substrate resulted in the formation of an intermediate complex containing the coordinated olefin. The rate determining step of the mechanism was the oxidative addition of dihydrogen onto this intermediate. Hydride transfer and reductive elimination of the saturated product completed the catalytic cycle. One striking observation was, however, that an enormous rate increase occurred upon lowering the pH from 4.5 to 3.2; the pseudo-first order rate constant,

k_{obs} increased from $0.21\ s^{-1}$ to $60\ s^{-1}$. α-Acetamidoacrylic acid has a pK_a of 3.26, so it is probable that at pH 3.2 it undergoes protonation in the intermediate complex to a certain extent, but why should this result in such a dramatic increase of the rate of hydrogenation remains elusive.

One must always keep in mind that in aqueous solutions the transition metal hydride catalysts may participate in further (or side) reactions in addition to being involved in the main catalytic cycle. ^1H and ^{31}P NMR studies established that in acidic solutions $[RhCl(TPPMS)_3]$ gave *cis-fac-* and *cis-mer-*$[RhClH_2(TPPMS)_3]$ [86,88], while in neutral and basic solutions these were transformed to $[RhHX(TPPMS)_3]$ ($X = H_2O$ or Cl^-) [86]. Simultaneous pH-potentiometric titrations revealed, that deprotonation of the dihydride becomes significant only above pH 7, so this reaction of the catalyst plays no important role in the pH effects depicted on Figs. 3.2.a and 3.2.b.

Th effect of pH on the rate of hydrogenation of water-soluble unsaturated carboxylic acids and alcohols catalyzed by rhodium complexes with PNS [24], PTA [29], or $MePTA^+I^-$ [32] phosphine ligands can be similarly explained by the formation of monohydride complexes, $[RhHP_n]$, facilitated with increasing basicity of the solvent.

An interesting effect of pH was found by Ogo et al. when studying the hydrogenation of olefins and carbonyl compounds with $[Cp^*Ir(H_2O)_3]^{2+}$ ($Cp^* = \eta^5$-C_5Me_5) [89]. This complex is active only in strongly acidic solutions. From the pH-dependence of the ^1H NMR spectra it was concluded that at pH 2.8 the initial mononuclear compound was reversibly converted to the known dinuclear complex $[(Cp^*Ir)_2(\mu\text{-}OH)_3]^+$ which is inactive for hydrogenation. In the strongly acidic solutions (e.g. 1 M $HClO_4$) protonation of the substrate olefins and carbonyl compounds is also likely to influence the rate of the reactions.

In conclusion, the peculiarities of hydrogenation of olefins in aqueous solutions show that by shifting acid-base equilibria the aqueous environment may have important effects on catalysis through changing the molecular state of the substrate or the catalyst or both.

3.1.2.4 Water-soluble hydrogenation catalysts with macromolecular ligands

Recovery of the soluble cattalysts presents the greatest difficulty in large scale applications of homogeneous catalysis. In a way, aqueous biphasic catalysis itself provides a solution of this problem. It is not the aim of this book to discuss the various other methods of *heterogenization* of homogeneous catalysts. The only exception is the use of water-soluble

macromolecules as ligands since with these supports catalysis takes place in a homogeneous solution and the macromolecular nature of the ligand aids the continous or post-reaction separation of the catalyst.

In most cases the catalytically active metal complex moiety is attached to a polymer carrying tertiary phosphine units. Such phosphinated polymers can be prepared from well-known water soluble polymers such as poly(ethyleneimine), poly(acrylic acid) [90,91] or polyethers [92] (see also Chapter 2). The solubility of these catalysts is often pH-dependent [90,91,93] so they can be separated from the reaction mixture by proper manipulation of the pH. Some polymers, such as the poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymers, have inverse temperature dependent solubility in water and retain this property after functionalization with PPh_2 and subsequent complexation with rhodium(I). The effect of temperature was demonstrated in the hydrogenation of aqueous allyl alcohol, which proceeded rapidly at 0 °C but stopped completely at 40 °C at which temperature the catalyst precipitated; hydrogenation resumed by cooling the solution to 0 °C [92]. Such "smart" catalysts may have special value in regulating the rate of strongly exothermic catalytic reactions.

Water-soluble complexes of the type $[Ir(COD)(PR_3)(py)]PF_6$ were prepared with PR_3 = PEG-$(OCH_2C_5H_4N)_2$ and PEG-$(OC_6H_4PPh_2)_2$ (PEG = poly(ethylene glycol), M 3400; py = pyridine) and used for hydrogenation of allylbenzene in aqueous bipasic systems. Although the activity of the complex with modified PEG ligands was somewhat lower in water than that of $[Ir(COD)(PPh_3)_3(py)]PF_6$ in CH_2Cl_2 the catalyst remained stable in the aqueous environment and allowed hydrogenation (and isomerization) of allylbenzene with close to complete conversion [95].

Unmodified poly(ethyleneimine) and poly(vinylpyrrolidinone) have also been used as polymeric ligands for complex formation with Rh(III), Pd(II), Ni(II), Pt(II) etc.; aqueous solutions of these complexes catalyzed the hydrogenation of olefins, carbonyls, nitriles, aromatics etc. [94]. The products were separated by ultrafiltration while the water-soluble macromolecular catalysts were retained in the hydrogenation reactor. However, it is very likely, that during the preactivation with H_2, nanosize metal particles were formed and the polymer-stabilized metal colloids [64,96] acted as catalysts in the hydrogenation of unsaturated substrates.

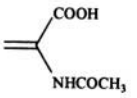
3.1.3 Enantioselective hydrogenations of prochiral olefins

Homochiral syntheses is one of the main objectives of production of biologically active substances such as Pharmaceuticals, agrochemicals, etc.

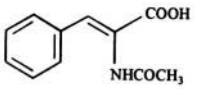
In many cases only one of the enantiomers displays the desired biological effect, the other is ineffective or even harmful. The development of enantioselective catalysis in non-aqueous solvents has been closely followed by the studies of similar aqueous systems - logically, attempts were made in order to solubilize the ligands and catalysts in aqueous media. Using aqueous/organic biphasic systems (often water/ethyl acetate) one may have a possibility of recovery and recycle of the often elaborate and expensive catalysts. However, with a few exceptions, up till now catalyst recovery has been rather a desire than a subject of intensive studies, obviously because of the lack of large-scale synthetic processes.

In asymmetric hydrogenation of olefins, the overwhelming majority of the papers and patents deal with hydrogenation of enamides or other appropriately substituted prochiral olefins. The reason is very simple: hydrogenation of olefins with no coordination ability other than provided by the C=C double bond, usually gives racemic products. This is a common observation both in non-aqueous and aqueous systems. The most frequently used substrates are shown in Scheme 3.6. These are the same compounds which are used for similar studies in organic solvents: salts and esters of *Z*-α-acetamido-cinnamic, α-acetamidoacrylic and itaconic (methylenesuccinic) acids, and related prochiral substrates. The free acids and the methyl esters usually show appreciable solubility in water only at higher temperatures, while in most cases the alkali metal salts are well soluble.

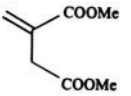
A compilation of the catalysts and reactions studied so far is shown in Table 3.5. The numbering of the ligands can be found in Chapter 2, while the abbreviations of the substrates are shown in Scheme 3.6. It is important to remember, that Table 3.5 displays only a selection of the results described in the relevant refences which are worth consulting for further details.



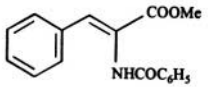
AAAH



AACH



ITAMe 2



BzACMe

Scheme 3.6

Table 3.5. Enantioselective hydrogenation of prochiral olefins in aqueous solutions

Catalyst	Substrate	e.e.	Conditions	Ref.
[{RhCl(COD)}$_2$] + **37**	AACH	35 % (*S*)	1 bar, 25 °C	[97]
[{RhCl(COD)}$_2$] + **35**	AACH	88 % (*R*)	10 bar, 25 °C	
[{RhCl(COD)}$_2$] + **115**	AAAH	46 % (*R*)	EtOH, 1 bar, 25 °C	[98]
	AAAH	11 % (*R*)	H_2O	
	AACH	65 % (*R*)	EtOH	
	AACH	30 % (*R*)	H_2O	
	ITAH	47 % (*S*)	EtOH	
	ITAH	9 % (*S*)	H_2O	
[[{RhCl(COD)}$_2$] + **116**	AAAH	60 % (*S*)	EtOH, 1 bar, 25 °C	[98]
	AAAH	30 % (*S*)	H_2O	
	AACH	35 % (*S*)	EtOH	
	AACH	28 % (*S*)	H_2O	
	ITAH	7 % (*R*)	EtOH	
	ITAH	7 % (*R*)	H_2O	
[{RhCl(COD)}$_2$] + **95**	AAAH	31 % (*R*)	H_2O/Na_2HPO_4,	[99]
	AACH	60 % (*R*)	1-5 bar, 25 °C	
	ITAH	16 % (*S*)		
[{RhCl(COD)}$_2$] + **29**	AAAH	34 % (*R*)	H_2O/Na_2HPO_4,	[99]
	AACH	no rxn	1-5 bar, 25 °C	
	ITAH	59 % (*S*)		
[{RhCl(COD)}$_2$] + **35** (tetrasulfonated)	AACH	87 % (*R*)	H_2O/EtOAc biphasic	[100]
	AACMe	81 % (*R*)	1-15 bar, 25 °C	
	ITAH	29 % (*S*)		
[{RhCl(COD)}$_2$] + **36** (tetrasulfonated)	AACH	65 % (*R*)	H_2O/EtOAc biphasic	[100]
	AACMe	45 % (*R*)	1-15 bar, 25 °C	
	ITAH	8 % (*R*)		
[{RhCl(COD)}$_2$] + **36** (monosulfonated)	AACH	87 % (*R*)	H_2O/EtOAc, 1/1	[101]
	AACMe	74 % (*R*)	biphasic	
	$ITAMe_2$	28 % (*R*)	10 bar, r.t.	
[{RhCl(COD)}$_2$] + **36** (di-sulfonated)	AACH	83 % (*R*)	H_2O/EtOAc, 1/1	[101]
	AACMe	71 % (*R*)	biphasic	
	$ITAMe_2$	1 % (*R*)	10 bar, r.t.	
[{RhCl(COD)}$_2$] + **36** (tri-sulfonated)	AACH	75 % (*R*)	H_2O/EtOAc, 1/1	[101]
	AACMe	59 % (*R*)	biphasic	
	$ITAMe_2$	1 % (*R*)	10 bar, r.t.	
[{RhCl(COD)}$_2$] + **36** (tetrasulfonated)	AACH	65 % (*R*)	H_2O/EtOAc, 1/1	[101]
	AACMe	45 % (*R*)	biphasic	

Catalyst	Substrate	e.e.	Conditions	Ref.
	$ITAMe_2$	8 % (*R*)	10 bar, r.t.	
$[\{RhCl(COD)\}_2]$ + **37** (tetrasulfonated)	AACH	34 % (*S*)	H_2O/EtOAc biphasic	[100]
	AACMe	20 % (*S*)	1-15 bar, 25 °C	
	ITAH	43 % (*S*)		
$[\{RhCl(COD)\}_2]$ + **38** (tetrasulfonated)	AACH	70 % (*R*)	H_2O/EtOAc biphasic	[100]
	AACMe	67 % (*R*)	1-15 bar, 25 °C	
	ITAH	7 % (*R*)		
$[Rh(COD)_2]BF_4$ + **113**	AAAH	99.6 % (*S*)	H_2O	[102]
	AAAMe	93.6 % (*S*)		
$[Rh(COD)_2]BF_4$ + **53a**	AAAH	9.8 % (*S*)	H_2O, 1 bar, 25 °C	[103]
	AAAMe	0		
	AAAMe	28.7 % (*S*)	with added SDS	
	AACMe	20.6 % (*S*)		
$[Rh(COD)_2]BF_4$ + **53b**	AAAH	7.5 % (*R*)	H_2O, 1 bar, 25 °C	[103]
	AAAMe	0		
	AACMe	7.2 % (*S*)		
	AACMe	24.2 % (*R*)	EtOAc	
	AACMe	22.1 % (*R*)	H_2O/EtOAc	
$[Rh(COD)_2]BF_4$ + **53c**	AAAH	16.3 % (*R*)	H_2O, 1 bar, 25 °C	[103]
	AAAMe	14.2 % (*R*)		
	AACMe	37.7 % (*R*)		
	AAACMe	66.3 % (*R*)	with added SDS	
$[Rh(COD)_2]BF_4$ + **53d**	AAAH	27.1 % (*R*)	H_2O, 1 bar, 25 °C	[103]
	AAAMe	16.6 % (*R*)		
	AACMe	31.5 % (*R*)		
$[Rh(COD)(\mathbf{81})](BF_4)_2$	AAC-Na salt	90 % (*S*)	H_2O, 50 bar, 22 °C	[104]
$[Rh(NBD)(\mathbf{78\text{-}H_4})]^{5+}$	AACH	95 %	H_2O, HBF_4, 14 bar,	[105]
	AACMe	50 %	20 °C	
	BzACMe	67 %	(also in H_2O/EtOAc)	
$[Rh(NBD)\{\mathbf{78\text{-}(CH_3)_4}\}]^{5+}$	AACH	93 %	H_2O, HBF_4, 14 bar,	[105]
	AACMe	45 %	20 °C	
	BzACMe	54 %	(also in H_2O/EtOAc)	
$[Rh(NBD)\{$(-)-(*R*,*R*)-**79-H$_4$**$\}]^{5+}$	AACH	34 % (*S*)	H_2O, HBF_4, 1 bar,	[106]
	AACMe	25 % (*S*)	25 °C	
	BzACMe	11 % (*S*)		
	BzACMe	14.5 % (*S*)	0.1 bar	
	BzACMe	2.5 % (*R*)	91 bar	

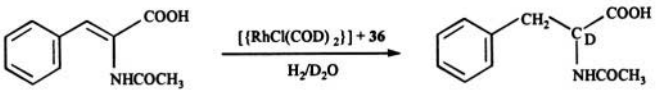
Catalyst	Substrate	e.e.	Conditions	Ref.
[Rh(NBD){(-)-(*S*,*S*)-**78**-H_4}]$^{5+}$	AACH AACMe BzACMe	71 % (*R*) 50 % (*R*) 67 % (*R*)	H_2O, HBF_4, 1 bar, 25 °C	[106]
[Rh(NBD){(-)-(*S*,*S*)-**77**-H_4}]$^{5+}$	AACH AACMe BzACMe	90 % (*R*) 74 % (*R*) 58 % (*R*)	H_2O, HBF_4, 1 bar, 25 °C	[106]
[Rh(NBD){(-)-(*S*,*S*)-**78**-H_4}]$^{5+}$	AACH AACMe BzACH BzACMe	67 % (*R*) 44 % (*R*) no rxn 54 % (*R*)	H_2O/EtOAc-benzene, 1 bar, 20 °C	[107]
[Rh(H_2O)$_2$(**52**)]$^+$	AAAH AAAMe AAAH AAAMe	70.4 % (*S*) 69.0 % (*S*) 58.0 % (*S*) 47.8 % (*S*)	H_2O, 1 bar, r.t. MeOH, 1 bar, r.t.	[108]
[Ru(C_6H_6)(**52**)]$^{2+}$	AAAH AAAMe AAAMe AACH AACH ITAH	68.5 % (*R*) 75.9 % (*R*) 50.6 % (*R*) 87.7 % (*R*) 68.3 % (*R*) 50.0 %	H_2O, 1 bar, r.t. 1 bar 10 bar 1 bar 50 bar 1 bar	[109]
[M(X)$_n$Q(BINAP-SO_3Na)]Y M=Ru, Ir, Rh, Pd; n=0,1 Q=C_6H_6, p-cymene; X=Cl, Br, I; Y= Cl, Br, ClO_4, PF_6	olefins ketones imines		H_2O	[110]
[RuCl(C_6H_6){(*R*)-(+)-**50**)}]Cl	AACH AACH	72 % (*R*) 72 % (*R*)	H_2O/EtOAc, 4 bar, r.t. MeOH, 4 bar, r.t.	[111]
[Rh(COD)(β,β-**124**)]BF_4	AAAMe AAAME AACH AACME AACMe BzACMe ITAH and others	80 % (*S*) 96 % (*S*) 99 % (*S*) 88 % (*S*) 99 % (*S*) 93 % (*S*) 71 % (*R*)	H_2O, 5 bar, r.t H_2O/SDS H_2O/SDS H_2O H_2O/SDS H_2O/SDS H_2O/SDS	[112] [113]
[Rh(COD)(α,α-**124**)]BF_4	AACMe AACMe and others	55 % (*S*) 90 % (*S*)	H_2O, 5 bar, r.t H_2O/SDS	[113]

Catalyst	Substrate	e.e.	Conditions	Ref.
$[Rh(NBD)_2]^+$ + (2*S*,4*S*)-**134a**	AACH	56 % (*R*)	H_2O/pH 8.26, 1 bar, r.t.	[114]
	AACH	70 % (*R*)	H_2O/EtOAc, pH 7.53	
	AACH	74 % (*R*)	H_2O/EtOAc, pH 7.00	
$[Rh(NBD)_2]^+$ + (2*S*,4*S*)-**134a**	AACH	89 % (*R*)	H_2O/EtOAc, 1 bar, r.t.	[115]
	AACH	74 % (*R*)	H_2O/slurry, 14 bar, 60 °C	
	AACH	60 % (*R*)	H_2O, 22 bar, r.t.	
	AACMe	67 % (*R*)	H_2O/EtOAc, 1 bar, r.t.	
$[Rh(NBD)_2]^+$ + (*R*,*R*)-**134b**	AACH	82 % (*S*)	H_2O, 1 bar, r.t.	[116]
	AACH	77 % (*S*)	H_2O, 1 bar, r.t., 70 mM $NaClO_4$	
[Rh(NBD){(*R*,*R*)-BDPBzPSO$_3$}]	$ITAMe_2$	66 %	MeOH/H_2O/*n*-Heptane 10 bar, r.t.	[117]
[Ir(NBD){(*R*,*R*)-BDPBzPSO$_3$}]	$ITAMe_2$	76 %	MeOH/H_2O/*n*-Heptane 10 bar, r.t.	

Inspection of the data in Table 3.5 reveals a few general features of enantioselective hydrogenations in aqueous solutions. Perhaps the most important of these is in that the selectivity in most reactions falls behind that achieved in non-aqueous solutions with the same or analogous catalysts, see e.g. [98] and [103]. Nevertheless, in a few cases the same [111,122] or even higher e.e.-s [108] could be obtained in water than in organic solvents. Strict comparison is rather difficult, even when using the same catalyst, since the solubility of H_2 varies from solvent to solvent. If hydrogen solubility really plays a role in the stereochemical outcome then one can expect a variation of the enantiomeric excess with pressure - indeed, it is observed in some reactions (e.g. [109], [115]) and changes in the pressure even may result in the reversal of the preferred conformation of the product [106]. However, similar observations are also known from investigations on purely organic solutions. What is perhaps more peculiar to water-soluble catalysts is that various derivatives of the same parent phosphine ligand may provide very similar enantioselectivity. This is the case with water-soluble BDPP derivatives, irrespective of the substituents being $-SO_3^-$ [101] or $-NMe_2H^+$ [107]. In other words, the distant ionic substituents seem to have no significant influence on the geometry of the activated complex, by which the enantioselection is decided. It was also shown [101] that in hydrogenation of Z-α-acetamidocinnamic acid and its methyl ester, an increase in the number of sulfonate substituents in the water soluble variant of BDPP, **36**, resulted in a gradual loss of enantioselectivity. This observation is also of interest with relation to the hydrogenation of imines, where outstandingly high e.e.-s were determined for cationic rhodium catalysts containing the

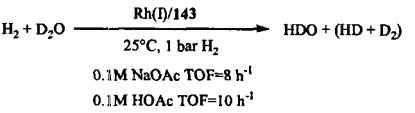
monosulfonated BDPP (see also 3.4.1) In addition to the effects of the aqueous solvent on the *enantioselectivity*, usually a very substantial decrease in the *rate* is found in aqueous solutions relative to the analogous organic systems. It is a very important finding, therefore, that both the rates and the e.e.-s can be dramatically increased by the addition of *surfactants* to the aqueous or aqueous/organic biphasic solutions. A few examples, such as [103], [112] and [113] are included in Table 3.5, and the effect is discussed in more detail in Chapter 3.1.4

The role of water in enantioselective hydrogenations was thoroughly investigated by several groups. As mentioned before, the general observation in hydrogenation of dehydro aminoacids with Rh-complexes of water-soluble chelating phosphines is the lowering of enantioselectivity in water compared to non-aqueous solvents. In case of the hydrogenation of **α-acetamidocinnamic** acid and its methyl ester [123] with Rh(I)-complexes of the water soluble diphosphines **36**, **37**, in various organic solvents and in their mixtures with water, a good linear correlation of log *(%S/%R)* and the solvofobicity parameter, S_p [124], was found. This was not true for the relation of log *(%S/%R)* and the solvent polarity parameter $E_T(30)$ [125]. It is hard to interpret and generalize these findings. The solvofobicity parameter, S_p, reflects the cohesive energy of the solvents and the energy needed to create a cavity within the solution. In this respect the solvent effect can be regarded similar to the effect of pressure, and indeed, the enantioselectivity of the hydrogenations of the same substrates with similar catalysts in organic solvents decreased upon increasing the pressure of hydrogen [126]. The picture, however, is complicated by the fact, that in D_2O instead of H_2O the same complexes of Rh(I) with **36** and **37** catalyze the selective deuteration of the resulting N-acetylamino acids in the **α-position** to the carboxylic and amide groups (Scheme 3.7) [126-128]; other mono and diacids and their methyl esters behave similarly [129].



Scheme 3.7

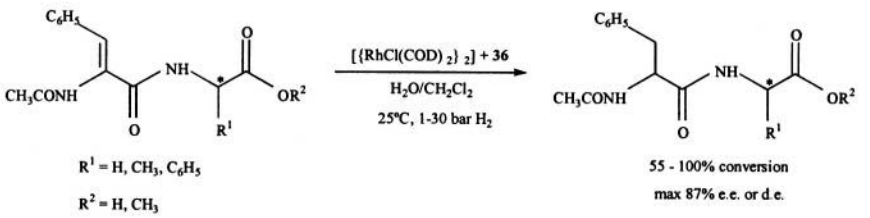
It is also known that the Rh(I)-complex of the chelating diphosphine **143** catalyzes the H-D exchange between H_2O and D_2 (Scheme 3.8) [59]. All these results point to a fast H-D exchange between an intermediate [Rh-H] species and D_2O and the resulting [Rh-D] would then transfer the deuterium into the **α-carbon** of the substrate [128,129].



Scheme 3.8

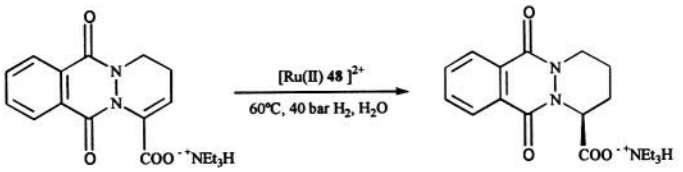
An interesting principle was put forward by Whitesides et al. who investigated the possible use of proteins as chiral supports for rhodium catalysts [59,60,118,119]. The cationic Rh(I)-complex of a biotin-containing chelating diphosphine **148**, was attached to avidin, a globular protein with extremely strong binding of biotin. The protein-bound catalyst hydrogenated α-acetamidoacrylic acid with moderate yield. The resulting N-acetylalanine was obtained with a maximum 44% enantiomeric excess. Albeit the process is not practical compared to other hydrogenation methods, these results proved the possibility of using proteins as sources of chiral induction. This is not a trivial result, since with other proteins, such as e.g. bovine serum albumin (BSA) strong inhibition of hydrogenations with the same [119] or other [120] catalysts have been observed.

Dehydropeptides were reduced (Scheme 3.9) on a preparative scale in two-phase systems with catalysts prepared in situ from [{RhCl(COD)}$_2$] and chiral water-soluble ligands **35**, **36**, and **37** (Ch.2). The highest (87%) diastereoselectivity was obtained with [{RhCl(COD)}$_2$] + tetrasulfonated 2,4-bis(diphenylphosphino)pentane, BDPPTS, **36** [121].



Scheme 3.9

An industrially interesting example of aqueous enantioselective hydrogenations is that of the reduction of the unsaturated acid in Scheme 3.10 where the e.e. was higher than 99%. High substrate/catalyst ratios could be applied, e.g. the S/C 10000 corresponds to an average turnover frequency of 480 h^{-1} [122]. In this particular case the Ru-based catalyst contained the tetrasulphonated MeOBIPHEP ligand, **48**, and produced practically the same e.e. in water than in methanol. The Ru(II)-(**48**) catalyst also hydrogenated geraniol to citronellol with 98 % e.e. in a water/ethyl acetate two-phase system [122].



Scheme 3.10

Product isolation and recovery of the catalyst is relatively easy in aqueous/organic biphasic systems and in several cases the aqueous solution of the catalyst was reused with only negligible loss of the reaction rate or of the enantioselectivity [105,112].

3.1.4 Effect of amphiphiles on the enantioselective hydrogenation of prochiral olefins in water

As mentioned briefly in the preceeding section, amphiphiles often eliminate the detrimental effects of water and bring about large increases in both the rate and the enantioselectivity of hydrogenations of prochiral olefins in aqueous solutions. This effect was studied in most detail in hydrogenation of enamides, e.g. Z-α-acetamidocinnamic acid (AACH) or its methyl ester (AACMe) catalyzed by cationic rhodium complexes of chelating diphosphine ligands, $[Rh(L_2)(COD)]^+$ [130]. These catalysts were used either in isolated form or were prepared in situ from $[Rh(COD)_2]BF_4$ and the appropriate diphosphine, L_2. In general, both the catalysts and the substrates have only limited solubility in water at ambient temperatures and in several instances such aqueous hydrogenation systems may not be truly homogeneous in the absence of micellar agents (although this is not always stated explicitly in the publications). Therefore the activity of a catalyst is usually characterized by the time needed to attain 50% conversion ($t_{½}$) of the substrate, however, the enantiomeric excess in the product is determined at full conversion. For example, with L_2 = BPPM, hydrogenation of AACMe proceeds fast in methanol ($t_{½}$ = 2 min) with 90% e.e. (BPPM = (2*S*,4*S*)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine [131]). In water the same reaction is much slower ($t_{½}$ = 90 min) and markedly less selective (78% e.e.). Addition of various amphiphiles to the aqueous systems leads to short reaction times and enantioselectivities as high as 95% which is even higher than that obtained in non-aqueous methanol. Data for this and other reactions can be found in Table 3.6, while several amphiphiles are shown on Scheme 3.11. Although a recent comprehensive review of this field is not

available, one may get a general impression of the use of amphiphiles in aqueous enantioselective hydrogenations from references [132-135].

Table 3.6. Hydrogenation of methyl Z-α-acetamidocinnamate with [Rh(BPPM)(COD)]BF_4 (for the amphiphiles see Scheme 3.11).

Solvent Amphiphile (c.m.c./M)	[Amphiphile] [Rh]	$t_{½}$/min	e.e./%	Ref.
MeOH		2	90	[136]
H_2O		90	78	[136]
H_2O + Brij 58 (7.7×10^{-5})	2	19	93	[136]
	10	10	93	
	20	9	95	
H_2O + Tween 20 (5.9×10^{-5})	1	35	87	[136]
	10	7	92	
	20	6	93	
H_2O + Triton X-100	1	35	87	[130]
	10	11	89	
	25	9	90	
H_2O + DDAPs (1.2×10^{-3})	2	45	84	[136]
	10	7	93	
	20	5	93	
H_2O + SDS (8.1×10^{-3})	2	80	62	[136]
	10	6	93	
	20	6	94	
H_2O + $CTA^+HSO_4^-$	2	10	90	[136]
	10	5	94	
	20	5	94	
H_2O + Pal-L-pro-ONa (2.3×10^{-5})	20	13	97[a)]	[137]
H_2O + Pal-L-pro-L-pro-ONa	20	11	93[a)]	[137]
H_2O + Tetradecyl-α-D-maltoside (2.2×10^{-5})	20	7	95	[138]
H_2O + Dodecyl-β-D-glucopyranoside (2×10^{-4})	20	23	82	[138]
H_2O + Decyl-β-D-glucopyranoside (2.2×10^{-3})	20	8	94	[138]
H_2O + Octyl-β-D-glucopyranoside (2.4×10^{-2})	20	23	81	[138]
H_2O + Decyl-α-D-glucopyranoside	20	43	82	[138]

Conditions: 25°C, 1 bar H_2, Rh = 0.010 mmol, BPPM = 0.011 mmol, substrate = 1 mmol, 15 mL solvent. Product configuration is *R* in all cases except [a)] *S*.

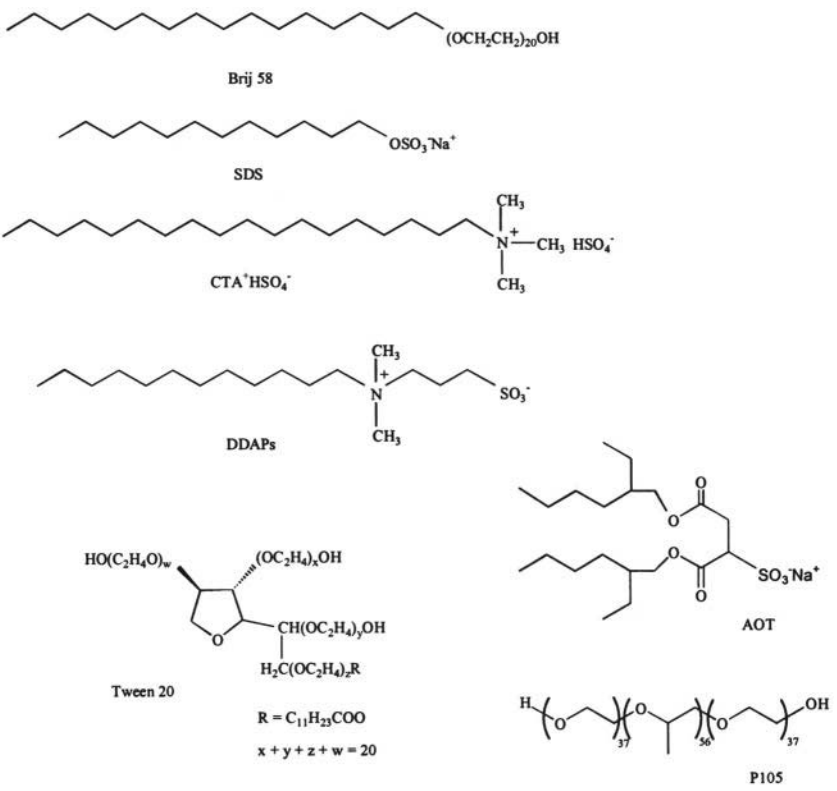
Inspection of Table 3.6 together with Scheme 3.11 reveals a few general trends. First of all, the effect seems to be connected to micelle formation. The data of Table 3.6 together with other results of detailed studies [132-133,136-139] show that the largest effect of the surfactants on the reaction rate can be observed around the critical micellar concentration (c.m.c.) of the amphiphiles. Accordingly, non-ionic surfactants (Brij, Tween) with very

low c.m.c. values are more effective in low concentration than either the anionic (SDS), cationic ($CTA^+HSO_4^-$) or zwitter-ionic (DDAPs) amphiphiles. However, the critical micellar concentration is not the only parameter which should be taken into consideration. For example, **decyl-β-D-glucopyranoside** is more effective than **dodecyl-β-D-glucopyranoside** despite its c.m.c. being eleven times higher. This shows the importance of the so-called hydrophilic-lipophilic-balance (HLB) characterizing the surfactants [140].

The mechanism of the hydrogenation of dehydroamino acid derivatives (including AACMe) with cationic rhodium complexes of chelating diphosphines was studied in very fine details and is one of the best known processes [141]. It seems that in this particular case the surfactants do not change the basic features of this mechanism, i.e. the catalytic cycle starts with the coordination of AACMe to the rhodium (unsaturate route of hydrogenation). This first step is accelerated due to the increased local concentration of the substrate and catalyst within the micelles. According to an idealized picture, the catalyst-substrate complex is incorporated into the micelle close to the head group of the amphiphiles, and the further steps of hydrogenation (**H_2-activation,** hydrogen transfer to the substrate, etc.) take place in the ordered environment provided by the micellar core. This suggestion is also supported by the finding, that amphiphilic chiral proline derivatives, such as the N-palmitoyl-L-prolyl-L-proline induced optical activity of the product (8% e.e., *S*) even when an *achiral catalyst* **[Rh(BDPB)(COD)]BF_4** was used (conditions of Table 3.6, BDPB = 1,4-bis(diphenylphosphino)butane) [137]. Similar results were obtained with cholesterol-derived chiral amphiphiles which form vesicles in aqueous dispersions [148].

Numerous other **$[Rh(L_2)(\dot{C}\dot{O}D)]^+$-type** catalysts (with ligands such as (–)-DIOP [130] or its derivatives [139,142] including **53c**, **53d** [103], several carbohydrate-derived bisphosphines [130,132,143], P~N chelating ligands [144]) and many commercial [138] or newly synthetized [145] surfactants) have also been studied in order to establish the source and characteristics of this micellar effect on enantioselective hydrogenations in aqueous systems. Although the basic features have been found similar to the above idealized picture, these studies also showed the complexities of such systems. It became clear, that in certain cases specific interaction of the surfactant molecules and the catalyst/substrate may play a decisive role. For example, the substantial difference in the efficiency of **decyl-α-D-glucopyranoside** and its **β-anomer** (Table 3.6) is probably due to different hydrogen bonding to the catalyst/substrate within the micelle. Another relevant finding is in that deuteration of the product in D_2O is significantly inhibited by certain amphiphiles already *below* the c.m.c.; alkyl sulfonates and sulfates are

especially effective in this respect. This observation refers to a specific interaction of the catalyst and the amphiphile (e.g. SDS). It is suggested [135] that deuteration proceeds via H-D exchange on an intermediate rhodium hydride which is believed to involve coordination of D_2O. It is this step, in which the oxygen-containing amphiphiles can compete and block the required coordination site. Indeed, it was shown by Buriak and Osborn that the sulfonate group of the surfactant bis(2-ethylhexyl)sulfosuccinate (AOT) did coordinate to the rhodium in $[Rh\{(-)\text{-BDPP}\}(NBD)\}]ClO_4$ (BDPP = 2,4-bis(diphenylphosphino)pentane, NBD = 2,5-norbornadiene [146, 147]) and most importantly, such coordination led to a switch from the dihydride route to the monohydride route of olefin hydrogenation [147].

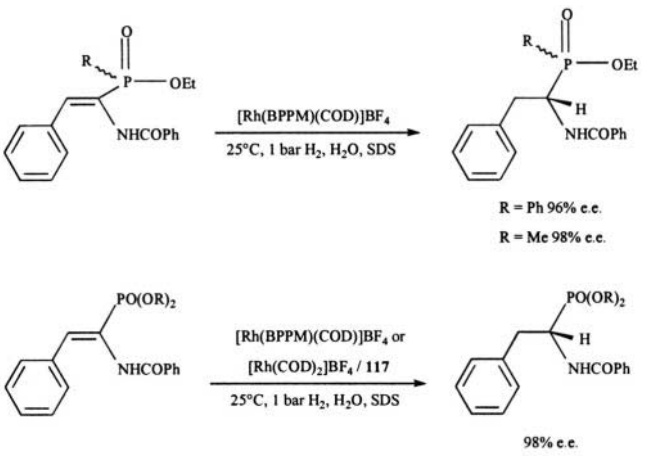


Scheme 3.11

In the preceeding paragraphs we described the effect of surfactants in reactions proceeding in a single liquid phase. A logical extension of this concept is in the use of surfactants in two-phase systems where their

solubilizing capability may facilitate mass transport between the two phases. Hanson et al. prepared the surfactant phosphines **41** which can be regarded as analogues to 2,4-bis(diphenylphosphino)pentane (BDPP) and its tetrasulfonated derivative (BDPPTS, **36**). It was established by dynamic light scattering measurements, that **41** formed aggregates in aqueous solutions. In the hydrogenation of AACMe in MeOH the catalysts prepared from [{RhCl(COD)}$_2$] and BDPP, **36** or **41** showed the same selectivity (72, 75 and 72 % e.e., respectively) although with [{RhCl(COD)}$_2$] + **36** 15 bar H_2 was needed in order to achieve 100% conversion in 1 h, in contrast to the atmospheric pressure necessarry for complexes of BDPP or **41**. In water-ethyl acetate biphasic mixtures the surfactant **41** proved even further superior to **36**. Its rhodium complex catalyzed the hydrogenation of AACMe at 1 bar H_2 pressure with 100% yield in 1.5 h and with 69% e.e., while with **36** only 32% conversion was observed in 20 h and the enantioselectivity was also poor (20% e.e.).

The beneficial effect of surfactants on enantioselective hydrogenations in water was exploited in the synthesis of α-aminophosphinic and α-aminophosphonic acids. These compounds are structural analogues of α-aminocarboxylic acids and their peptides find use as herbicides, bactericides and antibiotics [150,151]. With [Rh(BPPM)(COD)]BF_4 and similar catalysts fast ractions and e.e.-s up to 98% could be obtained in water in the presence of SDS (Scheme 3.12).



Scheme 3.12

The rhodium(I) complex of the *amphiphilized* derivative of the PPM ligand, **117** itself provided acceptable rates and selectivities ($t_{½}$ = 29-63 min, e.e. = 93-95%) under mild reaction conditions. Addition of SDS further

improved the efficiency of the reactions, with $t_{½}$ down to 4 min and e.e. up to 98%.

The interaction of surfactants and transition metal catalysts can be utilized for practical purposes of catalyst-product separation and catalyts recycling. Triblock copolymers of the type shown on Scheme 3.11, such as P105 can be dispersed in water and their high molecular weight allows their recovery by ultrafiltration through membranes. AAAMe was hydrogenated in aqueous solution with a **[Rh(BPPM)(COD)]$^+$** catalyst in the presence of P105 in a membrane reactor with ultrafiltration following each catalytic run. It was demonstrated that >99% of the catalyst + P105 was retained in the reactor after each reaction and hydrogenations could be repeated with unchanged rate and enantioselectivity after charging the reactor with new batches of solvent and substrate.

It deserves mentioning that appropriately designed unsaturated surfactants can be polymerized in order to obtain polymerized micelles [134] and others can be linked onto solid surfaces [134,153]. Interestingly, the "surfactant effect" is observed also with such polymerized and heterogenized amphiphiles which hold promise for new methods of catalyst recovery - however, this already falls outside the scope of this book.

3.2 HYDROGENATION OF ARENES AND HETEROARENES IN AQUEOUS SYSTEMS

Hydrogenation of arenes and heteroarenes is an important industrial process (e.g. in the fuel industry) and in the overwhelming majority of cases it is carried out by using heterogenous catalysts. Even then the use of an aqueous phase may lead to useful changes of selectivity as observed in the selective hydrogenation of benzene to cyclohexene [154,155]. The feasibility of large scale aqueous/organic biphasic catalysis, as demonstrated by several industrial processes [2] lends support to investigation of water-soluble catalysts in hydrogenation of arenes and heteroarenes, as well.

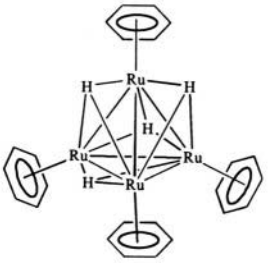
In the late nineteen-seventies Bennett and co-workers observed that areneruthenium(II) complexes, such as **[RuClH(η^6-C_6Me_6)(PPh_3)], Ru-1** [156] and **[Ru_2(μ_2-Cl)(μ_2-H)$_2$(η^6-C_6Me_6)$_2$]Cl, Ru-2**, were highly active in hydrogenation of benzene to cyclohexane and in that of several substituted benzenes to the corresponding cyclohexane derivatives. Although the reactions were run in the neat substrates the latter dinuclear hydride is water soluble and this opens the way to the use of aqueous/organic biphasic mixtures for catalysis.

A thorough study of the formation and catalytic properties of water-soluble multinuclear areneruthenium-complexes has been carried out by Süss-Fink et al. [70,158-163] with special emphasis on the homogeneous hydrogenation of arenes. It was established [162,163] that low-pressure (1.5 bar) hydrogenation of $[Ru_2Cl_4(\eta^6\text{-}C_6H_6)_2]$, **Ru-3** in the presence of tetrafluoroborate led to the tetranuclear dication $[Ru_4H_4(\eta^6\text{-}C_6H_6)_4]^{2+}$, **Ru-4**, while under higher pressure (60 bar H_2) the hexahydrido cluster dication $[Ru_4H_6(\eta^6\text{-}C_6H_6)_4]^{2+}$, **Ru-5** was obtained. A closer reinvestigation of the structure of **Ru-5** showed that it may contain an intact dihydrogen ligand [215]. However, in the presence of perchlorate, reaction of **Ru-3** resulted in the formation of the trinuclear cation $[Ru_3(\mu_2\text{-}Cl)(\mu_2\text{-}H)_2(\mu_3\text{-}O)(\eta^6\text{-}C_6H_6)_3]^+$, **Ru-6**. The mixed-arene, oxo-capped trinuclear cluster cation $[Ru_3(\mu_2\text{-}H)_3(\mu_3\text{-}O)(\eta^6\text{-}C_6H_6)(\eta^6\text{-}C_6Me_6)_2]^+$, **Ru-7** was synthetized by reacting $[Ru(\eta^6\text{-}C_6H_6)(H_2O)_3]^{2+}$, **Ru-8** with $[Ru_2(\mu_2\text{-}H)_3(\eta^6\text{-}C_6Me_6)_2]^+$, **Ru-9** [160]. Yet another cluster cation could be isolated from an active hydrogenation mixture of ethylbenzene (initial catalyst was **Ru-7**): $[Ru_3(\mu_2\text{-}H)_2(\mu_2\text{-}OH)(\mu_3\text{-}O)(\eta^6\text{-}C_6H_6)(\eta^6\text{-}C_6Me_6)_2]^+$, **Ru-10** in which one of the bridging hydrides of **Ru-7** is replaced by a μ_2-OH^-. All these hydrido-ruthenium clusters were isolated and characterized by single crystal X-ray diffractometry (some of them are shown on (Scheme 3.13), and applied as catalysts for the hydrogenation of various arenes. A selection of the results of such catalytic hydrogenations is contained in Table 3.7.

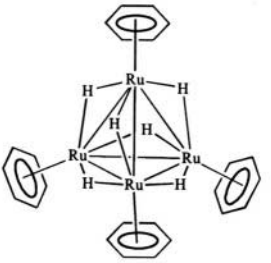
The figures in Table 3.7 clearly show that benzene and various substituted benzenes can be effectively hydrogenated in aqueous biphase systems with hydridoareneruthenium clusters as catalysts. Comparison of data of the original publications is not easy since the turnover frequencies are apparently calculated at high conversions of the substrates. However it is obvious that the highest rates are achieved with **Ru-10**. Benzene is hydrogenated with an outstanding activity, toluene and xylenes somewhat more slowly. For the substrates investigated the catalyst shows no sign of selectivity. Neither cyclohexene (in case of benzene) nor cyclohexylbenzene (in case of biphenyl) were detected. The mechanistic details are not clear, since **Ru-10** was isolated unchanged at the end of the hydrogenation of ethylbenzene. This implies, that the hexamethylbenzene and benzene ligands on the cluster framework are not replaced by the substrate molecules, neither are they removed by hydrogenation. This suggests a loose coordination of the substrate arenes to the open face of the cluster displaying a triangular arrangement of three ruthenium ions.

It is interesting to note, that the all-benzene clusters, **Ru-4** and **Ru-5** which were detected in the hydrogenation mixtures when **Ru-3** was applied as precatalyst [159] appeared distinctively less active than the mixed-arene clusters, **Ru-7** and **Ru-10**. The selectivities also differ in certain cases (see

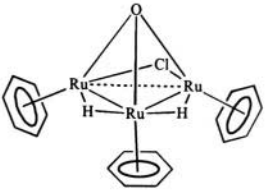
e.g. styrene, acetophenone and allylbenzene in Table 3.7). Nevertheless, the use of **Ru-3** and **Ru-4** still allowed useful rates of hydrogenation of various arenes with TOF-s in the range from several tens to several hundreds per hour [158].



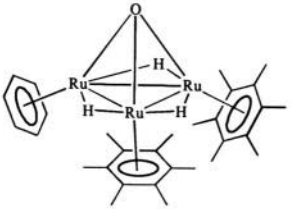
Ru-4



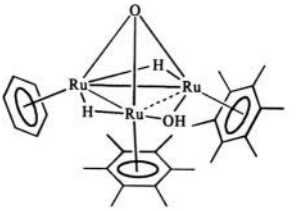
Ru-5



Ru-6



Ru-7



Ru-10

Scheme 3.13

Table 3.7 Hydrogenation of arenes with water-soluble hydridoruthenium-clusters

Substrate	Products	**Ru-3** [159]			**Ru-7** [160]			**Ru-10** [161]		
		Yield/%	time/h	TOF/h^{-1}	Yield/%	time/h	TOF/h^{-1}	Yield/%	time/h	TOF/h^{-1}
Benzene	Cyclohexane		0.5	1998		3.5	289		0.25	5466
Toluene	Methylcyclohexane		1.1	900		2.2	440		0.33	2769
Ethylbenzene	Ethylcyclohexane		8.1	103		-	-		0.25	3413
Propylbenzene	Propylcyclohexane		1.35	713		8.0	117		0.33	2913
Biphenyl[a)]	Cyclohexylbenzene	63.0	2.20	396	--	14.5	68	--	1.0	1000
	Bicyclohexyl	35.0			99.6			100		
o-Xylene	1,2-Dimethylcyclohexane		10	100		1.50	640		0.25	3736
m-Xylene	1,3- Dimethylcyclohexane		10	90		2.0	490		0.33	2922
p-Xylene	1,4-Dimethylcyclohexane		10	140		2.3	404		0.33	2640
Methyl benzoate	Methyl cyclohexanoate		21.0	42		20	45		--	--
Styrene	Ethylbenzene	95	3.3	288	75	3	323		--	--
	Ethylcyclohexane	--			22					
α-Methylstyrene	Cumene	--	21.4	27	--	1.5	661		--	--
	i-Propylcyclohexane	57			99					
Phenylacetylene	Styrene		--	--	1.0	2.0	494		--	--
	Ethylbenzene				71.8					
	Ethylcyclohexane				26.0					
Phenol[b)]	Cyclohexanol		24	41		14.5	68		--	--
Acetophenone	1-Cyclohexylethanol	74.5			97.8					
	Ethylcyclohexane	11.0	24	40	--	14.5	68		--	--
	Methylcyclohexylketone	8.0			--					
	Ethylbenzene	3.5			--					

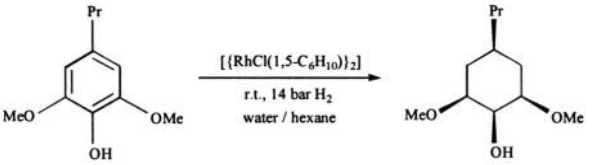
Substrate	Products	**Ru-3** [159]			**Ru-7** [160]			**Ru-10** [161]		
		Yield/%	time/h	TOF/h^{-1}	Yield/%	time/h	TOF/h^{-1}	Yield/%	time/h	TOF/h^{-1}
Allylbenzene	Propylbenzene	53			--					
	α-Methylstyrene	33	23.3	39	--	16.5	59		--	--
	β-Methylstyrene	5			--					
	Propylcyclohexane	--			96.5					

Conditions: Catalyst 0.04 mmol (**Ru-3**) or 0.01 mmol (**Ru-7** and **Ru-10**), water 5 mL, substrates added neat or [a]dissolved in 10 mL cyclohexane, substrate/catalyst =1000 or [b]500, T = 90 °C (**Ru-3**) or 110 °C (**Ru-7** and **Ru-10**), $p(H_2)$ = 60 bar. Data are given with the precision in the original publications.

In addition to benzene and alkylbenzenes several other aromatics (nitrobenzene, aniline, anisole, benzoic acid, etc.) were hydrogenated, usually with much lower rates. Benzoic acid and benzoates gave the corresponding cyclohexyl derivatives, however, in case of acetophenone some deoxygenation was also observed with the **Ru-3** catalyst [158]. This latter observation raises some doubts regarding the truly homogeneous nature of the reaction.

$[W(CH_3CN)(CO)_3(TPPMS)_2]$ was obtained in the reaction of TPPMS and $[W(CH_3CN)_3(CO)_3]$, and was used as catalyst in hydrogenation of benzene in water/heptane biphasic systems [164]. At 100 °C and 70 bar H_2 the catalytic activity was found rather low (average TOF $\approx 1\ h^{-1}$). The same complex is also active in the hydrogenation of olefins (e.g. 1-hexene, 2,3-dimethyl-1-butene).

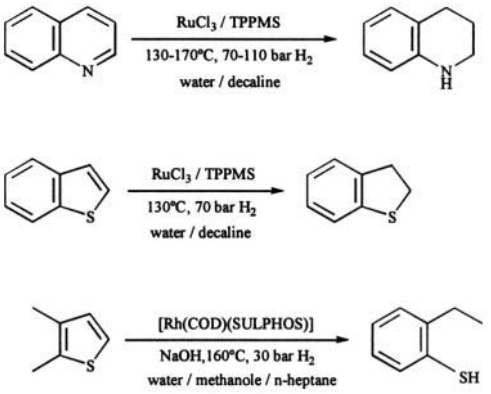
The ion-pairs formed in solutions of Group VIII metal halides and quaternary ammonium salts with long chain substituents can be extracted to organic solvents where they catalyze a range of reactions, such as isomerization, hydrogenation, etc. The $[(C_8H_{17})_3N(CH_3)][RhCl_4(H_2O)_2]$ ion-pair, prepared from $RhCl_3.3H_2O$ and Aliquat-336 actively hydrogenates arenes in water/dichloroethane at 30°C and 1 bar total pressure [165-169]. In water/diethyl ether and in the presence of tertiary amines (e.g. Et_3N) the catalyst shows high activity in reduction of alkenes, nitriles, aldehydes and nitro compounds in addition to that in hydrogenation of aromatics (benzene, toluene, phenol and methyl benzoate) [170]. Hydrated $RuCl_3$ could also be used in place of $RhCl_3.3H_2O$. In the presence of a quaternary ammonium salt, such as $[Bu_4N][HSO_4]$, hydrogenation of $[\{RhCl(1,5\text{-}C_6H_{10})\}_2]$ in aqueous/organic biphasic systems results in a (most probably colloidal) catalyst [171] which was recently used for the hydrogenation of lignin degradation model compounds in water/hexane solutions [172]. As an example, 2,6-dimethoxy-4-propylphenol gave exclusively the all-*cis* diastereomer of 2,6-dimethoxy-4-propylcyclohexanol (Scheme 3.14). Since lignin is produced in huge quantities (estimated approximately 50 million tons annually) as by-products of wood pulping, its chemical conversion to valuable substances is of paramount importance. Stabilized rhodium(0) nanoparticles were also used for the hydrogenation of arenes (phenol, anisole, aniline, ethyl benzoate, allylbenzene, etc.) in aqueous/organic biphasic systems under very mild conditions (20 °C, 1 bar H_2) with 100% conversion to the fuly saturated cyclohexane derivatives [63]. The catalyst could be recycled with an average 2% loss/run in five consecutive runs.



Scheme 3.14

Removal of the sulfur and nitrogen impurities from petroleum products is of major industrial interest and is practiced by using heterogeneous catalysis (HDS- and HDN processes). Considerable efforts have been made recently in order to understand the details of these processes by modelling them in homogeneous solution [173,174]. Biphasic solution catalysis is now viewed as a possible alternative method for desulfurization and denitrogenation of petroleum distillates and intensive studies were done on homogeneous hydrogenation and hydrogenolysis of model compounds such as tiophene, benzo[*b*]tiophene, quinoline, isoquinoline, acridine and similar other substrates.

The ruthenium(II) complexes of TPPMS and TPPTS (prepared in situ) selectively reduced quinoline to 1,2,3,4-tetrahydroquinoline and benzo[*b*]thiophene to 2,3-dihydrobenzo[*b*]tiophene under rather harsh conditions (Scheme 3.15). Chelating nitrogen ligands, such as 2,2`-biquinoline-5,5`-dicarboxylic acid (potassium salt) could also be used, either alone or in combination with the water soluble phosphines [175-177]. Nitrogen bases had a promoting effect on the reduction of thiophenic substrates, too. The rhodium complex of SULPHOS, **31** applied together with a strong Brønsted base, allowed hydrogenolysis of benzo[*b*]thiophene to 2-ethylthiophenol in a liquid biphasic system comprising n-heptane as hydrocarbon phase and water or methanol as polar phases [26,178]. The dimeric complex $[Ru_2(\mu\text{-}Cl)_3(SULPHOS)_2]^+$ was prepared and used as precatalyst in hydrogenation of benzo[*b*]thiophene and quinoline (140 °C, and 30 bar H_2); both substrates were efficiently and selectively reduced to 2,3-dihydrobenzo[*b*]tiophene and 1,2,3,4-tetrahydroquinoline, respectively [179]. The same catalyst is highly active in hydrogenation of various olefins, too. The bidentate phosphine $Na_2DPPPDS$, **182**, was also found to form active catalytic systems with rhodium and ruthenium. At 160 °C the isolated $[Rh(DPPPDS)(H_2O)_2]$ complex catalyzed the hydrogenation of the N-heteroaromatic ring with a TOF of 50 h^{-1}, however, benzo[*b*]tiophene reacted only sluggishly (TOF = 2 h^{-1}) [173].



Scheme 3.15

The SULPHOS-containing rhodium and ruthenium complexes retained their catalytic activity in heteroarene hydrogenation when supported on styrene-divinylbenzene polymer [180] or on silica [181], and showed even higher activity than in homogeneous solution. This effect is attributed to the diminished possibility of dimerization of the active catalytic species to an inactive dimer on the surface of the support relative to the solution phase. The strong hydrogen bonds between the surface OH-groups on silica and the $-SO_3$ substituent in **31** withheld the catalyst in the solid phase despite the rather drastic conditions (100 °C, 30 bar H_2).

In general, it can be concluded, that although a large scale biphasic solution process for hydrodesulfurization and hydrodenitrogenation is not likely to come soon, there are promising results in homogeneous catalysis which can lead to construction of such processes in the future.

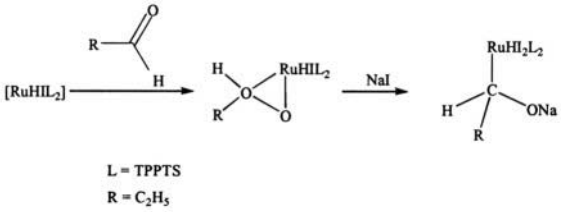
3.3 HYDROGENATION OF ALDEHYDES AND KETONES

Hydrogenation of the carbonyl function is an important synthetic transformation and can be catalyzed by complexes of several transition metals including -among others- Co, Rh, Ru, Ir, and Os. In aqueous organometallic catalysis the first examples were given by the hydrogenation of water-soluble 2-oxo-carboxylic acids, 1,3-dihydroxyacetone and fructose [47-54], later the same substrates were also used for testing new catalysts [29].

Several catalysts have been found to show considerable activity in aqueous systems for hydrogenation of aliphatic and aromatic aldehydes,

such as crotonaldehyde [23,82,186-189,193] propionaldehyde [196-198], 2-pentenal [82], prenal [186-188], citral [186-188,201] and benzaldehyde [82]. The catalysts are listed in Table 3.8 in connection with the hydrogenation of cinnamaldehyde. $[Ir(\eta^5\text{-}C_5Me_5)(H_2O)_3]^{2+}$ catalyzed the hydrogenation of n-butyraldehyde in strongly acidic solution **(TOF_{max} at pH 2.5)** [89]. A fairly recent review is available on homogeneous hydrogenation of aldehydes and aldoses in organic solvents and water [210].

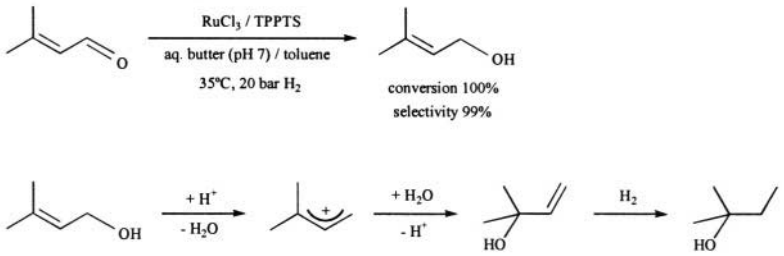
A thorough study of the hydrogenation of propionaldehyde with Ru-TPPTS catalysts, such as $[\{RuCl_2(TPPTS)_2\}_2]$, $[RuH(OAc)(TPPTS)_3]$, $[RuH_2(TPPTS)_4]$, $[RuHI(TPPTS)_3]$ was made by Basset and co-workers [196-198]. The reaction takes place at 100 °C and 50 bar H_2 with TOFs $>300\ h^{-1}$, and with a selectivity to propanol >99 %. A very interesting salt-effect was discovered in that addition of salts accelerated the reduction to a large extent. In the presence of an excess of NaI TOFs $>2000\ h^{-1}$ were determined with all the catalysts listed above. One reason for speeding up the reaction is in the formation of $[RuHI(TPPTS)_3]$ from all the other complexes by ion-exchange with NaI, and in this respect NaI cannot be regarded a "neutral" salt. However, there is a genuine salt effect also, and the efficiency of anions and cations seems to be independent. For a given cation the rate increases in the order: no salt $< SiF_6^{2-} < NO_3^- \ll Cl^- < Br^- < I^-$, while for a given anion the order of the cations is $NR_4^+ \approx Na^+ < Li^+ < K^+ < Mg^{2+} < Ca^{2+}$. It is suggested [196,198] that salts provide an electrophilic assitance for the C-coordination of the aldehyde which leads to higher reaction rates than the O-coordination in the absence of salts (Scheme 3.16). It is also very interesting, that in an aprotic organic solvent, such as tetrahydrofuran, sodium iodide inhibited the catalysis by $[RuCl_2(PPh_3)_3]$ or $[RuClH(PPh_3)_3]$, however, the activity was restored or even enhanced by traces of water. This is yet another example of the effect of the aqueous medium on the mechanism of a transition metal catalyzed reaction.



Scheme 3.16

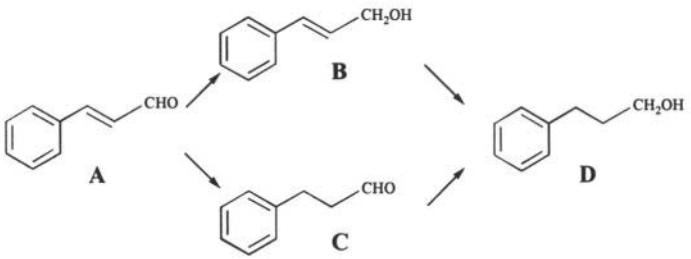
One of the major challenges is the selective hydrogenation of unsaturated aldehydes to unsaturated alcohols which attracted much interest [182]. The highly selective hydrogenation of 3-methyl-2-butenal (prenal) to 3-methyl-2-

butenol (prenol) was achieved with $RuCl_3$ + 4 TPPTS in a biphasic system when the aqueous phase was buffered to pH = 7 with KH_2PO_4/NaOH (Scheme 3.17) [186-188]. In the absence of a suitable buffer (i.e. in slightly acidic solutions) some 2-methylbutan-2-ol (*tert-amyl* alcohol) byproduct was also detected, arising from the acid catalyzed rearrangement of prenol and subsequent hydrogenation.



Scheme 3.17

It is convenient to investigate the selectivity provided by a given catalyst in the hydrogenation of *trans*-cinnamaldehyde (3-phenyl-2-propenal, **A**) which can yield three products: cinnamyl alcohol (3-phenyl-2-propenol, **B**), dihydrocinnamaldehyde (3-phenylpropanal, **C**) and 3-phenylpropanol (**D**) (Scheme 3.18). Data of a few catalytic systems are collected into Table 3.8.



Scheme 3.18

Table 3.8 Catalytic hydrogenation of cinnamaldehyde in aqueous/organic biphasic systems

Catalyst	Conditions	Conv. of **A** %	Product distribution (%) **B**	**C**	**D**	Ref.
$[RuCl_2(CH_3CN)_4]$ +	100 °C, 18 bar H_2, 8 h					
TPPMS	S/C = 100	87	24	26	50	[183]
	S/C = 25	90	90			
	0.2 M Na_2SO_4, S/C=50	100	100			
$[OsCl_2(CH_3CN)_4]$ +	100 °C, 18 bar H_2, 8 h	16	25	56	19	[183]

Catalyst	Conditions	Conv. of A %	Product distribution (%) B	C	D	Ref.
TPPMS	S/C = 100					
$[RuClH(CO)(TPPMS)_3]$	80-120 °C, 3-31 bar H_2, 8 h, water/toluene	70 [a]	43	14	43	[184]
$[RuClH(CO)(TPPTS)_3]$	80-120 °C, 3-31 bar H_2, 8 h, water/toluene	70 [a]	40	30	30	[184]
$[\{RuCl_2(TPPMS)_2\}_2]$	100 °C, 30 bar H_2, 3 h [P]/[Ru]=6, S/C=100	26	83	15	2	[185]
$[\{RuClH(TPPMS)_2\}_2]$	100 °C, 30 bar H_2, 3 h [P]/[Ru]=6, S/C=100	68	54	19	27	[185]
$[\{OsCl_2(TPPMS)_2\}_2]$	100 °C, 30 bar H_2, 14 h [P]/[Os]=6, S/C=100	6	100			[185]
$[OsH_4(TPPMS)_3]$	100 °C, 30 bar H_2, 3 h [P]/[Ru]=6, S/C=100	40	68	11	21	[185]
$[OsClH(TPPMS)_2]$	100 °C, 30 bar H_2, 6 h [P]/[Ru]=6, S/C=100	58	60	18	22	[185]
$RuCl_3$.aq + 3 TPPTS	35 °C, 20 bar H_2, 3 h S/C=200, water/toluene	99	98			[186] [187]
$RuCl_3$.aq + 4.5 TPPTS	35 °C, 20 bar H_2, 3 h S/C=135 buffer (pH=7)/toluene	99	99			[188]
$RuCl_3$.aq + 5 TPPTS	40 °C, 20 bar H_2, 3 h	81	96	2	2	[189]
$[\{RuCl_2(TPPTS)_2\}_2]$	S/C=200, water/toluene	14	91	9	0	
$[\{RuCl_2(TPPTS)_2\}_2]$	water/Et_2O	26	93	7	0	
$[RuClH(TPPTS)_3]$		73	96	1	3	
$[RuH_2(TPPTS)_4]$		97	95	2	3	
$[RuH(tol)(TPPTS)_2]Cl$ [b]	water/Et_2O	-	-	-	-	
$[Ru(OAc)(TPPTS)_3]$		92	96	0	4	
$[\{RuCl_2(TPPMS)_2\}_2]$	80 °C, H_2, P_{total} = 1 bar [P]/[Ru]=5, S/C=24 phosphate buffer/ chlorobenzene					[190] [191]
	pH = 3	11	18	82	0	
	pH = 8	100	100	0	0	
$[RuCl_2(pTPPMS)_4]$ [c]	80 °C, H_2, P_{total} = 1 bar [P]/[Ru]=6, S/C=54, aq. HCl or KOH/ chlorobenzene, 4 h					[192]
	pH = 1		0	98	0	
	pH = 13		100	2	0	
$[PdCl_2(TPPTS)_2]$	90 °C, 20 bar H_2, 1h water/benzene					[193]
	pH=12.2 (Na_2CO_3)	93.2		91		
	pH=12.2 (NaOH)	99.8		69		
$[Ir(COD)\{P(CH_2OH)_3\}_3]$ Cl	125 °C, 90 bar H_2, 24 h water/benzene [P]/[Ir]=8, S/C=500	97	97	2	0.3	[194]

Catalyst	Conditions	Conv. of A %	Product distribution (%) B	C	D	Ref.
$[Ru(6,6`Cl_2bpy)_2(H_2O)_2](CF_3SO_3)_2$	130 °C, 40 bar H_2, 4 h water/toluene S/C=1000	48	71	17	12	[82]

[a] estimated from the graphs in original publication, b) tol = η^6-$C_6H_5CH_3$, [c] pTPPMS = $Ph_2P(C_6H_4$-4-$SO_3Na)$, **4**

Although it is not easy to make direct comparisons of the systems of Table 3.8, it may be concluded that osmium complexes are less active catalysts of aldehyde hydrogenations than the corresponding Ru-compounds. Ru-carbonyl derivatives are also less active, than the ones without CO. The effect of pH is particularly important, since it can completely reverse the selectivity from 100% selective C=C hydrogenation in acidic solutions to 100% C=O hydrogenation under alkaline conditions [190-192]. The effect is very pronounced at 1 bar H_2 and less obvious at elevated pressure This phenomenon was studied in much detail by pH-potentiometric, ^1H and ^{31}P NMR and kinetic methods. It was established, that upon increasing the pH of a solution containing $[\{RuCl_2(TPPMS)_2\}_2]$ and excess TPPMS the following reactions took place under H_2:

$$[\{RuCl_2(TPPMS)_2\}_2] + H_2 \rightleftharpoons [\{RuClH(TPPMS)_2\}_2] + H^+ + Cl^- \quad (3.7)$$

$$\tfrac{1}{2}[\{RuCl_2(TPPMS)_2\}_2] + TPPMS + H_2 \rightleftharpoons [RuClH(TPPMS)_3] + H^+ + Cl^- \quad (3.8)$$

$$[RuClH(TPPMS)_3] + TPPMS + H_2 \rightleftharpoons [RuH_2(TPPMS)_4] + H^+ + Cl^- \quad (3.9)$$

Since all three reactions result in proton formation (which could be followed at any *constant* pH by using a pH-static titration apparatus [191]) the equilibria can be displaced to the right by increasing basicity of the solution until at high pH $[RuH_2(TPPMS)_4]$ becomes the sole observable Ru-hydride. The distribution of these hydride species, based on the integrated intensities of signals in the relevant ^1H and ^{31}P NMR spectra is shown on Figure 3.3. Assuming that $[RuClH(TPPMS)_3]$ is a good catalyst for C=C hydrogenation (which it is, indeed, see [53]) and a less active one for C=O, and that $[RuH_2(TPPMS)_4]$ hydrogenates aldehydes efficiently (as found with the TPPTS analogue by Hernandez and Kalck [189]), it is understandable, that a switch of the hydride composition of a Ru-TPPMS solution caused by the increase of its pH will result in a switch from selective C=C to selective C=O hydrogenation.

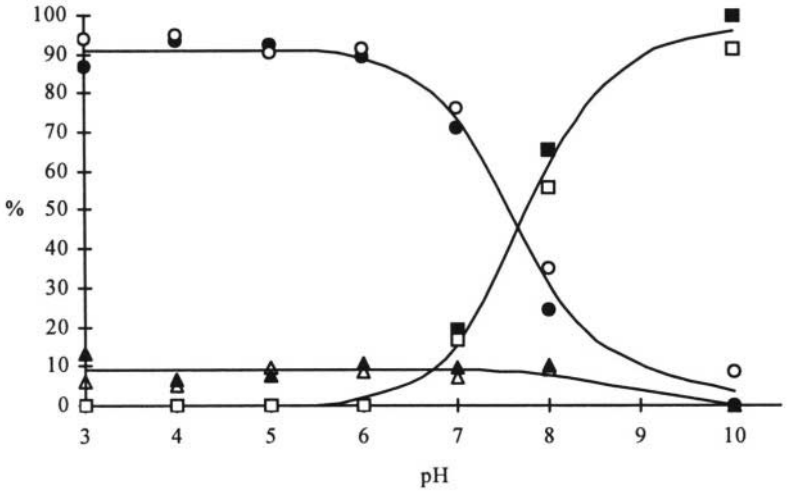


Figure 21. Distribution of water-soluble ruthenium(II)-hydrides as a function of pH, based on the avarage of ^{1}H and ^{31}P NMR integrated intensities. ■ [HRuCl(TPPMS)$_3$], ♦ [H_2Ru(TPPMS)$_4$], ● [HRuCl(TPPMS)$_2$]$_2$. [Ru]=2.4 x 10^{-2} M, [TPPMS]=7.2 x 10^{-2} M, 0.2 M KCl, 50°C, H_2, P_{total}=1 bar. Reprinted with permission from *Angew. Chem. Int. Ed.* **1998**, *37*, 969. Copyright (1998) Wiley-VCH Verlag GmbH.

It is also seen from Table 3.8, that with the various Ru-phosphine complexes as catalysts allowing high conversions of cinnamaldehyde at 35-120 °C under 20-30 bar H_2, in many cases water/toluene or water/benzene mixtures were used as solvent. Here the interesting point is in that in the absence of excess phosphine, arenes react the following way:

$$\tfrac{1}{2}[\{RuCl_2(TPPTS)_2\}_2] + \text{arene} + H_2 \rightleftharpoons [RuH(\eta^6\text{-arene})(TPPTS)_2]Cl + \\ + H^+ + Cl^- \qquad (3.10)$$

Such complexes of toluene, benzene, p-xylene, ethylbenzene, cumene, tetraline, dihydrocinnamyl alcohol and *cis*-cinnamyl alcohol were isolated and thouroughly characterized by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy [195]. They are formed easily also from [RuH(OAc)(TPPTS)$_3$] but not at all from [RuH_2(TPPTS)$_4$]. These complexes are suprisingly stable, e.g. the arene is displaced by CO only at 90 °C, and a reaction with $NaBH_4$ yields [RuH_2(TPPTS)$_4$] only slowly. Furthermore, [RuH(η^6-$C_6H_5CH_3$)(TPPTS)$_2$]Cl proved completely *inactive* for cinnamaldehyde hydrogenation in water/diethylether, despite that Et_2O did not decrease (in fact: slightly increased) the rate of the same reaction relative to a water/toluene mixture when catalyzed by [{$RuCl_2$(TPPTS)$_2$}$_2$] (see Table 3.8). The most likely

process, which can remove this apparent contradiction is the gradual transformation of all $[RuH(\eta^6\text{-arene})(TPPTS)_2]Cl$ (arene = toluene and/or cinnamaldehyde) under hydrogenation conditions to $[RuH_2(TPPTS)_4]$, which in turn catalyzes the reduction of cinnamaldehyde to cinnamyl alcohol. There are no direct observations on the replacement of toluene by cinnamaldehyde in the $Ru\text{-}\eta^6\text{-}C_6H_5CH_3$ complexes, but the remarkable changes in the selectivity as a function of the substrate/catalyst ratio (Table 3.8) tell about a strong interaction of the substrate (either as an arene, or through the aldehyde oxygen, or both) and the catalyst Ru-phosphine complex. (In a homogeneous organic solution a substrate inhibition is observed [202].)

Putting all evidence together, it is most likely, that from among the water-soluble Ru-tertiary phosphine complexes the active catalytic species for aldehyde reduction is $[RuH_2P_4]$ (P = TPPTS, TPPMS or *para*-TPPMS), formed in neutral or alkaline aqueous solutions. The extent to which $[RuH_2(PTA)_4]$ (PTA = 82) is produced under H_2 in aqueous solutions of $[RuCl_2(PTA)_4]$ is only a few per cent even at 80 °C and $p(H_2) = 60$ bar [203], hence the feeble activity of $[RuCl_2(PTA)_4]$ for aldehyde hydrogenation at low pressure [204].

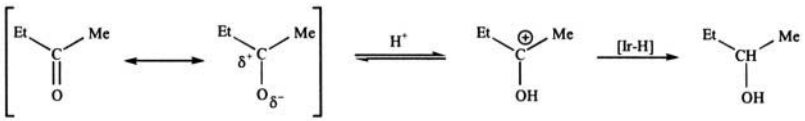
It is to be mentioned that water-soluble phosphine complexes of rhodium(I), such as $[RhCl(TPPMS)_3]$, $[RhCl(TPPTS)_3]$, $[RhCl(PTA)_3]$, either preformed, or prepared in situ, catalyze the hydrogenation of unsaturated aldehydes at the C=C bond [187, 204, 205]. As an example, at 80 °C and 20 bar H_2, in 0.3-3 h cinnamaldehyde and crotonaldehyde were hydrogenated to the corresponding saturated aldehydes with 93 % and 90 % conversion, accompanied with 95.7 % and 95 % selectivity, respectively. Using a water/toluene mixture as reaction medium allowed recycling of the catalyst in the aqueous phase with no loss of activity.

It is interesting to note that no specific study was devoted to the aqueous biphasic hydrogenation of aldehydes with water-soluble cobalt-phosphine complexes, although such a property has long been known from hydroformylation experiments [199,200].

Surprisingly, there are only a few catalysts known capable of hydrogenating *ketones* in fully or largely aqueous systems. For example, most of the water-soluble rhodium, ruthenium and indium phosphine complexes preferentially hydrogenate the C=C bonds in unsaturated ketones, as does the solvated ion pair formed from aqueous rhodium trichloride and Aliquat-336 [206].

2-Butanone was hydrogenated by $[Ir(\eta^5\text{-}C_5Me_5)(H_2O)_3]^{2+}$ in strongly acidic solution (25 °C, 5 bar H_2, TOF_{max} at pH 2.5) [89]. At higher pH the Ir-catalyst dimerizes to an inactive species. It was speculated, that the strongly acidic medium assisted the formation of an intermediate carbocation which

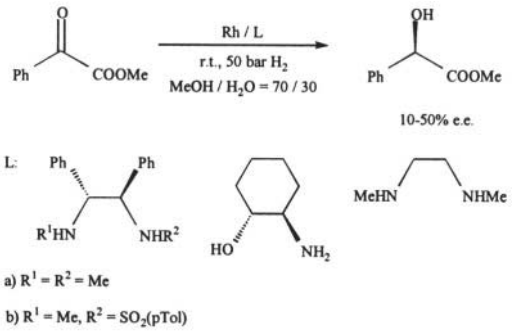
is favourable for the transfer of hydride from a putative iridium-hydride intermediate (Scheme 3.19).



Scheme 3.19

N-donor ligands play a successful role in reduction of ketones by hydrogen transfer (see 3.5) and this prompted their use in hydrogenation reactions as well. *cis*-$[Ru(6,6`\text{-}Cl_2bpy)_2(H_2O)_2](CF_3SO_3)_2]$ (6,6`- Cl_2bpy = 6,6`-dichloro-2,2`-bipyridine) catalyzed the hydrogenation of acetophenone and benzophenone to 1-phenylethanol and benzhydrol, respectively (130 °C, 40 bar H_2, S/C=1000, 85% and 46% yield), however, reaction of α,β-unsaturated ketones (e.g. benzylidenacetone and benzylidenacetophenone) resulted in exclusive C=C hydrogenation [82].

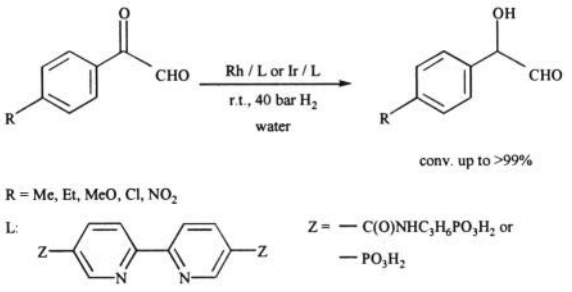
Hydrogenation of methyl phenylglyoxylate with Rh-, Ir- and Pd-based catalysts containing chelating diamine ligands was studied in methanol and in MeOH/H_2O mixtures. High conversions (95-100%) could be achieved in 15-20 h (r.t., 50 bar H_2), however the enantioselectivity was only modest (e.e. 10-50 %). Even that was diminished in MeOH/H_2O 70/30. However, addition of β-cyclodextrin improved the yield and restored the e.e. up to the value observed in MeOH (Scheme 3.20) [207].



Scheme 3.20

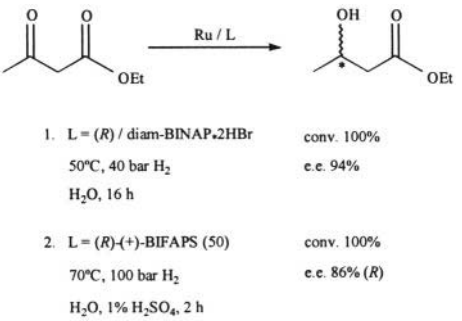
Water-soluble functionalized 2,2`-bipyridine ligands, carrying sodium phosphonate substituents were prepared. Their Rh- and Ir-complexes showed remarkable catalytic activity [208] in the hydrogenation of various

acetophenones in water under H_2 pressure (Scheme 3.21). Addition of a base (NaOH, 5-30 equivalents to Rh or Ir) accelerated the reaction. Some of these catalyst proved rather stable.



Scheme 3.21

Reaction of the hydrobromide of 6,6`-dimethylamino-BINAP (*diam*-BINAP) with $[Ru(\eta^3\text{-2-methylallyl})_2(\eta^2\text{-COD})]$ afforded a water soluble Ru-catalyst which proved active and highly enantioselective [209] in the hydrogenation of ethyl acetoacetate (Scheme 3.22). The catalyst could be recycled in the aqueous phase several times.

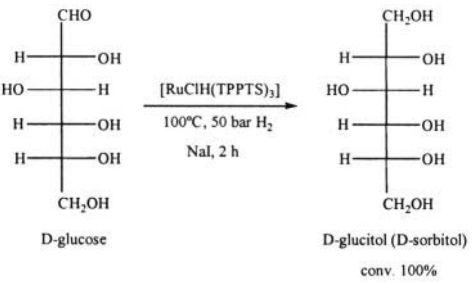


Scheme 3.22

Hydrogenation of methyl acetoacetate was successfully carried out in water catalyzed by a complex obtained in situ from $[\{RuCl_2(benzene)_2\}_2]$ + (*R*)-(+)BIFAPS (**50**) (Scheme 3.22). Spectacular effects of small amounts of added HCl or H_2SO_4 were found: under comparable conditions the conversion increased from 58% to 100% and the e.e. from 22% to 86% [111]. The origin of this effect of acids is unclear; it was speculated that

acids probably prevent formation of catalytically inactive trinuclear ruthenium complexes, however, no experimental evidence was mentioned.

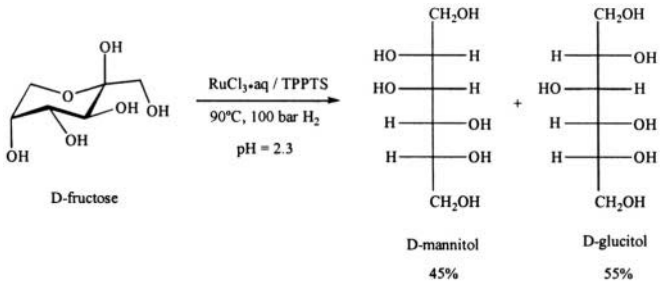
Synthetic transformations of *carbohydrates* draw much attention recently since these materials are available in enormous quantities from renewable sources. For solubility reasons it is very straightforward to use aqueous solutions for such processes. The first attempts on hydrogenation of carbohydrates [49] used $[RuClH(TPMS)_3]$ as catalyst which allowed hydrogenation of 1,3-dihydroxyacetone with a $TOF = 60\ h^{-1}$, and that of fructose with a $TOF = 5\ h^{-1}$ (60 °C, 0.8 bar H_2, solvent 0.1 M HCl). Later a detailed comparative study of hydrogenation of the epimeric aldoses D-glucose and D-mannose to D-sorbitol (D-glucitol) and D-mannitol (of which the latter is the more valuable product) was undertaken [211] with the aim to find suitable conditions under which hydrogenation could be run in the same pot with the ammonium heptamolybdate-catalyzed epimerization [212] of D-glucose to D-mannose. In principle, under ideal conditions, all D-glucose could be utilized for production of D-mannitol in such a combined process. In fact, $[RuClH(TPPTS)_3]$ was found effective for the hydrogenation of these aldoses at 100 °C and 50 bar H_2 (Scheme 3.23). D-mannose reacted faster and the reaction was accelerated by NaI, probably by the same mechanism what was suggested for the hydrogenation of propionaldehyde (vide supra). However, at the optimal pH of epimerization (pH 2.5) this hydrogenation process proved too slow for practical purposes.



Scheme 3.23

In a similar study, Sheldon et al. investigated in detail the hydrogenation of fructose [213]. Hydrolysis of inulin, a polysaccharide containing one D-glucose and 10-50 D-fructose units could supply a more attractive feedstock for D-mannitol than the 1:1 mixture of D-glucose and D-fructose (obtained from sucrose) presently used. A Ru(II)/TPPTS catalyst, prepared in situ from hydrated $RuCl_3$ and TPPTS was effective for the hydrogenation of inulin, D-fructose and D-glucose at 90 °C, 100 bar H_2, [TPPTS}/[Ru] = 4.8,

pH = 2.3 (Scheme 3.24). With most heterogeneous catalysts the selectivity of the hydrogenation of D-fructose to D-mannitol is about 45 % (the other major product is D-glucitol) and this was also observed with Ru-TPPTS. However, in combined experiments of hydrolysis + hydrogenation of inulin at **pH = 3.3** the [D-mannitol]/[D-glucitol] ratio was higher than in case of D-fructose itself which may show that the stereoselectivity of the hydrogenation of D-fructose units in partially hydrolyzed inulin is higher than in monomeric form.



Scheme 3.24

It is worth mentioning, that the initial rate of the hydrogenation of D-glucose was approximately 2.5 times lower than that of D-fructose. Besides that, in a competition experiment D-glucose inhibited the hydrogenation of D-fructose [213]. The inhibitory effect of D-glucose had also been observed on hydrogenation of aqueous phospholipid dispersions (model membranes) with $[\{RuCl_2(TPPMS)_2\}_2]$ and $[RhCl(TPPMS)_3]$ catalysts, therefore all samples of biological origin had to be hydrogenated in glucose-free culture media [214]. Such a possible inhibition is a very important point to be considered in hydrogenation of mixtures of carbohydrates from natural sources.

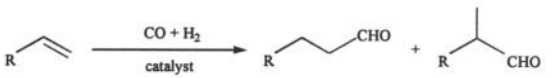
Metal complex catalyzed hydrogenations by an *ionic mechanism* would require the metal complex be capable of reacting with H_2, then delivering in a stepwise manner H^+ followed by H^- to a coordinated C=E double bond (C = C, O, N). Metal hydrides are known to function as proton donors, and cationic metal hydrides and dihydrogen complexes can be especially acidic [216,217]. Stoichiometric metal-mediated ionic hydrogenations of ketones [218,219], alkenes [220] and alkynes [221] in non-aqueous solutions have been reported. In CH_2Cl_2 solution $[WH(\eta^5\text{-}C_5H_5)(CO)_2(PPh_3)]$ reacted with $Ph_3C^+BAr_4'^-$ [Ar′ = 3,5-bis(trifluoromethyl)phenyl] and in the presence of 3-pentanone $[W(\eta^5\text{-}C_5H_5)(CO)_2(PPh_3)(\eta^1\text{-}O{=}CEt_2]BAr_4'^-$ could be isolated [222]. This complex proved to be a catalyst for the hydrogenation of 3-pentanone under 4 bar H_2 albeit of low activity (6 turnovers in a month!).

Chapter 4

Hydroformylation

4.1 Introduction

In today`s industry, hydroformylation is the largest volume homogeneous catalytic process employing organometallic catalysts [1]. The simplest representation of this process (Scheme 4.1) is the reaction of a terminal alkene with CO and H_2 to afford linear and branched aldehydes.



Scheme 4.1

n-Butyraldehyde is produced for manufacturing 2-ethylhexanol used on large scale as an additive in plastics industry. Therefore the straight chain product of propene hydroformylation (linear aldehyde) is more valuable than iso-butyraldehyde, although the branched isomer, as well, has a smaller but constant market. The selectivity of a catalyst towards the production of linear aldehyde is usually expressed as the n/i or l/b ratio. It is mentioned, though, that there are reactions, in which the branched product is the more valuable one, as is the case of the hydroformylation of styrene.

There is no need to treat here the basic chemistry of hydroformylation in much detail since these days it is covered by inorganic chemistry or catalysis courses at universities [2,3], moreover, there are numerous recent books devoted partly or entirely to hydroformylation; references [1-8] represent only a selection and many other would deserve mentioning. For this reason the details, not directly relevant to aqueous organometallic chemistry will be kept to a minimum.

Following O. Roelen`s original discovery in 1938, hydroformylation (the oxo-process) employed cobalt carbonyls as catalyst, which later became "modified" with tertiary phosphines, e.g. with P^nBu_3 (Shell, 1964). The modified cobalt catalyst allowed reactions run at lower temperature and pressure, but still suffered from rather low n/i selectivity. The next fundamental step in developing a less expensive and more selective way of industrial hydroformylation was the introduction of rhodium-phosphine catalysts in the mid-nineteen seventies, which allowed milder conditions and brought about high selectivity towards the linear product. It is now firmly established, that the two key catalytic species in the rhodium-catalyzed hydroformylation processes are the coordinatively unsaturated complexes $[RhH(CO)(PPh_3)_2]$ and $[RhH(CO)_2(PPh_3)]$. It is also generally accepted, that the n/i ratio of the resulting aldehydes is controlled by the concentration ratio of these two rhodium species, i.e. the more $[RhH(CO)(PPh_3)_2]$ is formed during catalysis relative to $[RhH(CO)_2(PPh_3)]$ the higher is the linear/branched selectivity. This is one of the reasons a high phosphine excess is needed for good linearity of the product aldehydes. The very mild conditions (120 °C, 30 bar $CO:H_2 = 1:1$, i.e. syngas) made possible by the $[RhH(CO)(PPh_3)_3]$ catalyst, eliminated most of the side-reactions (aldol-type condensations). However, with all three basic variants of industrial hydroformylation, the metal complex catalyst (plus the excess of phosphine) was dissolved in a common liquid phase together with the substrate and products. Special processes of catalyst recovery had to be operated and acocrding to some procedures the catalysts were oxidized and extracted into an aqueous phase as metal salts. In addition, the final aldehyde mixture had to be purified from the remaining alkene and phosphine by distillation, leading to further side reactions. Obviously, on the industrial scale significant loss of rhodium during catalyst recovery and recycling cannot be tolerated.

The idea of recovering the catalyst without distillation or destructive methods had surfaced rather early (1973) in connection with the phosphine-modified cobalt catalysts. Tris(aminoalkyl)phosphine complexes were examined as catalysts which were extracted from the product mixture without decomposition by an aqueous acid wash, and could be reextracted to the organic (reaction) phase after neutralization [9,10]. Although the feasibility of the method was demonstrated, perhaps the economic advantages of a better catalyst recovery were insufficient in the light of the relatively low cobalt price. It was in 1975 that Rhône Poulenc patented the process of aqueous/organic biphasic hydroformylation of olefins using the trisulfonated triphenylphoshine ligand, TPPTS, which later led to the development of the widely known Ruhrchemie-Rhône Poulenc process of propene hydroformylation.

With a water-soluble hydroformylation catalyst the overwhelming majority of the reactions take place in an aqueous/organic biphasic mixture for the simple reason of most olefins being insoluble in water. Research in aqueous organometallic hydroformylation is therefore directed to several aims:

- design and synthesis of new catalysts with improved *chemical* properties (activity, selectivity, stability)
- design and synthesis of new ligands and catalysts with improved *physical* properties (water solubility, distribution between the aqueous and organic phases, possibility to manipulate solubility properties by temperature variation, surface activity, etc.)
- *engineering* aspects (facilitating mass transport between the two phases, interphase engineering, volume ratio of aqueous to organic phase, continous or occasional counterbalancing of catalyst degradation, separation by membrane technics, etc.)
- use of *additives* to improve the catalysts` properties or engineering factors.

During the years many studies were directed to find optimal catalysts and conditions for aqueous (or aqueous/organic biphasic) hydroformylation. By nature of research, not all of them led to industrial breakthroughs but all contributed to the foundations of today`s practical processes and future developments. These investigations will not be treated in detail, however, a selection of them is listed in Table 4.1.

Table 4.1. Hydroformylation in aqueous/organic biphasic systems

Catalyst	Substrate	Ref.
$[RhH(CO)(TPPMS)_3]$, $[RuClH(TPPMS)_3]$	1-hexene	[36]
$[RhH(CO)(PPh_3)(\mathbf{67})_2]$	1-hexene	[37]
$[RhH_2(\mathbf{60})_2]$	1-hexene	[38]
$[Co(CO)_3(\mathbf{60})_2](PF_6)_2$	1-hexene	[39]
$[Ru(EDTA)(H_2O)]^-$	1-hexene	[40]
$[Rh(acac)(CO)_2]$ + **34**	1-octene	[41]
$[\{RhCl(CO)_2\}_2]$ + **158**	1-hexene	[42]
$[\{RhCl(COD)\}_2]$ + **54** or **57**	1-octene, styrene	[43]
$[Rh(acac)(CO)(PR_3)]$, PR_3: **3**, **58** or **82**	1-hexene	[44]
$[RhI(CO)(\mathbf{82}.MeI)_3]$, $[RhI(CO)(\mathbf{82}.EtI)_3]$	1-hexene	[45]
$[Rh(acac)(CO)_2]$ + **25**	1-hexene	[46]
$[RhH(CO)(\mathbf{119})]$	1-hexene	[47]
$[Rh(OAc)_3]$ + **121**	1-octene	[48]
$[\{RhCl(COD)\}_2]$ + $AgBF_4$ + **125**	1-heptene, 1-octene, styrene, allylbenzene allylphenyl ether	[49]
$[RhCl_3]$ + TPPTS	1-hexene to 1-hexadecene	[50]
$[RhH(CO)(TPPMS)_3]$	styrene	[51]
$[Ru_3(CO)_9(TPPMS)_3]$	ethene, propene	[52,53]

There are many reviews covering the field [1-31] and some of them are really authentic with regard to the industrial realization of aqueous/organic biphasic hydroformylation. The annual reviews on hydroformylation [32] also give more and more space to the biphasic oxo-reaction. It is appropriate to mention here, however, that aqueous organometallic hydroformylation covers more than the Ruhrchemie-Rhône Poulenc process, and offers a good chance to probe ideas on catalyst synthesis, catalyst recovery and reaction engineering in general.

4.2 Rhodium-catalyzed biphasic hydroformylation of olefins. The Ruhrchemie-Rhône Poulenc process for manufacturing butyraldehyde

In 1975 Kuntz has described that the complexes formed from various rhodium-containing precursors and the sulfonated phosphines, TPPDS (**2**) or TPPTS (**3**) were active catalysts of hydroformylation of propene and 1-hexene [15,33] in aqueous/organic biphasic systems with virtually complete retention of rhodium in the aqueous phase. The development of this fundamental discovery into a large scale industrial operation, known these days as the Ruhrchemie-Rhône Poulenc (RCH-RP) process for hydroformylation of propene, demanded intensive research efforts [21,28]. The final result of these is characterized by the data in Table 4.2 in comparison with cobalt- or rhodium-catalyzed processes taking place in homogeneous organic phases.

Table 4.2. Characteristic data of the RCH-RP process [1,6-8,26]

Conditions and products	Typical value
Temperature	125 °C
Pressure of synthesis gas	50 bar
Volume water/volume organics	6
[TPPTS]/[Rh]	≥ 60
Heat recovery	99 %
Conversion	99 %
Selectivity towards C4 aldehydes	95 %
n-Butanal	95 %
i-Butanal	4.5 %
n/i selectivity	19
E-factor	0.04

The process itself is stunningly simple [1, 6-8]. Propene and syngas are fed to a well stirred tank reactor containing the aqueous solution of the

catalyst. By the time the organic phase leaves the reactor conversion of propene is practically complete. Part of the reaction mixture is continously transferred to a separator where the organic and aqueous phases are separated, and the aqueous catalyst solution is taken back to the reactor. The organic phase is stripped with fresh synthesis gas and finally the the product is fractionated to n- and iso-butyraldehyde.

The first plant of 100.000 t/year capacity in Oberhausen, Germany started operation in 1984. The capacity at that site (now belonging to Celanese AG) has been expanded and today, together with the production of a new plant in South Korea, the amount of butyraldehyde manufactured by the RHC-RP process totals around 600.000 t/year. The average results of fifteen years of continous operation show that for Celanese, using an own technology (i.e. no license fees have to be paid) the overall manufacturing costs are about 10 % less for the aqueous/organic biphasic process than for a classical rhodium-phosphine catalyzed homogeneous hydroformylation. An additional environmental benefit is in the reduced amount of byproducts and wastes characterized by the low E-factor of 0.04 (ratio of byproducts to the desired product(s), weight by weight [59]), which at some point becomes an economic benefit, too. All the experience gained since 1984 confirm that even large scale industrial processes can be based on (biphasic) aqueous organometallic catalysis.

There are many important points and lessons to be learned from the development and operation of the Ruhrchemie-Rhône Poulenc process and we shall now have a look at the most important ones.

The *mutual solubility* of the components of the reaction mixture in each other is the Alpha and Omega of the development of a biphasic system. The *distribution of the catalyst* within the aqueous/organic mixture defines the concentration of rhodium carried away from the reactor in the product stream. Was this concentration high (above *ppb* level) it would mean a serious economic drawback due to loss of an expensive component of the reaction system. In addition, the product would have to be purified from traces of the catalyst. The same is true for the *distribution of the ligand*, especially when a high ligand excess is required, which is the case with the rhodium-phosphine catalyzed hydroformylation. The need for a high phosphine excess can be satisfied only with ligands of sufficiently high absolute *solubility*. The choice of trisulfonated triphenylphosphine seems to be the best compromise of all requirements. TPPTS has an enormous solubility in water (1100 g/L [7]), yet it is virtually insoluble in the organic phase of hydroformylation due to its high ionic charge. For the same reason, TPPTS has no surfactant properties which could lead to solubilization of hidrophilic components in the organic phase. (This is also important from engineering points of view: surfactants may cause frothing

and incomplete phase separation during the workup procedure.) Consequently, TPPTS stays in the aqueous phase and at the same time it is able to keep all rhodium there. It is also expected on these grounds, that any products of catalyst/ligand *degradation* will have a preferential solubility in water. It is worth comparing these properties of TPPTS and TPPMS. Monosulfonated triphenylphosphine has a much lower solubility in water (12 g/L [55]). In addition, TPPMS is a pronounced surfactant [56], which may be beneficial for the mass transport between the phases (see later) but certainly diadvantageous in phase separation. From the solubility side and in principle, the same is true for any surfactant in the system, be it a specifically designed surfactant phosphine ligand [30,57] or special additives [16,58]. In practice, phase separation difficulties and minute losses of catalyst may go unnoticed or may be tolerable in laboratory experiments but could cause serious problems on larger scale.

Solubility of the reactants and products in the catalyst-containing aqueous phase is another factor to be considered. The solubility of >C3 terminal olefins rapidly decreases with increasing chain length [7] as shown in Table 4.3. The solubility data in the middle column of Table 4.3 refer to room temperature, therefore the values for ethene through 1-butene show the solubility of *gases,* while the data for 1-pentene through 1-octene refer to solubilities of *liquids.* For comparison, the solubilities of liquid propene and 1-butene are also shown (third column), these were calculated using a known relation between aqueous solubility and molar volume of n-alkenes [60].

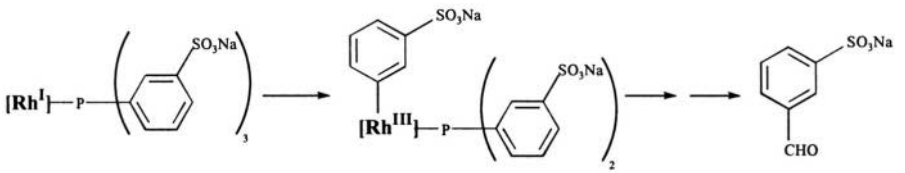
Table 4.3. Solubility of n-alkenes in water [60]

Alkene	Solubility at room temperature/ppm	Calculated solubility of liquid alkane at 25 °C/ppm
Ethene	131	
Propene	200	2040
1-Butene	222	615
1-Pentene	148	
1-Hexene	50	
1-Octene	2.7	

The consequence of low alkene solubility is in that industrially the RCH-RP process can be used only for the hydroformylation of C2-C4 olefins. In all other cases the overall production rate becomes unacceptably low. This is what makes the hydroformylation of higher olefins one of the central problems in aqueous/organic biphasic catalysis. Many solutions to this problem have been suggested (some of them will be discussed below), however, any procedure which increases the mutual solubility of the organic components and the aqueous ingredients (co-solvents, surfactants) may

threaten the complete recycling of rhodium. Interestingly, although the solubility of ethene is high enough for an effective hydroformylation with the $[RhH(CO)(TPPTS)_3]$ catalyst dissolved in water, propanal is not produced by this method. The reason is in that propanal is fairly miscible with water. Consequently, the water content of the product has to be removed by distillation, moreover, the wet propanal dissolves and removes some of the catalyst out of the reactor, necessitating a tedious catalyst recovery. This calls attention to the importance of the *solubility of water* in the organic phase (and not only vice versa). It is also good to remember, that mutual solubilities of the components of a reacting mixture may change significantly with increasing conversion.

Formation of the catalyst and catalyst *degradation* are also important questions. The rhodium-TPPTS catalyst is usually pre-formed from Rh(III)-precursors, e.g. Rh(III)-acetate, in the presence of TPPTS with synthesis gas under hydroformylation conditions. During this process the precursors are transformed into the Rh(I)-containing catalyst, $[RhH(CO)(TPPTS)_3]$. Catalyst degradation during hydroformylation arises from side reactions of TPPTS leading to formation of phosphido-bridged clusters, inactive in catalysis. Oxidative addition of a coordinated phosphine ligand onto the rhodium leads to formation of a phosphidorhodium(III)-aryl intermediate which under hydroformylation conditions yields 2-formyl-benzenesulfonic acid (Scheme 4.2). In fact, the *meta*-position of the formyl and sulfonate groups in the product gives evidence in favour of this route as opposed to *ortho*-metallation [23].



Scheme 4.2

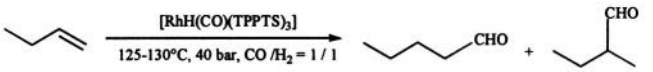
TPPTS is periodically added to the reactor in order to keep the catalyst activity above a technologically desired value, but when it still declines below that then the whole aqueous phase is taken out of the reactor and replaced by a fresh aqueous solution of $[RhH(CO)(TPPTS)_3]$ and TPPTS. The spent catalyst solution is then worked up for rhodium and for the non-degraded part of TPPTS.

When working with aqueous solutions one always has to keep in mind the possible effects of H^+ or OH^-. This is the case here, as well. The pH of the solutions has to be controlled to avoid side reactions of the product

aldehydes. Equally important is the fact, that the catalyst is also influenced by changes in the pH - this will be discussed in 4.1.4. For this reason the pH of the aqueous phase in the RCH-RP process is kept between 5 and 6.

4.3 Aqueous/organic biphasic hydroformylation butenes and other alkenes

The only other olefin feedstock which is hydroformylated in an aqueous/organic biphasic system is a mixture of butenes and butanes called raffinate-II [8,61,62]. This low-pressure hydroformylation is very much like the RCH-RP process for the production of butyraldehyde and uses the same catalyst. Since butenes have lower solubility in water than propene, satisfactory reaction rates are obtained only with increased catalyst concentrations. Otherwise the process parameters are similar (Scheme 4.3), so much that hydroformylation of raffinate-II or propene can even be carried out in the same unit by slight adjustment of operating parameters.



Scheme 4.3

Raffinate-II typically consists of 40 % 1-butene, 40 % 2-butene and 20 % butane isomers. [RhH(CO)(TPPTS)$_3$] does not catalyze the hydroformylation of internal olefins, neither their isomerization to terminal alkenes. It follows, that in addition to the 20 % butane in the feed, the 2-butene content will not react either. Following separation of the aqueous catalyts phase and the organic phase of aldehydes, the latter is freed from dissolved 2-butene and butane with a counter flow of synthesis gas. The crude aldehyde mixture is fractionated to yield n-valeraldehyde (95 %) and isovaleraldehyde (5 %) which are then oxidized to valeric acid. Esters of n-valeric acid are used as lubricants. Unreacted butenes (mostly 2-butene) are hydroformylated and hydrogenated in a high pressure cobalt-catalyzed process to a mixture of isomeric amyl alcohols, while the remaining unreactive components (mostly butane) are used for power generation. Production of valeraldehydes was 12.000 t in 1995 [8] and was expected to increase later.

Hydroformylation of higher olefins provide long chain alcohols which find use mainly as plasticizers. No aqueous/organic biphasic process is operated yet for this reaction, for several reasons. First, solubility of higher olefins is too small to achieve reasonable reaction rates without applying special additives (co-solvents, detergents, etc.) or other means (e.g.

sonication) in order to facilitate mass transfer between the phases. Second, the industrial raw materials for production of plasticizer alcohols contain mainly internal alkenes which cannot be hydroformylated with the **[RhH(CO)(TPPTS)$_3$]** catalyst. The catalyst`s activity is even more important in the light of the fact that with longer chain olefins (>C10) the crude aldehyde cannot be separated from the unreacted olefin by distillation; therefore a complete conversion of the starting material is highly desired.

4.4 Basic research in aqueous organometallic hydroformylation; ligands and catalysts

In the preceeding two sections aqueous hydroformylation was mostly discussed in the context of industrial processes. It is, of course, impossible to categorize investigations as "purely industrial" and "purely academic" since the driving force behind the studies of a practically so important chemical transformation such as hydroformylation, ultimately arises from industrial needs. Nevertheless, several research projects have been closely associated with the developmental work in industry, while others explore the feasibility of new ideas without such connections.

Ligand synthesis and purification, coordination chemistry of transition metals (Ag, Au, Mn, Fe, Ru, Co, Rh, Ir, Ni, Pd, Pt) with TPPTS, and catalysis by the new complexes has been significantly advanced by studies of the Munich group of Herrmann [1,4-8,63-65] in close collaboration with researchers of Ruhrchemie, later Hoechst AG. Among the new phosphines synthetized purposefully for aqueous biphasic hydroformylation the sulfonated diphosphines BISBIS (**46**) [66], NAPHOS (**45**) and BINAS (**44**) [67-69] deserve special mention. In fact, the rhodium complexes of these chelating phosphines showed much higher activity and (with the exception of NORBOS) an even better selectivity, than the Rh/TPPTS catalyst. For example, with Rh/BINAS turnover frequencies of **10.000 h^{-1}** could be achieved [69] under optimal conditions (100-130 °C, 20-60 bar syngas, [P]/[Rh] 10:1-50:1). This means, that the activity of this catalyst is approximately ten times higher, than that of Rh/TPPTS. At the same time Rh/BINAS gives a n/i selectivity of 99/1 in contrast to 95/5 with Rh/TPPTS. These figures are very impressive, however, the industrial process still uses the Rh/TPPTS catalyst, mostly due to the higher cost and easier degradation of BINAS compared to TPPTS.

A water-soluble diphosphine ligand with large bite angle was prepared by controlled sulfonation of XANTHPHOS. The rhodium complex of the resulting (**2,7-bis(SO$_3$Na)-XANTHPHOS** (**51**) showed a catalytic activity in propene hydroformylation comparable to Rh/TPPTS (TOF 310 vs **500 h^{-1}** at 120 °C, 9 bar propene and 10 bar **CO/H$_2$ = 1/1**) [70]. The regioselectivity

was very high (n/i ratio 30-35) as expected taking the large bite angle of the phosphine ligand [71]. Conversely, $[Rh(acac)(CO)_2]$ and the dibenzofuran-based phosphine ligand **28** gave a catalyst which was much inferior to Rh/TPPTS both in activity ($TOF = 30\ h^{-1}$) and in selectivity (n/i ratio 2.4) [72].

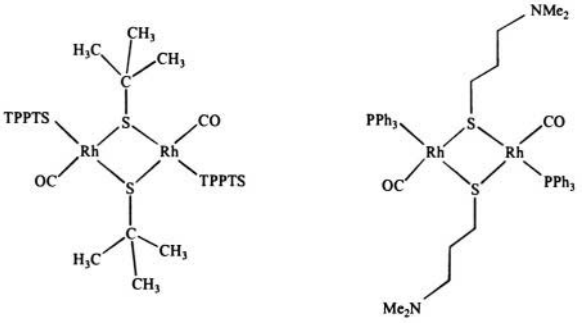
Although cobalt is prominently featured in the history of oxo-synthesis and in industrial hydroformylation, only a few papers deal with the formation and catalytic properties of its water-soluble phosphine complexes [65]. Most probably the reason is in that these cobalt-phosphine complexes show modest catalytic activity under hydroformylation conditions in aqueous/organic biphasic systems. This has been demonstrated by using cobalt based catalysts with TPPTS and with **21** as ligands for the hydroformylation of 1-hexene and 1-octene [73]. Under 15 bar (room temp.) syngas and at 190 °C 10-100 turnovers were observed in 14 h with a n/i ratio generally less than 2. It is of interest that alcohol formation was negligible. Nevertheless, cobalt/TPPTS is suggested for hydroformylation of internal olefins ([154]).

The reaction of $[RhCl(COD)_2]$ and four equivalents of $P(CH_2OH)_3$ in THF gave *cis*-$[RhH_2\{P(CH_2OH)_3\}_4]$, which actively catalyzed the biphasic hydroformylation of 1-pentene [74]. In a water/benzene mixture, at 100 °C and 40 bar syngas this substrate was quantitatively converted to hexanal (43 % yield) and 2-methylpentanal (57 %) in 20 h. At the [substrate]/[catalyst] ratio of 90 this is equivalent to a minimum TOF of $4.5\ h^{-1}$. The catalyst was recycled in the aqueous phase three times with no changes in its activity or selectivity.

In biphasic hydroformylations with the $[RhH(CO)(TPPTS)_3]$ catalyst, polyethylene glycols (PEG-s) of various chain lengths can be used to increase the solubility of higher olefins in the aqueous phase with no apparent losses of the catalyst [8]. Very interestingly, $RhCl_3$ was found to react with neat PEG with liberation of HCl which had to be pumped off for quantitative complex formation. An aqueous solution of the resulting glycolate complex $[Rh(PEG)_x]$ was used for hydroformylation of various olefins including 1-dodecene, 2,4,4-trimethylpent-l-ene and styrene in biphasic systems [75]. The most surprising in these findings is the high reactivity of the hindered olefins comprising technical diisobutylene (a mixture of 76 % 2,4,4-trimethylpent-l-ene and 24 % 2,4,4-trimethylpent-2-ene) for which a TOF $450\ h^{-1}$ could be achieved at 100 °C with 100 bar initial syngas pressure. Aldehyde selectivity was almost quantitative for 1-hexene, 1-dodecene, diisobutylene and styrene, and the latter was hydroformylated with an outstanding regioselectivity ($b/l = 31$). As mentioned in 4.1.2 alkene mixtures such as diisobutylene are used as raw materials for the production of plasticizer alcohols in homogeneous catalytic

hydroformylations with cobalt catalysts. Therefore a metal complex capable of efficient catalysis of the same reaction under mild conditions in a biphasic system would be most valuable. It should be noted, however, that low level rhodium leaching (1.9 ppm) from the aqueous to the organic phase was determined by photometric analysis.

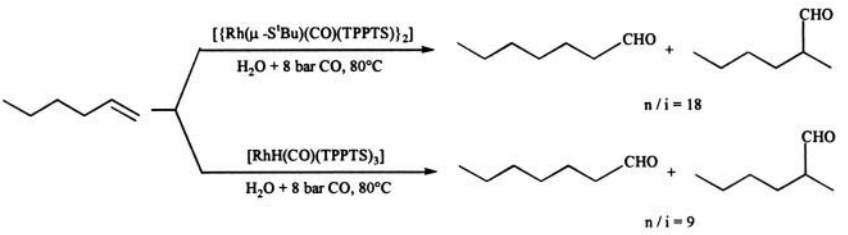
A series of studies deals with the catalytic activity of the dinuclear thiolate-bridged rhodium complex $[\{Rh(\mu\text{-}S^tBu)(CO)(TPPTS)\}_2]$ in the hydroformylation of propene, 1-hexene and 1-octene (Scheme 4.4) [76-80]. Turnover frequencies up to 3100 h^{-1} were detected.



Scheme 4.4

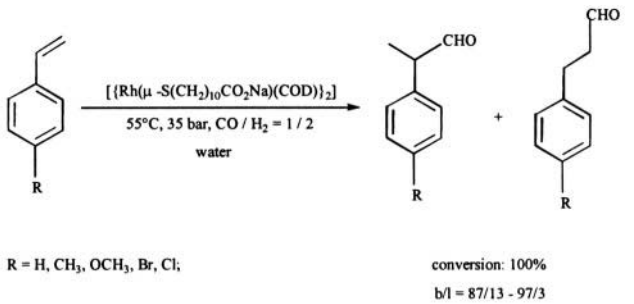
The basic question here is in that whether the dinuclear structure breaks up or remains intact during catalysis. With propene and 1-hexene it was found that at low syngas pressures (5-10 bar) the dinuclear catalyst showed higher selectivity (n/i = 22-36) towards the formation of linear aldehydes than $[RhH(CO)(TPPTS)_3]$, referring to the existence of different catalytic species in the two systems [76-80]. Similarly, the analogous $[\{Rh(\mu\text{-}S(CH_2)_3NMe_2)(CO)(PPh_3)\}_2]$ could be recovered *unchanged* from a reaction mixture of 1-hexene hydroformylation [81]. (It seems appropriate to mention here that recovery of the catalyst was achieved by treating the homogeneous organic reaction mixture with dilute aqueous sulfuric acid; the N-protonated complex precipitated quantitatively. The catalyst could be reextracted to the organic phase after regeneration of the organosoluble dinuclear complex by the addition of aqueous base.) The $[\{Rh(\mu\text{-}S^tBu)(CO)(TPPTS)\}_2]$ complex was also active in the hydroformylation of 1-hexene with $CO + H_2O$ (up to TOF = 40 h^{-1}, calculated for the *dimer*) [76], and again showed different properties than $[RhH(CO)(TPPTS)_3]$ (Scheme 4.5). However, in another study on the hydroformylation of 1-octene in the presence of various cosolvents, it was concluded that most of the catalytic activity was due to mononuclear rhodium complex(es) formed by decomposition of the dinuclear catalyst [78]. This question is still not completely resolved, most

probably both mono- and dinuclear species act as catalysts in such hydroformylations.



Scheme 4.5

Very recently it was disclosed, that the water-soluble dinuclear complex obtained in the reaction of $[\{RhCl(COD)\}_2]$ and 11-mercaptoundecanoic acid catalyzed the aqueous/organic biphasic hydroformylation of styrene and various arene-substituted styrenes with good activity and useful selectivity to the branched aldehydes (Scheme 4.6) [82]. Below pH 4 the acid form of the complex $[\{Rh(\mu\text{-}S(CH_2)_{10}CO_2H)(COD)\}_2]$ precipitated virtually quantitatively but could be redissolved in water on addition of base. Importantly, higher olefins could also be hydroformylated by this catalyst (for 1-octene: **TOF = 17.5 h^{-1}** at 55 °C, 35 bar syngas, **n/i = 1.0**).



Scheme 4.6

In the quest for suitable solvent systems the $[Rh(CO)_2(SULPHOS)]$ complex **(SULPHOS = 31)** was found to catalyze the hydroformylation of 1-hexene in water-methanol/isooctane (1/1/1, v/v/v) yielding heptanal and 2-methylhexanol in a ratio of 2.2 (80 °C, 30 bar syngas) [83]. An important point here is in that the biphasic micture becomes homogeneous above 60 °C, but phase separation occurs again upon cooling to room temperature. This kind of solvent behaviour may lead to fast reactions at higher

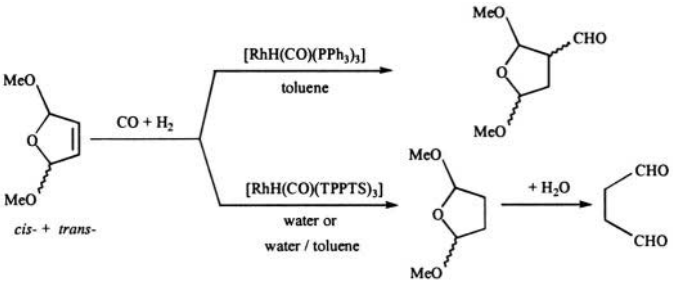
temperature where the system is homogeneous, coupled with the possibility of catalyst recovery after phase separation at low temperatures.

4.5 Mechanistic considerations

4.5.1 Effects of water

The *effect of water* on the conversion and selectivity of cobalt-catalyzed hydroformylations has long been noticed in industry [7,85,86]. A systematic study [87] of this effect in hydroformylation of 1-octene with $[Co_2(CO)_8]$ with and without P^nBu_3 revealed that addition of water, and especially when it formed a separate aqueous phase, significantly increased the hydrogenation activity of the phosphine-modified catalyst. Under the same reaction conditions (190 °C, 56 bar $CO:H_2$ 1:1, P:Co 3:1), approximately 40 % nonanols were formed instead of 5 % observed with water-free solutions. No clear explanation could be given for this phenomenon, although the possible participation of water itself in the hydroformylation reaction through the water gas shift was mentioned. It was also established, that the $[Co_2(CO)_8]$-catalyzed hydroformylation was severly retarded in the presence of water. Under the conditions above, 95 % conversion was observed in 15 hour with no added water, while only 10 % conversion to aldehydes (no alcohols) was found in an aqueous/organic biphasic reaction.

Similar observations were made in the hydroformylation of 2,5-dimethoxy-2,5-dihydrofuran [88]. While in toluene the Rh/PPh_3 catalyst led to exclusive formation of 2,5-dimethoxy-tetrahydrofuran-3-carbaldehydes, in an aqueous solution or in water/toluene mixtures only hydrogenated products were formed with Rh/TPPTS (Scheme 4.7). Direct involvment of H_2O was suggested through the WGSR giving preference for hydrogenation over hydroformylation. Support for this idea comes from experiments with surfactant phosphines (e.g. $Ph_2P\text{-}(CH)_{12}\text{-}PO_3Na_2$), since with such ligands the rhodium catalyst gave increased amounts of aldehydes. This phenomenon was rationalized in that with surfactant ligands the catalyst acts in the less-aqueous environment of micelles unlike $[RhH(CO)(TPPTS)_3]$ which is dissolved in the bulk aqueous phase. Although this explanation may be true, it does not account for the lack of hydrogenation activity of the Rh/TPPTS catalyst in hydroformylation of other olefins (e.g. practically no propane is formed in the RCH-RP process).



Scheme 4.7

In the hydroformylation of alkenes, the major differences between the $[RhH(CO)(PPh_3)_3]$, and $[RhH(CO)(TPPTS)_3]$ catalysts are the lower activity and higher selectivity of the water-soluble complex in aqueous/organic biphasic systems. Lower activity is not unexpected, since alkenes have limited solubility in water (see 4.1.1.1, Table 3). On the other hand, the higher selectivity towards formation of the linear product deserves more scrutiny.

In general, the mechanism of alkene hydroformylation with an $[RhH(CO)P_3]$ catalyst in water or in aqueous/organic biphasic systems (P = TPPTS) is considered to be analogous [61] to that of the same reaction in homogeneous organic solutions ($P = PPh_3$) [84], a basic version of which is shown on Scheme 4.8.

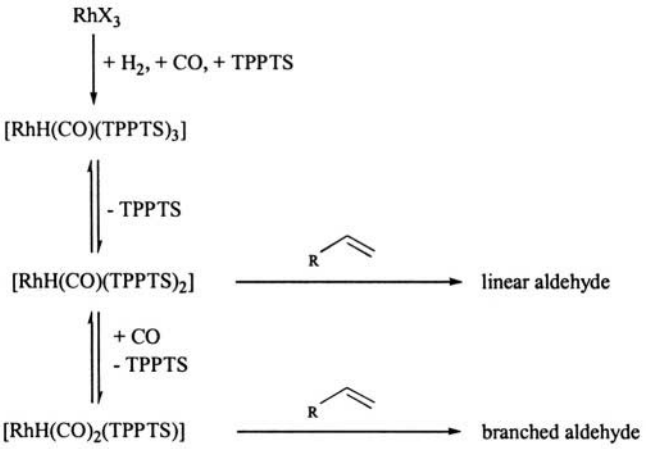


Figure 22. Scheme 4.8

High pressure ^{13}C and ^{31}P NMR measurements showed no formation of any new species in a solution of $[RhH(CO)(TPPTS)_3]$ + 3 TPPTS up to 200

bar $CO:H_2$ 1:1 [89]. This is in sharp contrast to the case of $[RhH(CO)(PPh_3)_3]$ which quantitatively gives $[RhH(CO)_2(PPh_3)_2]$ already under 30 bar $CO:H_2$ 1:1, in the presence of 3 equivalents of PPh_3. These observations refer to a less probable dissociation of TPPTS from $[RhH(CO)(TPPTS)_3]$ than that of PPh_3 from $[RhH(CO)(PPh_3)_3]$. The activation energy of phosphine exchange, calculated from the line width of variable temperature ^{31}P NMR spectra was, indeed, higher for TPPTS than for PPh_3, notably 125 ± 4 kJ mol^{-1} vs. 79 ± 4 kJ mol^{-1}. The value for the water-soluble complex was later redetermined at somewhat higher ligand excess ($[RhH(CO)(TPPTS)_3]$:TPPTS 1:6) as a function of the ionic strength arising from the ionic nature of the complex and TPPTS, as well as from added Na_2SO_4 (if any). For solutions of [Rh] = 10 mM an activation energy of phosphine exchange of 94 kJ mol^{-1} was determined, while in the presence of 100 mM Na_2SO_4 an E_a = 108 kJ mol^{-1} was found [90]. However, at high catalyst concentration ([Rh] = 100 mM) a much higher activation energy, 128 kJ mol^{-1} was given by the measurements, in perfect agreement with the earlier investigations.

If we look now at the accepted mechanism of hydroformylation we can easily recognize that the higher kinetic barrier to phosphine exchange (dissociation) in case of $[RhH(CO)(TPPTS)_3]$+TPPTS will result in a relatively low concentration of $[RhH(CO)_2(TPPTS)]$, the species responsible for the formation of branched aldehydes. The high excess of TPPTS applied in industrial hydroformylation will shift the equilibria (Scheme 4.8) in favour of higher phosphine species anyway, and this is further aided by the increased ionic strength provided by the triply charged TPPTS. These two effects will result in a concentration distribution of the active catalytic species in favour of $[RhH(CO)(TPPTS)_2]$ and hence in the observed high selectivity towards linear aldehydes.

While this argument may explain the higher regioselectivity of hydroformylations, the question still remains that why is it so, what makes $[RhH(CO)(TPPTS)_3]$ more stable in water than $[RhH(CO)(PPh_3)_3]$ is in toluene? At the first look one would expect just the opposite behaviour: nine negative charges in one molecule should facilitate dissociation by mutual repulsion. It has been suggested [89], that the cations of TPPTS and the water molecules in the first hydration shell effectively shield this repulsion, moreover, a network of ionic and hydrogen bonds with participation of the SO_3^- groups, water and the cations, makes the three phosphine molecules a virtual tridentate macroligand. Dissociation of a TPPTS molecule necessitates a substantial reorganization of this network with considerable energy requirement. Obtaining a direct proof for such a suggestion is not easy, however, the effect of inert salts (or "spectator" cations) is in accordance with the above hypothesis. It was demonstrated in

hydroformylation of 1-octene [91] and 1-hexene [92] that salts like Li_2SO_4, Na_2SO_4, Cs_2SO_4 and Na_2HPO_4 generally increased the n/i selectivity of hydroformylations catalyzed by rhodium complexes of sulfonated phosphine ligands. The effect was more pronounced with surfactant phosphines in which case the higher ionic strength is known to stabilize the micelles formed by these ligands.

4.5.2 Effects of pH

As mentioned earlier, in the Ruhrchemie-Rhône Poulenc process for propene hydroformylation the pH of the aqueous phase is kept between 5 and 6. This seems to be an optimum in order to avoid acid- and base-catalyzed side reactions of aldehydes and degradation of TPPTS. Nevertheless, it has been observed in this [93] and in many other cases [38,94-96,104,128,131] that the $[RhH(CO)(P)_3]$ (P = water-soluble phosphine) catalysts work more actively at higher pH. This is unusual for a reaction in which (seemingly) no charged species are involved. For example, in 1-octene hydroformylation with $[\{RhCl(COD)\}_2]$ + TPPTS catalyst in a biphasic medium the rates increased by two- to five-fold when the pH was changed from 7 to 10 [93,96]. In the same detailed kinetic studies [93,96] it was also established that the rate of 1-octene hydroformylation was a significantly different function of reaction parameters such as catalyst concentration, CO and hydrogen pressure at pH 7 than at pH 10.

In a related study the hydrogenation of $[RhCl(CO)(TPPMS)_2]$ was investigated as a function of pH [97]. The reactions were run in a *pH-static* hydrogenation reactor in which the amount of eventual acid (proton) production could be measured quantitatively. By these measurements (and with simultanous ^1H and ^{31}P NMR spectroscopy) it was unambigously established that the formation equilibrium of $[RhH(CO)(TPPMS)_3]$ (Eq. 4.1, Figure 4.1) is *mobile*, and –other parameters being constant– is *governed by the pH.* The most important conclusion which can be drawn from the data on Figure 4.1 is in that $[RhH(CO)(TPPMS)_3]$ is formed only to a negligible extent below pH 5, but becomes the major species (>80 %) at pH 8 (under conditions of Figure 4.1).

$$[RhCl(CO)(TPPMS)_2] + H_2 + TPPMS \rightleftharpoons [RhH(CO)(TPPMS)_3] + H^+ + Cl^- \quad (4.1)$$

Although the measurements were made with the chloro-complex, it is worth repeating the equation in a more general way (Eq. 4.2, X^- = halide, acetate, etc.):

$$[RhX(CO)(TPPMS)_2] + H_2 + TPPMS \rightleftharpoons [RhH(CO)(TPPMS)_3] + H^+ + X^- \quad (4.2)$$

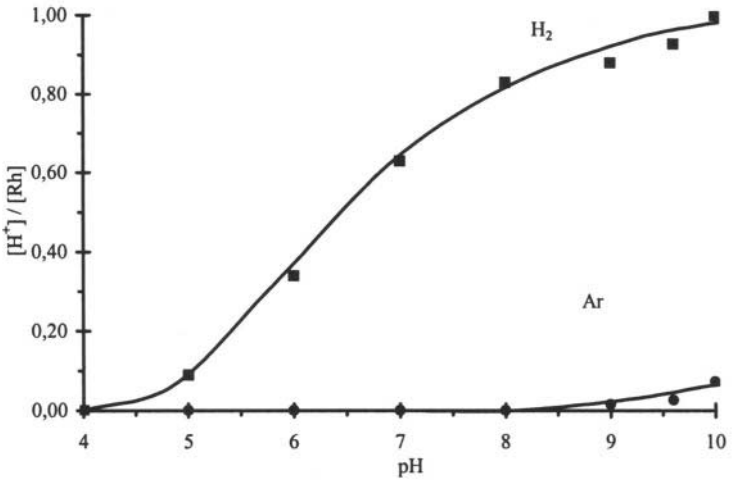


Figure 4.1. Proton production upon hydrolysis and hydrogenation of *trans*-[RhCl(CO)(TPPMS)$_2$] at various constant pH in the 4 < pH < 10 range. [Rh] = 2.4 x 10^{-3} M, [TPPMS] = 7.2 x 10^{-3} M, 1 bar Ar or H_2, T = 35 °C. Reprinted with permission from *Chem. Eur. J.* **2001**, *7*, 193. Copyright (2001) Wiley-VCH Verlag GmbH.

Mobility of equilibrium (4.2) results in the situation, that the concentration ratio of $[RhH(CO)(TPPMS)_3]$ to $[RhX(CO)(TPPMS)_2]$ at any time will depend solely on $[H^+]$, i.e. on the pH. An increase of pH will increase the concentration of the immediate catalyst precursor, which, in turn, should result in an increased rate of hydroformylation.

According to these assumptions, the position of equilibrium (4.1 or 4.2) should be independent of the way by which $[RhH(CO)(TPPMS)_3]$ gets into the system. It can be formed from $[RhX(CO)(TPPMS)_2]$ as written in the equation, or can be prepared in situ from RhX_3 or from any other starting material. Once it is there, however, its concentration will follow the pH changes according to Eq. 4.2. With an in situ preparation from RhX_3, one has to consider also that there is more X^- in the solution than written in Eq. 4.2, influencing unfavourably the formation of the hydride species. This effect, as well as the actual position of the equilibrium, may depend to a large extent on the nature of X^-. Similarly, there can be other equilibria (e.g. formation of catalytically inactive dimers, such as $[\{Rh(CO)(\mu\text{-}CO)(L)_2\}_2]$) which are not taken into account by Eq. 4.2.

Unfortunately, for all these reasons the conclusions cannot be applied *quantitatively* for description of the pH effects in the RCH-RP process. There are gross differences between the parameters of the measurements in [97] and those of the industrial process (temperature, partial pressure of H_2, absence or presence of CO), furthermore the industrial catalyst is pre-formed from rhodium acetate rather than chloride. Although there is no big difference in the steric bulk of TPPTS and TPPMS [98], at least not on the basis of their respective Tolman cone angles, noticable differences in the thermodynamic stability of their complexes may still arise from the slight alterations in steric and electronic parameters of these two ligands being unequally sulfonated. Nevertheless, the laws of thermodynamics should be obeyed and equilibria like (4.2) should contribute to the pH-effects in the industrial process, too.

4.6 Asymmetric hydroformylation in aqueous media

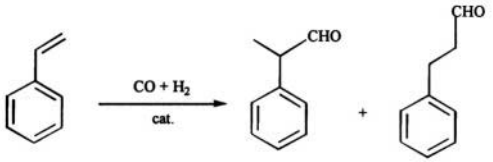
There is very little information available on asymmetric hydroformylation in aqueous solutions or biphasic mixtures despite that asymmetric hydroformylation in organic solvents has long been studied very actively. This is even more surprising since enantioselective hydrogenation in aqueous media has been traditionally a focal point of aqueous organometallic catalysis and several water soluble phosphine ligands have been synthetized in enantiomerically pure form.

The earliest study is from 1995, when the rhodium complex of a menthyl-substituted phosphine (**22**) was used for the hydroformylation of styrene [99]. Although the catalytic activity was quite good (TOF up to 245 h^{-1}), regioselectivity was low (**b/l = 1.0 - 2.5**) and no optical induction was observed in 2-phenylpropanal.

The other three studies in the literature also deal with the asymmetric hydroformylation of styrene and all three applied water soluble rhodium - phosphine catalysts (Scheme 4.9). BINAS (**44**), sulfonated BIPHLOPHOS (**43**), tetrasulfonated (R,R)-cyclobutane-DIOP (**37, m=0**) and tetrasulfonated (S,S)-BDPP (**36, m=0**) were applied as ligands of the rhodium catalyst prepared in situ from [Rh(acac)$(CO)_2$] or [{Rh(μ-OMe)(COD)}$_2$] and the phosphines. The results are summarized in Table 4.4.

The very limited set of data in Table 4.4 does not allow extensive generalizations. The most obvious conclusion is that with analogous pairs of ligands (NAPHOS/**44**, CBD/**37**, BDPP/**36**) lower enantioselectivities are obtained in water than in organic solvents. Conversion to aldehydes can be higher in aqueous systems, although in several reactions increased hydrogenation of the product aldehydes to alcohols was also observed [102].

The pH of the aqueous phase may significantly influence both the rate and the enantioselectivity of the reaction.



Scheme 4.9

Table 4.4.. Asymmetric hydroformylation of styrene in organic and in aqueous biphasic media[a]

Ligand	Solvent	P[b] bar	T °C	t h	Conv. %	b/l	e.e. %	Ref.
NAPHOS	toluene	100	40	24	53	83/17	34 (S)	[100]
(S)-(-)-**44**	toluene/water/ methanol	100	40	25	92	95/5	18 (S)	[100]
(±)-**43**	toluene/ water	50	40	16	16	82/18	-	[101]
(R,R)-CBD	THF	14	50	24	23	73/27	<1 (S)	[102]
(R,R)-**37**	water/methanol	14	50	24	76	70/30	9 (S)	[102]
(R,R)-**37**	water[c]/methanol	14	50	24	67	76/24	17 (S)	[102]
(S,S)-BDPP	THF	8	65	22	33	95/5	43 (S)	[103]
(S,S)-BDPP	THF	30	80	22	45	94/6	58 (S)	[103]
(S,S)-**36**	water/methanol	14	65	24	48	94/6	2 (R)	[102]
(S,S)-**36**	water[c]/methanol	14	65	24	4	90/10	14 (R)	[102]

[a]Substrate/catalyst ratio 300-500, [b]P_{total}, $CO:H_2$ = 1:1, [c]pH = 7.0

The maximum enantioselectivity of 18 % achieved so far in aqueous hydroformylations may not seem very promising. However, the history of asymmetric hydrogenation of prochiral olefins and ketones demonstrates that such a situation may change fast if there is a strong drive behind the case.

4.7 Surfactants in aqueous hydroformylation

The use of surfactants in hydrogenation and hydroformylation immediately followed the practical implementation of the original idea of aqueous biphasic catalysis [57, 118]. Not only the effect of well-known tenzides (SDS, CTAB, etc.) was studied, but new amphiphilic phosphine

ligands of the type $Ph_2P(CH)_nCOOH$ (n = 3, 5, 7, 9, 11) were synthetized for this purpose.

The influence of surfactants and micelle forming agents on the rate of a hydroformylation reaction may arise from two sources. Due to the decreased surface tension at the boundary of the aqueous and organic phases a larger interphase area is produced which facilitates mass transport. Perhaps more important is the effect which can be linked to the apperance of micelles (Fig. 2., A) or vesicles. Water-insoluble olefins show increased concentration in the aqueous phase in the presence of surfactants above the critical micelle forming concentration (c.m.c.). The solubilized olefin is preferentially located in the hydrophobic region of micelles and if the catalyst can also be concentrated into that region then a very efficient catalytic reaction can occur. To put it simply, in such microheterogeneous systems metal complex catalysis and micellar catalysis jontly contribute to fast hydroformylation.

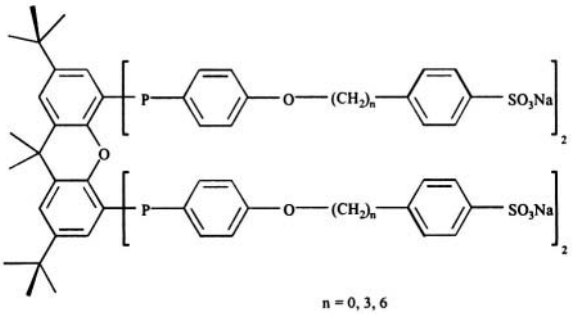
The studies listed in Table 4.5 illustrate the practical realization of the above principles. Not surprisingly, research into the use of surfactants is directed mainly to the hydroformylation of higher olefins, which show negligibly small solubility in water. Four main approaches are clearly distinguishable (but not always separable):

1. synthesis and application of surfactant phosphines which can be used as ligands in rhodium-catalyzed hydroformylation,
2. application of inorganic salts in order to influence micelle formation and hence the catalytic reaction,
3. application of various surfactants in combination with rhodium-phosphine complexes which themselves do not possess obvious micelle forming properties, and
4. catalysis in microemulsions.

Amphiphilic tertiary phosphines have their phosphorus donor atom located somewhere in the hydrophobic part of the molecule and should have at least one long alkyl or alkyl-aryl chain carrying a polar head group (Scheme 4. 10). Some of them, such as the sulfonated derivatives, are quite well soluble in water, others, such as $Ph_2P(CH)_nCOOH$ (n = 3, 5, 7, 9, 11) are practically insoluble, however, can be easily solubilized with common surfactants (SDS, CTAB etc.).

1. Concerning *monodentate* amphiphilic phosphines one of the latest developments is the use of Rh/phosphonate-phosphine catalysts for the hydroformylation of 1-octene and 1-dodecene [54]. The catalysts were prepared in situ from $[Rh(acac)(CO)_2]$ and from the appropriate $Ph_2P(CH_2)_{10}PO_3M_2$ ($M = Na^+, K^+, NH_4^+, {}^+NH_3Pr$) phosphine. Pretreatment under 30 bar syngas significantly improved the catalytic performance. At 120 °C, 30 bar syngas, [P]/[Rh] = 5, in 4 h, 1-octene reacted with 52 % conversion and 47 % aldehyde yield. This means a 91 % selectivity to

aldehydes with n/i = 87/13 and only 9 % isomerization to internal olefins. The same figures for Rh/TPPTS (100 °C, [P]/[Rh] = 10): 17 % aldehydes, n/i = 71/29, 83 % internal olefins. In these terms the phosphonate-phosphine-based catalyst is superior to Rh/TPPTS, however with the former some rhodium (0.8 ppm) and phosphine leaching into the organic phase was determined.



Scheme 4.10

Bidentate phosphines of large natural bite angle [71] form Rh-complexes with outstanding regioselectivity in hydroformylation. The successful XANTHPHOS structure was also functionalized to yield amphiphilic phosphines with -4-$C_6H_4O(CH_2)_nC_6H_4$-4-SO_3Na (n = 0, 3, 6) pendant groups (Scheme 4.10) [108]. Molecules with a sufficiently large hydrophobic part (n = 3, 6) form large aggregates (vesicles) varying in size from 50 nm to 250 nm (determined by dynamic light scattering and transmission electron microscopy) which significantly increase the solubility of olefins in the aqueous phase. Consequently, their rhodium complexes provided up to 12-14 times higher rates in hydroformylation of 1-octene (70-90 °C, 15 bar syngas) than the catalyst containing **51**, i.e. a ligand with the same backbone but lacking surfactant properties. As expected, the l/b selectivity was high, in the range of 97/3 to 99/1. The vesicles are stable even at 90 °C but become partially disrupted at 120 °C, therefore the difference in the activity of catalysts with surfactant and non-surfactant ligands is less pronounced at elevated temperatures. Importantly, the catalyts could be recycled in the aqueous phase several times with nearly unchanged activity and selectivity, and less than 1 ppb Rh leached to the organic phase. Another advantageous property of these catalysts is in that no emulsification was observed, which often makes troubles in phase separations in similar systems.

Table 4.5. Surfactants in rhodium-catalyzed aqueous hydroformylation

Phosphine ligand	Surfactants/salts	1-alkene	Ref.
21	SDS, Na_2HPO_4	C_8	[90]
21	Na_2SO_4, Na_2HPO_4	C_8	[91]
21	NaCl	C_8	[105]
TPPTS	Li_2SO_4, Na_2SO_4, Cs_2SO_4	C_6	[92]
21	-	C_8	[106]
22	-	styrene	[99]
42, 47	-	C_8	[107]
51, 183-185	-	C_8	[108]
$Ph_2P(CH_2)_{10}PO_3M_2$	M = Na^+, K^+, NH_4^+, $^+NH_3Pr$	C_8, C_{12}	[54]
$P(OC_6H_5)_{3-n}(C_6H_4\text{-}4\text{-}SO_3NR_4)$	-	C_6, C_{14}	[109]
30	-	C_{14}	[110]
TPPTS	anionic, cationic, zwitter-ionic and nonionic tensides	ω-unsat. FAME-s[a]	[111]
$Ph_2PCH_2CH_2(OCH_2CH_2)_{111}OBu$	-	C_{12}	[112]
TPPMS and **87**	SDS[b], CTAB, Brij 35[b], Tween 40, Aliquat 336, etc.	C_3, C_6, C_8-C_{18}	[16, 113]
TPPTS	SDS[b], CTAB, DTAB, BDAC, Tween 20[b], Span 40	C_{12}	[58]
TPPTS	microemulsion (SDS[b])	C_{12}	[114]
TPPTS	microemulsion (SDS[b], AOT[b], alkene sulfonate)	C_6-C_{16}	[115]
TPPTS	microemulsion (nonionic surfactant: Marlipal 013/70)	C_{12}	[116]
TPPMS	foszfolipid (DPPC) vesicles	C_{10}-ol[c] C_{11}-ol[d]	[117]

[a] fatty acid methyl esters, [b]see Scheme 3.11, [c]9-decen-1-ol, [d]10-undecen-1-ol

CTAB: cetyltrimethylammonium bromide, DTAB: dodecyltrimethylammonium bromide, BDAC: benzyltetradecyldimethylammonium chloride, Span 40: sorbitan monopalmitate, Tween 40: polyoxyethylene(40)sorbitan monolaurate, Aliquat 336: tricaprylmethylammonium chloride, DPPC: dipalmitoylphosphatidylcholine

2. In general, inorganic salts enhance the catalytic activity of rhodium complexes in hydroformylation of olefins when the catalysts contain surface active ligands. For example, with a catalyst prepared in situ from $[Rh(acac)(CO)_2]$ and $P[C_6H_4(CH_2)_nC_6H_4SO_3Na]_3$ (**21**, **n = 3,** 6), the rate of hydroformylation of 1-octene was about doubled in the presence of Na_2SO_4 and Na_2HPO_4. Conversely, in the activity of the Rh/TPPTS catalyst a significant drop was observed. In both cases the n/i selectivity towards formation of linear aldehydes increased from 4 to about 8-10 [90-92]. In the case of amphiphilic ligands the rate increase can be rationalized by assuming increased partition of 1-octene into the hydrophobic region of micelles which are -in fact- formed by the catalyst and excess ligand. Similarly, proper positioning and restricted motion of the micelle-

incorporated olefin explains the higher regioselectivity (Fig. 2, C). However, the case of Rh/TPPTS should be different, since this catalyst is not able to form micelles. The decrease in the rate of hydroformylation in the presence of inorganic salts is understandable if we think of the reduced solubility of olefins (salting out effect), but the explanation of increased selectivity for linear aldehydes is not straightforward. A slightly higher activation energy was determined for TPPTS-exchange in $[RhH(CO)(TPPTS)_3]$ in the presence of Na_2SO_4 than without added salt [90]. This may translate to a higher stationary concentration of $[RhH(CO)(TPPTS)_2]$ under hydroformylation conditions with Na_2SO_4, hence to higher n/i ratios compared to reactions with no added salt (see also 4.5.1).

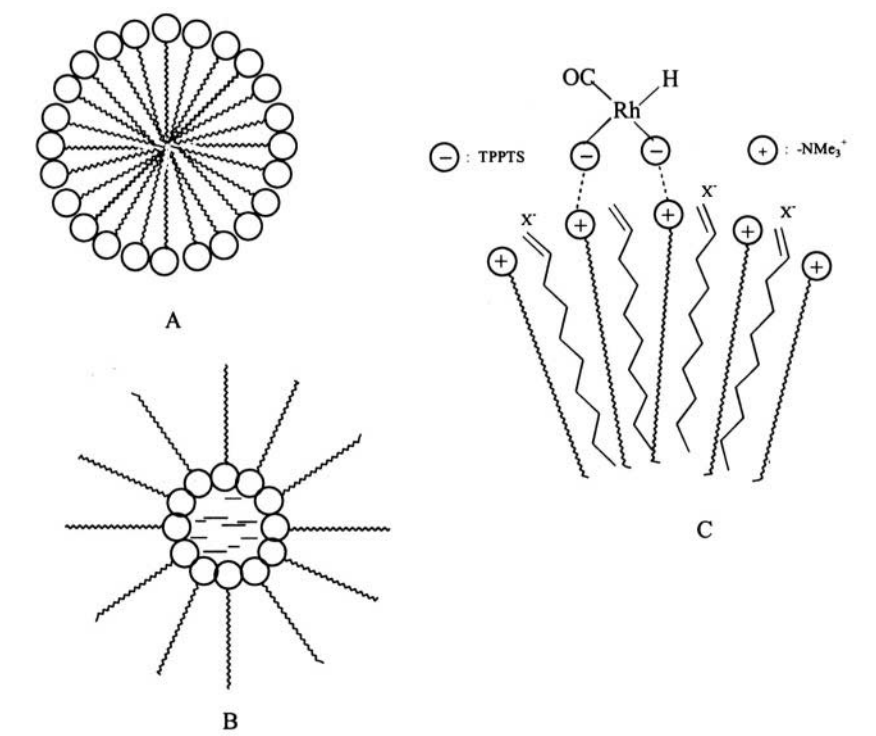


Figure 4.2. Normal (A) and reversed (B) micelles and a possible orientation of substrate and catalyst in and around a micelle (C)

3. The seemingly simplest approach to improve the catalysts` performance in biphasic hydroformylation is the addition of well known micelle- or vesicle-forming agents to the aqueous phase. Nevertheless, great care should be taken in choosing the proper surfactant. In order to achieve high conversions and good selectivities, a fine match is required between the

size [57,117] and charge [58] of the micelle or vesicle and those of the catalyst and substrate molecules (Fig. 2, C). For example, in the hydroformylation of 1-dodecene with the negatively charged Rh/TPPTS catalyst 45-60 % conversions **(TOF = 400-530 h^{-1})** were achieved with $RN(CH_3)_3^+X^-$ amphiphiles in contrast to no conversion in the presence of SDS or nonionic detergents (100 °C, 50 bar syngas, **[alkene]/[Rh] = 1765**).

4. Microemulsions consist of water inside reverse micelles very finely dispersed in a non-aqueous medium (Fig. 2, B). In this version of microheterogeneous liquid systems the combined surface of the aqueous phase (present as 10-100 nm diameter droplets) is enormous compared to even a well agitated (e.g. sonicated) aquous/organic mixture. In principle, such an intimate contact of the two phases should allow fast catalytic reactions, especially when the organic phase is the substrate (olefin) itself. Yes, this is true [114] – with limitations. In microemulsions the relative amount of surfactants can be as high as 30-40 % w/w, which means that each catalytic system has to be individually checked for the mutual compatibility of catalyst, substrate and surfactant and optimized for catalytic efficiency and product/catalyst separation. Nevertheless, a detailed study on the hydroformylation of dodecene has shown [115], that with proper choice of the components and the composition of microemulsion high turnover frequencies of the Rh/TPPTS catalyst can be achieved. In hydroformylation of 1-decene the TOF in microemulsion was **1003 h^{-1}**, while in a non-micellar biphasic mixture practically no reaction was observed **(TOF = 12 h^{-1})** with n/i selectivities of 79/21 and 89/11, respectively. The biggest problem with microemulsions is the separation of the aqueous and organic phases with no rhodium leaching.

In conclusion it can be said, that micellar effects offer useful possibilities to tune the reactivity and separation characteristics of aqueous/organic biphasic hydroformylations. Nevertheless, the added sensitivity of the systems to small changes in process variables and the added cost of surfactants and/or specially synthetized ligands have to be justified by high added value products or on grounds of process cost savings. Whether this will happen on industrial scale (perhaps in the hydroformylation of higher olefins) remains to be seen.

4.8 Water soluble polymeric ligands in aqueous hydroformylation

Soluble polymers are often used as carriers of catalytic units [119] and the idea has also been applied in the field of aqueous organometallic hydroformylations. In this case, of course, the polymers are water-soluble, and are designed to retain the catalytically active complexes (mainly of

rhodium) in the aqueous phase. Several laboratories choosed this approach and some of their results are summarized in Table 4.6

The phosphinated ligands **135** and **136** prepared from poly(acrylic acid) and from poly(ethyleneimine), respectively, gave active hydroformylation catalysts in reaction with **[Rh(acac)(CO)$_2$].** Under the conditions of Table 4.6 low conversions were observed in aqueous/organic biphasic systems, due to the low solubility of 1-octene. Addition of a surfactant (SDS) or an organic co-solvent (MeOH) led to dramatic increases in the yield of aldehydes, revealing the high intrinsic activity of the catalyst [120].

Table 4.6. Rhodium-catalyzed hydroformylation in aqueous-organic biphasic media with polymeric phosphine ligands[a]

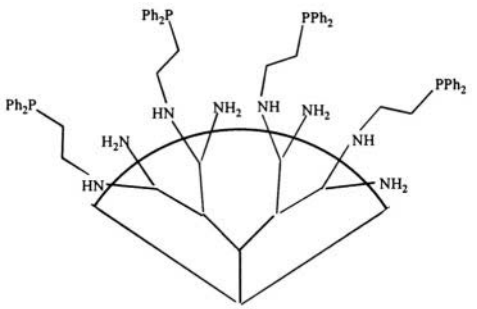
Ligand	Solvent	Olefin[b]	P[c] bar	T °C	t h	Conv. %	Yield %[d]	n/i	Ref.
135	water/toluene	C_6, C_8	40	60	20		25	2.85	[120]
136									
137	water	C_8-C_{12} others	41	40	22	49	48	1.14	[121]
130	water	C_8-C_{12} others	42	90	16	45	40	2.9	[122]
		styrenes	42	70	24	100	>98	1/24	
138	water	C_6	60	70					[123] [124]
Dendr[e]	Water/toluene	C_8	20	40	16	≤82		4.2	[125]
		styrene	20	40	16	≤75		1/29	
HSA	water/pentane	C_8	80	60	24	>99	>99	1/19	[126]
		styrene	80	60	24	>99	>99	0.89	

[a]not including poly(oxyethylated) phosphine ligands, [b]1-alkenes, [c]total pressure, CO/H_2 = 1/1, [d]yield of aldehydes, [e]Scheme 4.11

Controlled oxidation of poly(vinyl alcohol-*co*-vinyl acetate) with sodium hypochlorite yielded the water soluble polymer, poly(enolate-*co*-vinil alcohol-*co*-vinyl acetate), **137**. The rhodium complex of this macroligand showed outstanding activity in hydroformylation of olefins [121]. For example, in the reaction of 1-dodecene a TOF = 87.5 h^{-1} was observed, which is much higher than the activity of **[HRh(CO)(TPPTS)$_3$] (TOF = 2.9 h^{-1})** under similar conditions. The catalyst in the aqueous phase was recycled three times without changes in the activity or selectivity indicating no rhodium leaching to the organic phase. In a related study [122] the rhodium complex of a water-soluble polymeric bisphosphine, **130,** was found an excellent catalyst for hydroformylation of styrene, substituted styrenes a 2-vinylnaphtalene. The regioselectivity in these reactions was

generally very high (b/l ratios ranged from 92/8 to 96/4) with the exception of p-methoxystyrene (b/l 88/12).

The water soluble poly(amidoamine) (PAMAM) dendrimer, generation 3.0 with 32 terminal amine groups (G_3) was functionalized with $Ph_2P(CH_2OH)_2Cl$ in order to obtain water-soluble dendritic phosphine macroligands (Scheme 4.11). An in situ reaction with $[Rh(acac)(CO)_2]$ provided catalysts which were used for hydroformylation of higher olefins and styrene [125]. Under the conditions of Table 4.6 the overall activities were quite good (TOF-s: 1-octene $24.6\ h^{-1}$, styrene $10.5\ h^{-1}$) and in case of styrene an excellent regioselectivity to the formation of the branched product was found (b/l = 29). However, as judged by the colour of the organic phase, some rhodium leaching certainly took place. No attempt was made to determine the leaching of catalyst quantitatively or to separate the outcome of hydroformylations catalyzed by the rhodium complexes in the aqueous and in the organic phase, respectively.



Scheme 4.11

Proteins are water-soluble biopolymers with a huge number of potential donor atoms and coordination sites which could make them useful carriers of metal complex catalysts. Indeed, a few successful attempts can be found in the literature [139] but often the interaction of proteins and metal complexes lead to a loss of catalytic activity [140]. This was not the case with human serum albumin (HSA) which formed a stable and active catalytically active complex with $[Rh(acac)(CO)_2]$. In the hydroformylation of 1-octene and styrene the selectivity towards aldehydes was excellent, moreover styrene reacted with high regioselectivity (b/l = 19). The activity

of the Rh-HSA catalyst also seems good, despite that at 100 % conversion only limiting values can be calculated for the turnover frequency ($TOF \geq 25\ h^{-1}$) [126].

It seems worth pointing out, that **137** and human serum albumin contain no pendant phosphines and the donor atoms in the complexes formed with rhodium can be only O (**137**) or O, N and perhaps S (HSA), which are not the most suitable for stabilizing low oxidation state metal ions. Still these macroligands gave active and stable catalysts with rhodium, which shows that perhaps in the high local concentration provided by the polymer even these hard donor atoms are able to save the metal ion against hydrolysis or other deterioration.

An interesting family of polymeric ligands show inverse temperature dependence of solubility in water, i.e. they can be precipitated from aqueous solutions by increasing the temperature above the so-called cloud point. Typically these ligands contain poly(oxyalkylene) chains, but the phenomenon can be similarly observed with poly(N-isopropyl acrylamide) derivatives (e.g. **132**) and methylated cyclodextrins, too. At or above their cloud points these compounds fall off the solution, due to the break-up and loss of the hydration shell which prevents aggregation and precipitation of their molecules. Conversely, upon cooling below this temperature (also called the lower critical solution temperature, LCST) these substances dissolve again.

Table 4.7. Poly(ethylene oxide)-substituted phosphine ligands in rhodium-catalyzed hydroformylation[a]

Ligand	Solvent	Olefin[b]	P[c] bar	T °C	t h	Conv %	Ald. %[d]	b/l	Ref.
112	water/toluene	C_6, C_{12},	50	100	7	96	87		[127]
m=1-3		C_{18},c-C_6							[128]
n=6, 16		styrene							[129]
112	water/ethanol/	C_6	60	100	6	97	84		[130]
m=1-3	hexane, 2/2/1								[131]
n=6									[132]
112	water/toluene	styrene	60	90	4	98.0	94.4	1.4	[133]
m=3									
n=6									
129	water/heptane	styrene	60	80	6	99.9	99.5	5.2	[134]
129	water/heptane	IBS[e]	40	80	5	99.5	99.0	2.5	[135]
AEOPP	water/toluene	C_{12}	50	100	5				[136]
PEO-DPPSA	water/toluene	C_{10}	50	100	5	98.3	97.0	1.52	[137]
112	*no* aqueous phase	C_{12}	40	130	6	95.8	93.7		[138]

[a]highest conversions, yields and selectivities, [b]1-alkenes, c-C_6 = cyclohexene, [c]total pressure, CO/H_2 = 1/1, [d]yield of aldehydes, [e]4-isobutylstyrene

Several ligands with diphenylphosphino **(Ph_2P-)** coordinating units and with poly(oxyethylene) or mixed poly(alkylene) chains have been prepared in order to capitalize on the inverse temperature dependence of solubility. It is anticipated, and, indeed, has been observed, that complexation with rhodium does not influence dramatically this solubility behaviour. Table 4.7 shows some of the results. In its simple form, catalyst recovery means isolation of the solid catalyst precipitating from the aqueous phase at sufficiently high temperatures. A further extension of this concept is based on the temperature-dependent distribution of the solute between two immiscible liquid phases. This implies, that above the cloud point the then water-insoluble poly(oxyethylene)-substituted phosphines and their complexes will move from the aqueous phase into the organic one. Consequently, at sufficiently high temperature, reactions of the substrates residing in or themselves forming the organic phase, will happen in a homogeneous manner with the catalyst dissolved in the same phase. The concept has got the acronym TRPTC for temperature regulated phase transfer catalysis. The results of studies listed in Table 4.7 demonstrate that the concept works well, and such catalyst systems are capable of hydroformylating higher olefins and styrene, or styrene derivatives with good activity. For example, isobutylstyrene gave the more valuable branched aldehyde with execellent comversion and aldehyde selectivity, although the l/b ratio was hardly satisfactory (2.5) [135]. A further logical step is the use of such catalysts in purely organic solutions and to recover the catalyst by phase separation upon cooling ([138], last line of Table 4.7). Although such a method may be useful for practical purposes, however, this already leads out of the field of *aqueous* organometallic catalysis.

4.9 Aqueous extractions for efficient catalyst recovery

Reading the literature of aqueous biphasic hydroformylation it`s hard to avoid the feeling, that this method can be used with success only for the hydroformylation of propene and 1-butene, and the rest of research is just a persistent struggle with the problems of hydroformylation of higher olefins. All the ingenious concepts of using thermoregulated catalysts, co-solvents, surfactants, salts, and other additives (for cyclodextrins see Chapter 10) are stages of this battle which has not been won yet. On the other hand, industry needs productive catalysts for this purpose and efficient ways for their recycling, and is ready to use proven methods of chemical engineering when the chemistry itself cannot be improved further within a process.

One such method can be the separation of the catalyst and products (plus unreacted starting material and inert components of the feed) by extraction.

In case of the few water soluble substrates it is the product aldehydes which can be extracted into water leaving behind the water-insoluble catalyst, e.g. $[RhH(CO)(PPh_3)_3]$ and excess phosphine in the organic phase. This concept dates back to the origin of aqueous biphasic catalysis [141] and surfaces time by time since than [104]. In fact, the hydroformylation of allyl alcohol is carried out this way with a Rh/PPh_3 catalyst (Kuraray`s 1,4-butanediol process). Since the reaction takes place in a homogeneous organic solution, the details do not belong to the scope of this book; a condensed description of the process can be found in the excellent paper of Arnoldy [142].

The other way around, i.e. the extraction of a water-soluble catalyst into an aqueous phase after hydroformylation has also reached the stage of commercialization. The technology for hydrofomylation of higher olefins, developed by Union Carbide uses an **ω-diphenylphosphinoalkylsulfonate (18)**, such as $Ph_2P(CH_2)_nSO_3Na$, $n = 2, 3$ (TPPMS has also suitable solubility properties) as ligand. The rhodium catalyst is dissolved in N-methyl-pyrrolidone containing 1-2 % water and the reaction takes place in a one-phase system. Following the reaction, sufficient amount of water is added to induce phase separation, upon which the catalyst moves entirely to the aqueous phase. The phases are separated and most of the water is evaporated from the aqueous phase to leave behind an N-methyl-pyrrolidone solution of the catalyst which is then recycled to the reactor (Figure 3) [142].

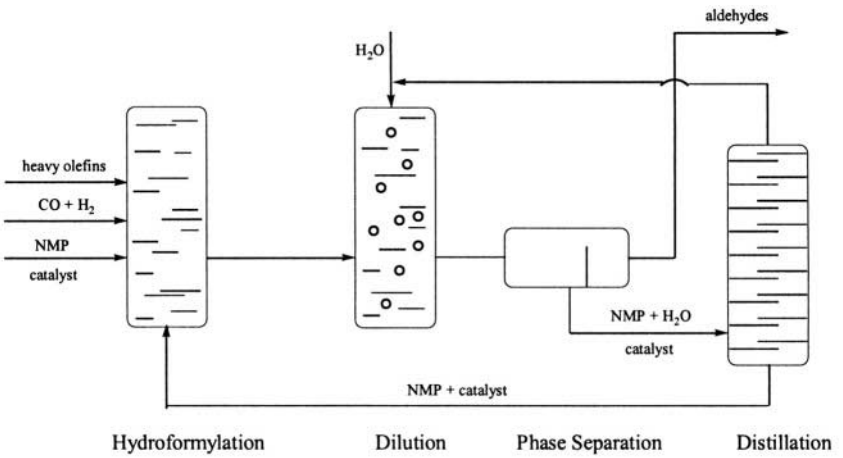


Figure 4.3. Scheme of a hydroformylation process with recovery of the catalyst based on phase separation induced by the addition of water to the catalyst-containig polar phase (N-methyl-pyrrolidone)

The same general principles and the same phosphines (**18**) can be used for still another variation of catalyst recovery which was demonstrated in the hydroformylation of 1-tetradecene [143]. The reaction, catalyzed by the Rh/**18** catalyst, was run in a homogeneous methanolic solution and gave slightly better results than the Rh/PPh_3 catalyst under identical conditions. After the reaction most of the methanol was distilled off and the remaining solution was extracted with water. The catalyst-containing aqueous phase was evaporated to dryness, the catalyst was taken up in methanol and reused. No loss of activity and selectivity was observed in three recycles.

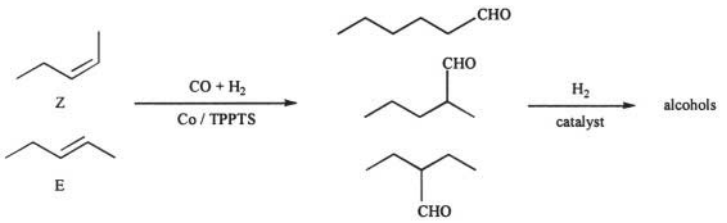
The success of the last two methods for catalyst recycling is in the complete separation of the product-containing apolar phase and the catalyst-containing aqueous phase, despite that the latter contains polar organic solvents (N-methyl-pyrrolidone or methanol). It should be noted, that there is no need for alterations in the chemical composition of the solutions other than dilution. Evaporation of water from the aqueous extracts (and that of the methanol in the second case) requires considerable energy and this adds up to the process costs, but catalyst degradation during this stage does not seem a problem. Since water (and methanol) are also recycled there is no inherent generation of waste in the chemistry of these processes (other than formation of the byproducts of hydroformylation).

This latter aspect becomes important if we look at the other methods developed for extractive recycling of the catalyst. These are based on the use of amphiphilic ligands, the solubility of which can be changed by manipulation of the pH. The ligands which were suggested for this purpose so far included several tertiary phosphines with N-containing (amine: **59**, pyridyl: **67**) or carboxyl (**87**) substituents. The solubilities and complex formation ability of these ligands, as well as the catalytic properties of their complexes in hydroformylations were studied in detail (**59** [10], $Ph_2PC_6H_4CH_2N(CH_2CH_2NEt_2)_2$ [144], **67** [37,145,146] and **87** [145,146]). However, no real breakthrough regarding catalyst recycling emerged from these studies. Importantly, one cycle of catalyst extraction and reextraction consumes amounts of acid and base equivalent to the combined amounts of catalyst and excess phosphine, which is usually present in rhodium-catalyzed hydroformylations. Though this may not seem too much, it inherently leads to batchwise but constant production of an inorganic salt waste. The suggested use of an aqueous solution of carbon dioxide in order to extract highly basic aminophosphine ligands [e.g. $P(CH_2CH_2CH_2NEt_2)_3$, **59**] and their complexes under CO_2 pressure sounds very elegant, since the reextraction of the catalyst into a fresh organic phase of the substrate needs only decompression (CO_2 can be recycled) [10]. No real application of this early "green" concept is known in hydroformylation or in other reactions.

4.10 Synthetic applications

In this chapter we shall review the aqueous hydroformylation of substrates other than simple terminal alkenes. Of course, preparation of butyraldehyde or plasticizer alcohols is also a synthetic application but in the following a few examples are given for application of hydroformylation in reactions of more complex substrates and in synthesis of more elaborate molecules. Most of these chemical transformations could also be effected in one-phase reactions (organic or aqueous), however, the biphasic variants were not inferior in chemistry and offered the advantage of easy catalyst-product separation.

Rhodium-phosphine catalysts are unable to hydroformylate internal olefins, so much that in a mixture of butenes only the terminal isomer is transformed into valeraldehydes (see 4.1.1.2). This is a field still for using cobalt-based catalysts. Indeed, $[Co_2(CO)_6(TPPTS)_2]$ +10 TPPTS catalyzed the hydroformylation of 2-pentenes in a two-phase reaction with good yields (up to 70%, but typically between 10 and 20 %). The major products were 1-hexanal and 2-methylpentanal, and n/i selectivity up to 75/25 was observed (Scheme 4.12). The catalyst was recycled in four runs with an *increase* in activity (from 13 to 19 %), while the selectivity remained constant (n/i = 64/36).

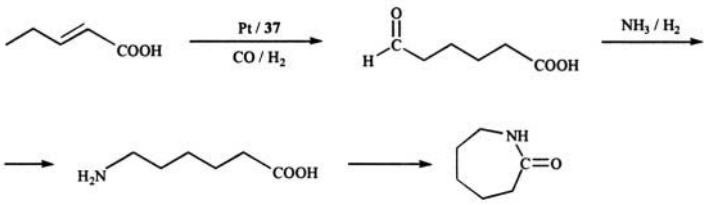


Scheme 4.12

Under the conditions used (150 °C, 40 bar syngas) there is a chance for reaction of $[CoH(CO)_3(TPPTS)]$ to yield $[CoH(CO)_4]$ which moves to the organic phase. In addition to some cobalt leaching (a real problem with this system) $[CoH(CO)_4]$ certainly contributes to the overall hydroformylation [157].

Internal olefins (2-butene, 2-hexene) were also successfully hydroformylated in water with complexes prepared in situ from $[PtCl_2(COD)]$ and the tetrasulfonated diphosphines **37** at 100 °C and 80 bar syngas [148,149]. The same catalysts were suitable for the hydroformylation of 2- and 3-pentenoic acids and trans-2-pentenenitrile, too [150]. The ω-

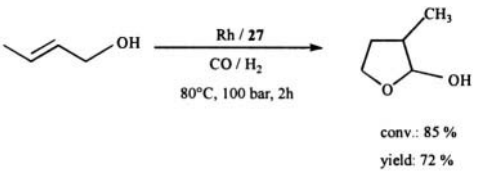
formylcarboxylic acids prepared this way can be reacted further to produce **ε-caprolactam** (Scheme 4.13).



Scheme 4.13

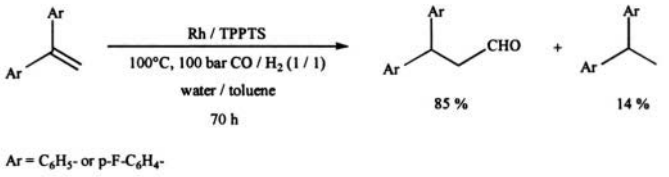
Industrial hydroformylation of allyl alcohol employs **[RhH(CO)(PPh$_3$)$_3$]** as catalyst (Kuraray; see also 4.1.1.4). In an aqueous solution K[Ru(EDTA-H)Cl] catalyzed both the water gas shift and hydroformylation under 10-40 bar CO at 100-130 °C. The major product was **γ-hydroxybutyraldehyde** (35%) but large amounts of **γ-butyrolactone** and dihydrofuran were also produced [151].

Cyclization also accompanies the hydroformylation of unsaturated **C$_4$-alcohols** catalyzed by a rhodium/PNS (**27**) complex (Scheme 4.14). Interestingly, an approximately 3-fold increase was observed in the activity of the catalyst upon increasing the pH from 7 to 9.5 [95]. Rhodium could be efficiently recycled in the aqueous phase, but since there was a considerable pH-drop during the reaction (from 9 to 5) the activity of the catalyst had to be regenerated by addition of a base (NaOH).

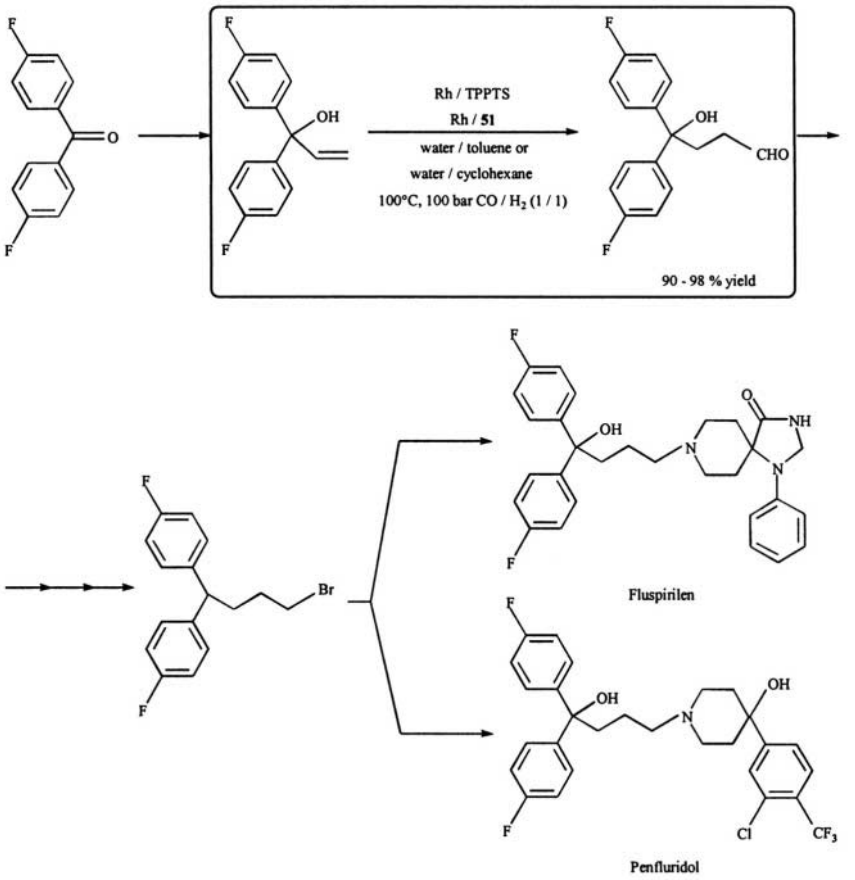


Scheme 4.14

1,1-Diarylethenes, 1,1-diarylallylalcohols and aryl vinyl ethers were succesfully hydroformylated in water/toluene or water/cyclohexane biphasic mixtures with a catalyst prepared in situ from **[{RhCl(COD)}$_2$]** and TPPTS (Scheme 4.15). Yields of the desired linear aldehyde product were around 80%. This method was applied for the synthesis of the neuroleptics Fluspirilen and Penfluridol (Scheme 4.16) and for other pharmaceutically active compounds containing the 4,4-bis(p-fluorophenyl)butyl group [153].



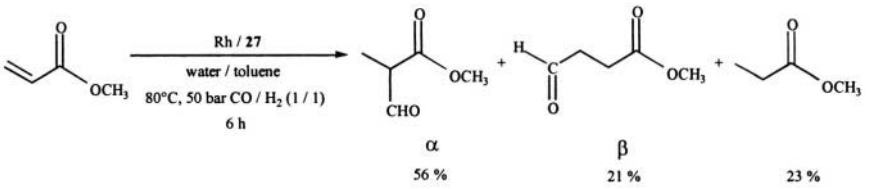
Scheme 4.15



Scheme 4.16

Hydroformylation of methyl acrylate provides racemic methyl 2-formylpropanoate (Scheme 4.17, **α-aldehyde**) which can be enzymatically reduced to yield important chiral 3-hydroxypropanoic acid derivatives [154]. This reaction was catalyzed by the Rh/PNS (**27**) and Rh/PC (**25**) catalysts in

water/toluene, with high aldehyde yields and excellent selectivity for the α-aldehyde (α/β 1/20). After the reaction the rhodium was present in the aqueous solution as $[Rh_4(CO)_{12-x}P_x]$ which, however, should rapidly yield $[RhH(CO)P_3]$ (P = **25** or **27**) under the reaction conditions since the catalysts could be reused with only a slight drop in acitivity but with an increase in selectivity. Similar reactions of various acrylic esters were catalyzed by the Rh/TPPTS catalyst in water/toluene. Very interestingly, the rate of the reaction was considerably higher (by a factor of 2-14) in the biphasic system than in homogeneous organic solution. The effect of water is attributed to the diminished probability of formation of bidentate acyl intermediates in water due to hydrogen bonding [163,164].

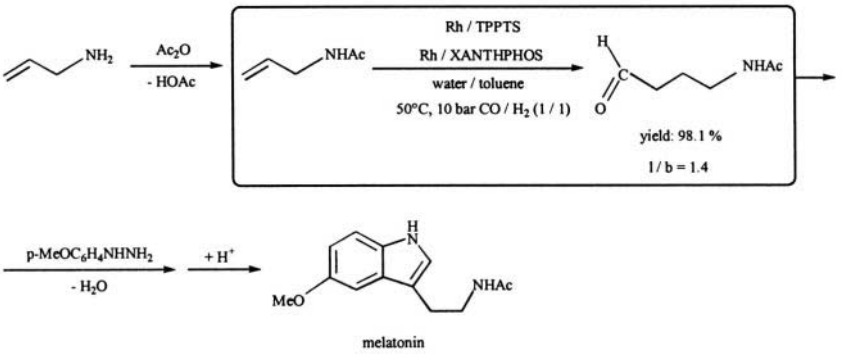


Scheme 4.17

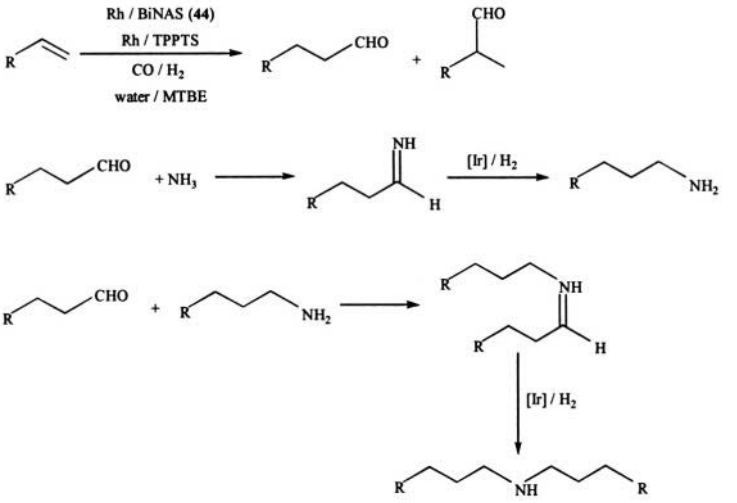
The aqueous/organic biphasic hydroformylation of N-allylacetamide was catalyzed with both water-soluble (Rh/TPPTS) and organosoluble catalysts (Rh/PPh_3, Rh/XANTHPHOS) [104,155]. However, the partition [104] of N-allylacetamide, 4-acetamidobutanal and 3-acetamido-2-methylpropanal is much in favour of water in a water/toluene biphasic mixture. Since almost all N-allylacetamide and the products are in the aqueous phase, a liquid/liquid phase separation cannot be used for the recovery of the highly water soluble Rh/TPPTS catalyst. Conversely, with the organosoluble catalysts useful rates still could be achieved with outstanding regioselectivities in case of Rh/XANTHPHOS (l/b ratios 15.3-20.1). The linear product can be easily transformed to the human hormone, melatonin (Scheme 4.18).

Aqueous organometallic catalysis allows the use of NH_3-solutions in water for the direct synthesis of amines from olefins in a combined hydroformylation/reductive amination procedure (Scheme 4.19). The hydroformylation step was catalyzed by the proven Rh/TPPTS or Rh/BINAS (**44**) catalysts, while the iridium complexes formed from the same phosphine ligands and $[\{IrCl(COD)\}_2]$ were found suitable for the hydrogenation of the intermediate imines. With sufficiently high NH_3/olefin ratios (8/1) high selectivity towards the formation of primary amines (up to 90 %) could be achieved, while in an excess of olefin the corresponding

secondary amines were formed in excess (99% with the BINAS-containing system). Linear to branched isomeric ratios were high (76/24-87/13 with TPPTS) or excellent (99/1 with BINAS).



Scheme 4.18



Scheme 4.19

4.11 Miscellaneous aspects of aqueous-organic biphasic hydroformylation

4.11.1 Interphase engineering using "promoter ligands"

It is discussed briefly in Chapter 2, that addition of PPh_3 to a biphasic system of 1-octene hydroformylation with $[RhH(CO)(TPPTS)_3]$ catalyst had been found to produce a spectracular increase in the reaction rate [158]. According to the concept of "promoter ligands" derived from these observations, a water-soluble MA_n catalyst can be attracted to and immobilized in the interphase region by interaction with a ligand B in the organic phase, provided B is capable of complex formation with M, furthermore ligand A is completely insoluble in the organic phase while B is insoluble in the aqueous phase. In principle A and B need not necessarily be similar, but the idea was developed on experimental findings with PPh_3 and TPPTS (Figure 4.4).

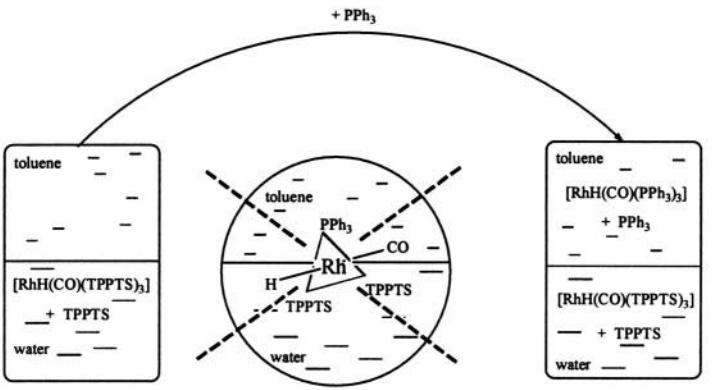


Figure 4.4. Schematic representation of the (invalid) principle of interface localization of soluble catalysts

The concept sounds attractive, but there is a flaw in the explanation. Assuming an equilibrium situation between the two bulk phases and the interphase, complex formation *at the interfacial region* requires the same complexes are formed also in the bulk phases. Consequently, in order to produce a considerable amount of the mixed species $MA_{n-x}B_x$ in the liquid-liquid boundary layer some B must be dissolved in the aqueous, as well as some A in the organic phase. Since by definition this condition is not met, the relative amount of M present at the interphase region as $MA_{n-x}B_x$ must be negligible. However, now the metal ion will be distributed between MA_n in the aqueous phase and MB_p in the organic layer (n and p are the

maximum coordination numbers for A and B, respectively) governed by the relative stability of MA_n and MB_p. (For related ligand pairs such as PPh_3 and TPPTS the difference in stabilities is not exptected very great.) Briefly, "promoter ligands" promote the distribution of the catalyst between the two phases, in other words: leaching. In fact, a thorough rexamination of the original discovery concluded, that the hydroformylation of 1-octene was accelerated by formation of and catalysis by $[RhH(CO)(PPh_3)_3]$ in the organic phase [79,80].

4.11.2 Gas-liquid-liquid reaction engineering

The influence of process variables such as the temperature, pressure of H_2 and CO on the hydroformylation reaction is well recognized by all researchers. However, other aspects, such as stirring speed, the shape and size of the stirrer, relative amounts of the aqueous and organic phases, etc. are usually overlooked by people working in laboratories far from the actual chemicals production. A few papers in the open literature deal with these questions, of which perhaps the most important concerns the location of the chemical reaction. Does it takes place in the bulk phases or at the interphase region?

Perhaps this question is impossible to answer in a general way. Since mass transfer between the liquid phases and furthermore: between the gas phase and the liquid phases is influenced by the parameters of all ingredients in the reaction system (the substrate olefin, aqueous phase, co-solvents or other additives) a conclusion for one particular system may not be valid for the other. For propene hydroformylation it was established, that most probably it takes place in the interphase region [159]. In case of 1-octene it was concluded, that mass transfer limitations had their origin in the dissolution of gases (H_2, CO) in the liquid phases, while the liquid phases were in equilibrium with each other at all times [160,161]. It is worth remembering, that less-than-equilibrium concentration of gases may result not only in lower rates but even in changes of selectivity as demonstrated in hydrogenation reactions [162].

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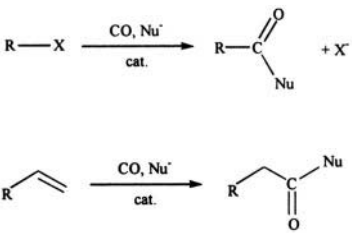
Chapter 5

Carbonylation

5.1 Introduction

Carbonylation is one of the most important reactions leading to C-C bond formation. Direct synthesis of carbonyl compounds with CO gives rise to carboxylic acids and their derivatives, such as esters, amides, lactones, lactams etc. The process can be represented by the simple reactions of Scheme 5.1.



Scheme 5.1

In general, carbonylation proceeds via activation of a C-H or a C-X bond in the olefins and halides or alcohols, respectively, followed by CO-insertion into the metal-carbon bond. In order to form the final product there is a need for a nucleophile, Nu^-. Reaction of an R-X compound leads to production of equivalent amounts of X^-, the accumulation of which can be a serious problem in case of halides. In many cases the catalyst is based on palladium but cobalt, nickel, rhodium and ruthenium complexes are also widely used.

One of the most common nucleophiles in these reactions is OH^- which can be logically supplied by H_2O or aqueous base solutions. By this,

aqueous organometallic catalysis gets a special flavour, since water now is not only a solvent but one of the reactants. Aside chemistry this means, that the amount of water in such systems may vary from stoichiometric quantities (usually homogeneously dissolved in the organic solvent or in the substrate of the reaction) to larger volumes, in form of a separate aqueous phase. Although both kinds of reaction media are "aqueous", in the following we shall mostly quote examples of the second variant. In such aqueous/organic biphasic systems the catalyst can be dissolved in the organic or in the aqueous phase, and we shall include both methods into our description, since water is essential in both cases.

This is also a field of chemistry, where biphasic and phase transfer-assisted organometallic catalysis [11-12] are very close and sometimes may even overlap. One reason for this closeness is in that inorganic bases are often used in aqueous solutions. Of them, OH^- is so strongly solvated in water that it will practically not transfer to non-polar organic solvents without a phase transfer (PT) agent, e.g. a quaternary ammonium cation. However, some reactions proceed readily with H_2O dissolved in the organic phase, or can take place with reasonable rates at the liquid-liquid interface, and in these cases addition of PT catalysts is not essential.

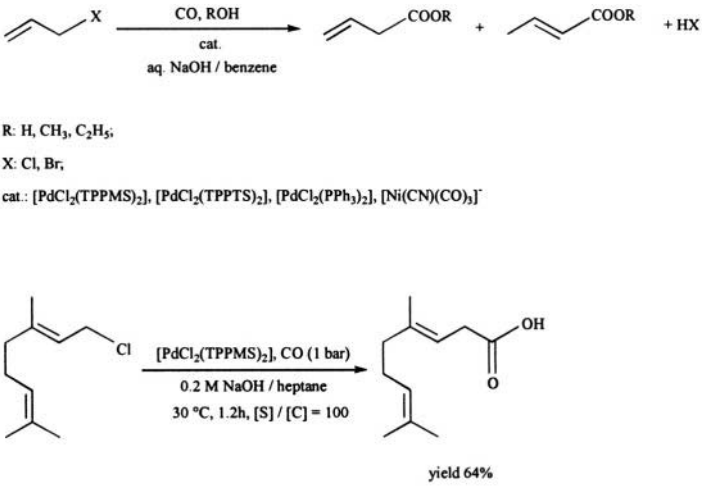
In addition to this chapter, there are several books and reviews [1-8] which –inter alia– deal with carbonylations with CO and H_2O, two of them [9-10] specifically addressed to this topic.

5.2 Carbonylation of organic halides

Allyl chlorides and bromides can be carbonylated to afford the respective unsaturated acids and esters with a variety of catalysts under relatively mild conditions such as 30-50 °C and 1 bar CO (Scheme 5.2). Most prominent are the palladium-containing catalysts and both $[PdCl_2(TPPMS)_2]$ or $[PdCl_2(TPPTS)_2]$ and $[PdCl_2(PPh_3)_2]$ were used, dissolved in the aqueous and in the organic phases, respectively [14-16].

When aqueous NaOH is given as a base, isomerization of the product butenoic acids can be extensive depending on the nature and concentration of base. In dilute aqueous solutions alcohols do not react to form the respective esters, however, the reactions are strongly accelerated due to the increased solubility of the substrates in the catalyst-containing aqueous-alcoholic phase. For example, with 23-33 % (v/v) ethanol in water the $[PdCl_2(TPPTS)_2]$-catalyzed hydroxycarbonylation of allyl chloride proceeded with TOF-s of 1850-2400 h^{-1} and with a vinylacetic/crotonic acid ratio of 21 [16]. Addition of $[CuCl_2]$ increased the overall conversion rate (by a factor of 2 at $[Cu]/[Pd] = 8$) but at the same time the side reactions

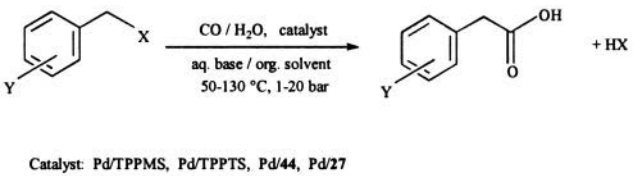
were also accelerated so the selectivity for butenoic acids dropped from 92 to 62 %.



Scheme 5.2

In the carbonylation of allyl halides the highly toxic $[Ni(CO)_4]$ catalyst could be replaced by $[Ni(CN)_2]$, which yielded $[Ni(CN)(CO)_3]^-$ under the reaction conditions [17]. The cyanotricarbonylnickel(0) anion is a versatile catalyst of carbonylations under phase transfer conditions [18], however, hydroxycarbonylation of allyl chloride proceeds effectively without PT catalysts in a genuine biphasic system, as well.

Benzyl halides are easily carbonylated to phenylacetic acid derivatives which are valuable intermediates for Pharmaceuticals, cosmetics and fragrances [2,3]. Several papers report the aqueous/organic biphasic realization of this reaction [1,19-22] (Scheme 5.3). The main characteristics of these processes are summarized in Table 5.1.

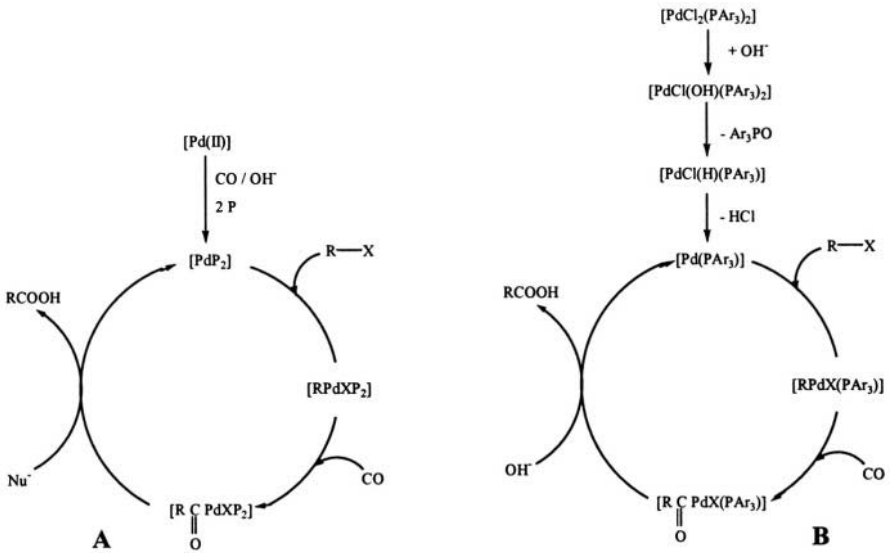


Scheme 5.3

Table 5.1. Catalytic hydrocarboxylation of benzyl halides in aqueous systems

Ref.	[19]	[20]	[20]	[21]	[22]
Catalyst	$[PdCl_2(TPPMS)_2]$	Pd/TPPTS	Pd/BINAS (**44**)	Pd/PNS (**27**)	Pd/(**153**)
X	Cl	Cl	Cl	Br	Cl
Y	H	H, Cl, F, Me	H, Cl, F, Me	H	H
P(CO)	1 bar	1 bar	20 bar	10 bar	0.6 bar (r.t.)
T	50 °C	70 °C	70 °C	130-140 °C	55 °C
Organic phase	heptane, benzene, anisole, butanol	o-xylene toluene	o-xylene toluene	toluene	benzene
Typical yield	80-90 %	80-95 %	≤ 97 %	87 %	91 %

The mechanism of palladium-catalyzed carbonylation of organic halides is generally assumed to involve oxidative additon of R-X to a Pd(0) species which is formed from the precursors on the action of $CO + OH^-$. Migratory insertion of R onto a coordinated CO followed by reaction with a nucleophile generates the product and gives back the catalytically active palladium(0) species (Scheme 5.4 A).



Scheme 5.4

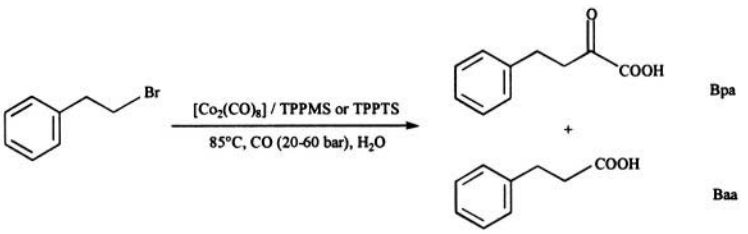
The mechanistic suggestion depicted on Scheme 5.4 may be true in an excess of phosphine ligands, and in fact, the [phosphine]/[palladium] ratio has a pronounced influence on the rate and selectivity of the reactions. However, it has also been demonstrated [20,58] that the palladium(II)-phosphine complexes used as catalyst precursors are reduced to Pd(0) in the

presence of OH^-, and in the absence of excess ligand, monophosphine species and their dimers can also participate in the catalytic cycle (Scheme 5.4 B).

Benzyl halides are usually carbonylated using an excess of a base and then the product is deprotonated and accumulates in the aqueous phase; with a water-insoluble catalyst, such as $[PdCl_2(PPh_3)_2]$ this gives a possibility of catalyst-product separation. It was discovered not long ago [20], that with Pd/BINAS as catalyst the carbonylations proceeded smoothly even at pH 1. According to this method, slightly less than stoichiometric amount of base is used and then the final pH of the aqueous phase is strongly acidic due to the formation of HCl in the carbonylation reaction. At this pH 99 % of the phenylacetic acid product becomes protonated and moves to the *organic* phase, consequently it can be separated from the catalyst. Although the catalyst in the aqueous phase can be reused, accumulation of NaCl in successive runs generates additional problems. The Pd/TPPTS catalyst cannot be used this way due to precipitation of palladium black when all the substrate is consumed.

Mono- and double carbonylation of phenetyl bromide with cobalt-phosphine catalysts afforded benzylacetic (Baa) and benzylpyruvic (Bpa) acids respectively [23] (Scheme 5.5). The highest yield of benzylpyruvic acid (75 %) was obtained with $[Co_2(CO)_8]$, while addition of the water soluble phosphines TPPMS or TPPTS decreased both the yield of carbonylated products and the selectivity to Bpa.

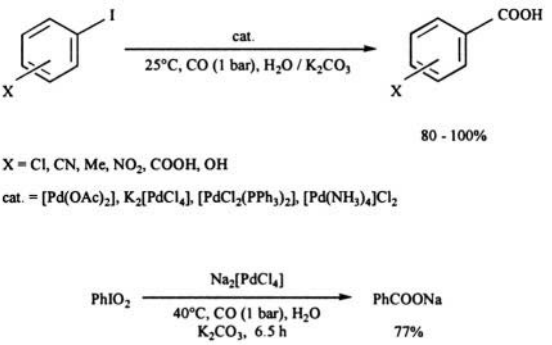
Carbonylation of aromatic halides is of great industrial interest and several efforts were made to produce the corresponding benzoic acids in aqueous (biphasic) reactions. The tendency of an aromatic C-X bond to react in an oxidative addition onto Pd(0) as required by the reaction mechanism (Scheme 5.4) decrease in the order $X = I > Br > Cl$ so much that chloroarenes are notoriously unreactive in such reactions.



Scheme 5.5

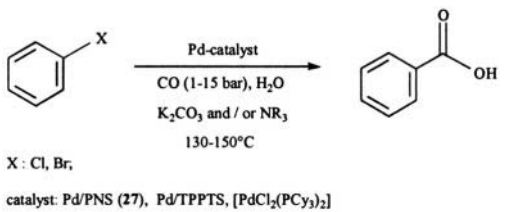
Water-soluble aryl iodides can be easily carbonylated under mild conditions (Scheme 5.6) using K_2CO_3 as base [24]. The same does not hold

for water-insoluble iodoarenes which require higher temperature (100 °C) to proceed. The latter, however, can be oxidized to iodoxyarenes **($PhIO_2$)** by simple stirring with sodium hypochlorite (household bleach), slightly acidified with acetic acid. The resulting iodoxyarenes can be efficiently carbonylated with **$Na_2[PdCl_4]$** as catalyst under very mild conditions (40 °C, 1 bar); iodobenzene and nine substituted iodobenzenes were carbonylated with excellent yields in such two-step biphasic procedures [25].



Scheme 5.6

Carbonylation of bromobenzene (Scheme 5.7) with **[$Pd(TPPTS)_3$]** required still higher temperatures (150 °C). The possible acyl intermediates of such reactions **[$PdBr(C_6H_5CO)(PPh_3)_2$]** and **[$PdBr(C_6H_5CO)(TPPTS)_2$]** were synthetized and characterized [26]. Bromobenzene was also carbonylated to benzoic acid in water/toluene using a catalyst prepared from **[$PdCl_2(COD)$]** and **27** in the presence of **NEt_3** [21].

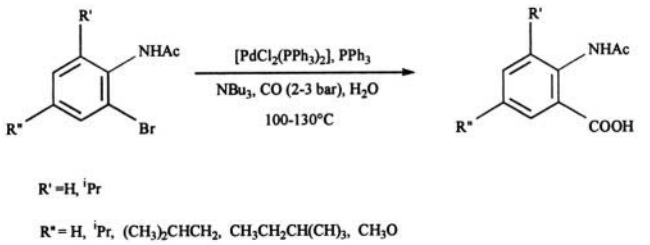


Scheme 5.7

An exceptionally simple procedure was developed for the catalytic carbonylation of chloroarenes using **[$PdCl_2(PCy_3)$]** as catalyst. According to this method the neat chloroarene, e.g. m-chlorotoluene and the catalyst are stirred with 20 % (w/w) aqueous KOH at reflux temperature with bubbling CO. The benzoic acids are extracted from the aqueous phase after

acidification with diethyl ether. Although the reactions are rather slow, in 24-72 hours 5-116 catalytic turnovers could be achieved (Scheme 5.6). This method was improved further by using 20-40 % aqueous K_2CO_3 *and* NEt_3 instead of KOH [29]. At 180 °C high turnovers (TO up to 1000) were obtained. It is speculated that the triethylammonium chloride, formed from NEt_3 and HCl produced in the reaction acts as a phase transfer catalyst for hydroxide and by doing so it facilitates the reaction.

Water-insoluble amines can be used as base and a second phase at the same time. A series of anthranilic acids was prepared by carbonylation of o-bromoacetamides at 100-130 °C with $[PdCl_2(PPh_3)]$ as catalyst (Scheme 5.8). Isolated yields were as high as 85 % (R` = H, R`` = ^{i}Pr) [30].

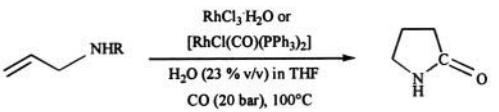


Scheme 5.8

5.3 Carbonylation of methane, alkenes and alkynes

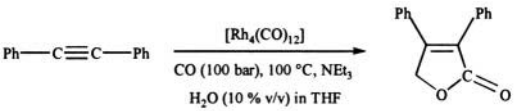
Oxidative carbonylation of methane to acetic acid is one of the pursued ways to solve the fundamental problem of direct methane utilization. Partly aqueous systems with $RhCl_3$-HCl-KI catalyst mixture were applied with some success for this purpose. However, the reaction proceeds faster in *acetic acid* as solvent, containing only a small percentage of water [34].

Reductive carbonylation of isopropylallylamine catalyzed by $RhCl_3.aq$ or $[RhCl(CO)(PPh_3)_2]$ in aqueous tetrahydrofuran afforded the corresponding γ-lactam (Scheme 5.9) [31]. With the former catalyst at 91 % conversion 75 % lactam yield was observed. PPh_3 and 1,2-, 1,3- and 1,4-diphosphines all led to somewhat higher conversions (95-100 %) but to diminished yield of the γ-lactam product (45-61 %).



Scheme 5.9

Rhodium carbonyl cluster catalysts $[Rh_4(CO)_{12}]$ and $[Rh_6(CO)_{16}]$ were effective to produce lactones in carbonylation of alkynes (Scheme 5.10) [32,33]. In these systems, however, water is rather a reagent than a solvent and its amount can be as low as 216 μL in 45 mL $CHCl_3$ [33].



Scheme 5.10

Hydroxycarbonylation *of olefins* (Scheme 5.11) in fully aqueous solution was studied using a ruthenium-carbonyl catalyst with no phosphine ligands [35]. In a fine mechanistic study it was shown, that (the WGS) reaction of *fac*-$[Ru(CO)_3(H_2O)_3]^{2+}$ and water provided *fac*-$[RuH(CO)_2(H_2O)_3]^+$. At 70 °C and in the presence of CF_3SO_3H the latter compound reacted with ethene (10 bar) giving a σ-alkylruthenium complex, solutions of which absorbed CO and yielded the corresponding acyl-derivative:

$$fac\text{-}[RuH(CO)_2(H_2O)_3]^+ + C_2H_4 \rightarrow fac\text{-}[Ru(C_2H_5)(CO)_2(H_2O)_3]^+ \quad (5.1)$$

$$fac\text{-}[Ru(C_2H_5)(CO)_2(H_2O)_3]^+ + CO \rightarrow fac\text{-}[Ru\{C(O)C_2H_5\}(CO)_2(H_2O)_3]^+ \quad (5.2)$$

The alkylruthenium species obtained in eq. 5.1 is very stable in water, neither the addition of strong acids nor boiling for several hours lead to its decomposition. In aqueous solution it exists as a monomeric cation, however, it was isolated in solid state and characterized by X-ray crystallography as a dimer $[\{Ru(C_2H_5)(CO)_2(H_2O)_2\}_2]^{2+}$. The stability of this ruthenium alkyl is attributed to the stabilization effect of strong hydrogen bonds which could be detected in the crystal structure and are postulated also in its aqueous solutions. Finally, elimination of propionic acid from the acyl could be induced by raising the temperature; this reaction closes the catalytic cycle:

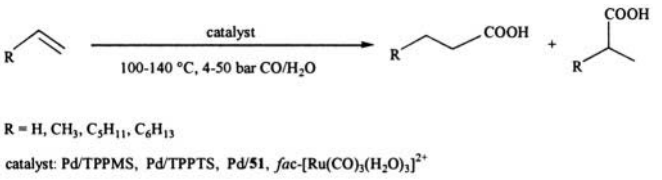
$$fac\text{-}[Ru\{C(O)C_2H_5\}(CO)_2(H_2O)_3]^+ \rightarrow fac\text{-}[RuH(CO)_2(H_2O)_3]^+ + EtCO_2H \quad (5.3)$$

The rate of the overall catalytic reaction is not very high, TOF = 15.4 h^{-1} at 140 °C, 4 bar CO, 30 bar ethene, 0.01 M [Ru] and 0.1 M CF_3SO_3H. Infrared spectroscopic studies revealed no change in the concentration of the acylruthenium species during the reaction which suggests that the rate

determining step of the catalytic reaction is the elimination of propionic acid. It is worth mentioning, that accumulation of the product propionic acid changes the course of the reaction and with its concentration being higher than 3 M, substantial amounts of diethyl ketone are formed:

$$2\ C_2H_4 + 2\ CO + H_2O \rightarrow EtC(O)Et + CO_2 \qquad (5.4)$$

The importance of this study is given by the fact the carbonylation is run in water with no need for co-solvents, furthermore the catalyst precursor and the intermediates do not contain other ligands than the constituents of the final product (C_2H_4, CO and H_2O). Besides, all elementary steps of the catalytic cycle were studied separately, and all intermediate complexes were characterized unambiguously either in isolated form by X-ray crystallography or/and in solution by NMR techniques.



R = H, CH_3, C_5H_{11}, C_6H_{13}

catalyst: Pd/TPPMS, Pd/TPPTS, Pd/**51**, *fac*-$[Ru(CO)_3(H_2O)_3]^{2+}$

Scheme 5.11

Practical hydroxycarbonylation of olefins is usually carried out with palladium catalysts and requires rather elevated temperatures. Pd/TPPTS [36-39], Pd/TPPMS [40] and Pd/sulfonated XANTHPHOS (**51**) were all applied for this purpose. In general, TOF-s of several hundred h^{-1} can be observed under the conditions of Scheme 5.11, and with propene the concentration ratio of linear and branched acids is around l/b = 1.3-1.4 [36,38]. At elevated temperatures and at low phosphine/palladium ratios precipitation of palladium black can be observed. It is known, that the highly reactive $[Pd(TPPTS)_3]$ forms easily under CO from a Pd(II) catalyst precursor and TPPTS [37], and that in the presence of acids it is in a fast equilibrium with $[PdH(TPPTS)_3]^+$ [39]:

$$[Pd(TPPTS)_3] + HX \rightleftharpoons [PdH(TPPTS)_3]^+ + X^- \qquad (5.5)$$

Insertion of ethene into the Pd-H bond provides the ethyl complexes $[Pd(Et)(TPPTS)_3]$ and *trans*-$[Pd(Et)(TPPTS)_2]$ which take up CO and yield *trans*-$[Pd\{C(CO)Et\}(TPPTS)_2]$. These complexes were all characterized by NMR techniques in separate reactions. Again, elimination of propionic acid from the acylpalladium intermediate (eq. 5.6) was found rate-determining:

$$\textit{trans}\text{-}[Pd\{C(CO)Et\}(TPPTS)_2] + TPPTS \rightarrow [PdH(TPPTS)_3]^+ + EtCO_2H \quad (5.6)$$

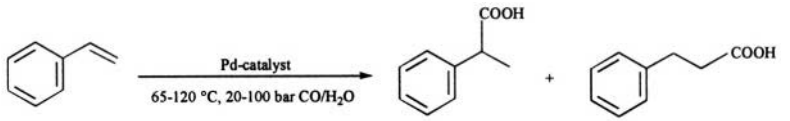
Until there is a sufficient excess of ethene over $[PdH(TPPTS)_3]^+$ their fast reaction ensures that all palladium is found in form of *trans*-$[Pd\{C(CO)Et\}(TPPTS)_2]$. However, at low olefin concentrations (e.g. in biphasic systems with less water-soluble olefins) $[PdH(TPPTS)_3]^+$ can accumulate and through its equilibrium with $[Pd(TPPTS)_3]$ (eq. 5.5) can be reduced to metallic palladium. This is why the hydroxycarbonylation of olefins proceeds optimally in the presence of Brønsted acid cocatalyts with a weekly coordinating anion. Under optimised conditions hydrocarboxylation of propene was catalyzed by $PdCl_2$ + TPPTS with a TOF = 2507 h^{-1} and l/b = 57/43 (120 °C, 50 bar CO, [P]/[Pd] = 4, p-$CH_3C_6H_4SO_3H$) [38]. In neutral or basic solutions, or in the presence of strongly coordinating anions the initial hydride complex cannot be formed, furthermore, the fourth coordination site in the alkyl- and acylpalladium intermediates may be strongly occupied, therefore no catalysis takes place.

In line with the above mechanism, catalyst deactivation by formation of palladium black can be retarded by increasing the [P]/[Pd] ratio, however, only on the expense of the reaction rate. Bidentate phosphines form stronger chelate complexes than TPPMS which may allow at working with lower phosphine to palladium ratios. Indeed, the palladium complex of sulfonated XANTPHOS (**51**) proved to be an effective and selective catalyst for hydroxycarbonylation of propene, although at [**51**]/[Pd] < 2 formation of palladium black was still observed. The catalyst was selective towards the formation of butyric acid, with l/b = 65/35 [41].

The hydrocarboxylation of styrene (Scheme 5.12) and styrene derivatives results in the formation of arylpropionic acids. Members of the α-arylpropionic acid family are potent non-steroidal anti-inflammatory drugs (Ibuprofen, Naproxen etc.), therefore a direct and simple route to such compounds is of considerable industrial interest. In fact, there are several patents describing the production of α-arylpropionic acids by hydroxycarbonylation [51,53] (several more listed in [52]). The carbonylation of styrene itself serves as a useful test reaction in order to learn the properties of new catalytic systems, such as activity, selectivity to acids, regioselectivity (l/b ratio) and enantioselectivity (e.e.) in the branched product. In aqueous or in aqueous/organic biphasic systems complexes of palladium were studied exclusively, and the results are summarized in Table 5.2.

Table 5.2. Hydroxycarbonylation of styrene catalyzed by Pd-complexes

Catalyst	Acid additive	organic solvent	P(CO)/bar	T/°C	t/h	Conv./%	b/l ratio	TOF/h^{-1}	e.e./%	Ref.
Pd/TPPTS	TsOH	--	50	65	10	100	9	5		[38]
Pd/TPPTS	HCl	toluene	40	100	20	100	1.25	25		[43]
[$Pd(OAc)_2$] + TPPTSH	AcOH	AcOH	100	100	18	90	44	10		[42]
Pd/**51**	TsOH	--	30	70	3		1.86	40		[41]
Pd/TPPTS + pyridinecarboxylate	TsOH	toluene	54	115	1.42	94.5	12.8	302		[44]
[PdCl(o-amino-arenethiolate)]	--	dimethoxy-ethane	30	100	20	97	9	3		[46]
Pd/BDPPTS (**36**)	pH 12.7	--	20	120	16	57	0.23	2	<1 % (S)	[45]
Pd/CBDTS (**37**)	pH 12.1	--	20	120	16	100	0.41	3.5	10 (S)	[45]
Pd/BDPPTS (**36**)	pH 3.4	--	20	120	16	99	0.52	3.5	32 (S)	[45]
Pd/CBDTS (**37**)	pH 3.2	--	20	120	16	100	0.41	3.5	14 (R)	[45]



Scheme 5.12

As can be seen from the table the reactions are rather slow, with the exception of the system using a mixed TPPTS/pyridine-2-carboxylate complex as catalyst [44]. In most cases the catalyst could be recycled in the aqueous phase, either following phase separation or after extraction of the product from the aqueous phase (e.g. with diethyl ether). Styrene is easily polymerized and therefore selectivity to acids is sometimes low but can be improved by working at lower temparatures of by adding polymerisation inhibitors such as 4-*tert*-butylcatechol [41]. Hydrocarboxylation is often accompanied by formation of palladium black. Asymmetric hydroxycarbonylation of styrene could be achieved with palladium complexes of the chiral bidentate phosphines BDPPTS (**36**) and CBDTS (**37**). The highest optical induction (e.e. 43 %) was observed in the reaction of p-methoxystyrene catalyzed by Pd/**36**. It is of interest, that these catalyst were recycled four times without noticable changes in the catalytic activity or regio- and enantioselectivity [45].

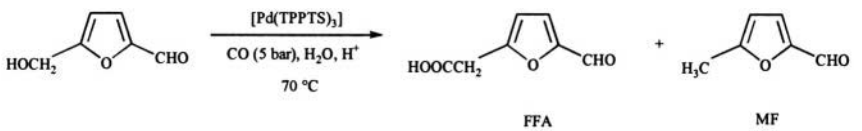
Higher olefins have negligible solubility in water therefore their hydrocarboxylation in aqueous/organic biphasic systems needs co-solvents or phase transfer agents. With the aid of various PT catalysts 1-octene and 1-dodecene were successfully carbonylated to the corresponding carboxylic acids with good yields (**≤ 85 %**) and up to 87 % selectivity towards the formation of the linear acid with a **$[Co_2(CO)_8]$** catalyst precursor under forcing conditions (150 °C, 200 bar CO) [57].

5.4 Carbonylation of alcohols

Carbonylation of *alcohols* to the corresponding carboxylic acids avoids the formation of halide wastes and therefore is a more desirable approach for green chemistry than similar reactions of organic halides. Carbonylation of benzyl alcohol can be catalyzed by **$[Pd(PPh_3)_4]$** (1 mol %) in the presence of 10 mol % of hydrogen iodide (90-110 °C, 90-100 bar) [48,48]. Less than 10 mol % HI led to formation of ester (benzyl benzoate) while at higher HI concentrations increased production of toluene was detected. The reaction mechanism is thought to be similar to the carbonylation of metanol to acetic

acid in that the role of the HI promoter is to form benzyl iodide in rection with benzyl alcohol. Oxidative addition of BzI to Pd(0) generates an intermediate palladium-benzyl species, which upon carbon monoxide insertion reductively eliminates phenylacetyl iodide. Hydrolysis of the latter provides the product phenylacetic acid. Toluene is produced in strongly acidic media by protolysis of the P-C bond in the benzylpalladium intermediate. Several arylmethanols were carbonylated this way with medium to excellent yields.

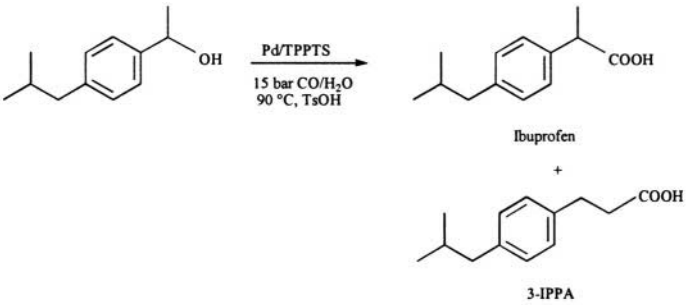
Somewhat similar observations were made in the carbonylation of 5-hydroxymethylfurfural (HMF) catalyzed by a Pd/TPPTS catalyst system (Scheme 5.13). The reaction proceeded smoothly in the presence of Brønsted acids, and depending on the nature and concentration of the acid and on the [P]/[Pd] ratio varying amounts of 5-formylfuran-2-acetic acid (FFA) and 5-methylfurfural (MF) were obtained [49,50]. Acids of weakly or non-coordinating anions, such as phosphoric, hexafluorophosphoric, p-toluenesulfonic and trifluoracetic acid, afforded mainly carbonylation ([FFA]/[MF] = 83:16), while the addition of acids with strongly coordinating anions (hydrogen bromide and hydrogen iodide) changed the selectivity exclusively in favour of MF (99.8 % yield with HI). It is concievable that in the reaction of $[Pd(TPPTS)_3]^+$ and ROH a *bisphosphine* alkylpalladium intermediate, i.e. $[Pd(R)L_2]^+$ is formed provided the anion of the acid promoter is not strongly coordinating. Coordination of a CO molecule into this intermediate produces $[Pd(R)(CO)L_2]^+$, further reactions of which afford the carbonylated product FFA. However, if a strongly coordinating anion, such as iodide, blocks the fourth coordination site and prevents the coordination of CO, then protonation of the Pd-C bond leads to the formation of MF.



Scheme 5.13

5-Hydroxymethylfurfural (HMF) can be readily obtained from acid-catalysed dehydration of carbohydrates. On the other hand, FFA can be further reacted to produce 2,5-furandiacetic acid and 5-carboxyfuran-2-acetic acid which could form polymers, much like tereftalic acid. Therefore the carbonylation of MF can be regarded as the first step of the green manufacture of polymers on the basis of renewable (carbohydrate) raw materials.

Ibuprofen is industrially produced by hydroxycarbonylation of l-(4-isobutylphenyl)ethanol (IBPE) (Scheme 5.14) with Pd/PPh_3 complexes dissolved in organic media [51,52]. This reaction can also be run with $[Pd(TPPTS)_3]^+$ in aqueous media [52,53]. No catalytic carbonylation was observed with $PdCl_2$ alone, the only product was isobutylstyrene formed by dehydration of IBFE with low conversion (12 %) but high selectivity (99.7 %). Tis side reaction could be completely supressed by addition of only 2 equivalents of TPPTS, however a higher [P]/[Pd] ratio increased both the conversion and the selectivity to Ibuprofen. In a biphasic system (no organic solvent) with careful choice of the acid promoter (p-toulenesulfonic acid), [P]/[Pd] ratio (10), CO pressure (15 bar) and temperature (90 °C), 83 % of IBPE was converted to acids of which the major product was Ibuprofen (82 %) together with 17.8 % of the linear isomer (traces of IBS only) [52].

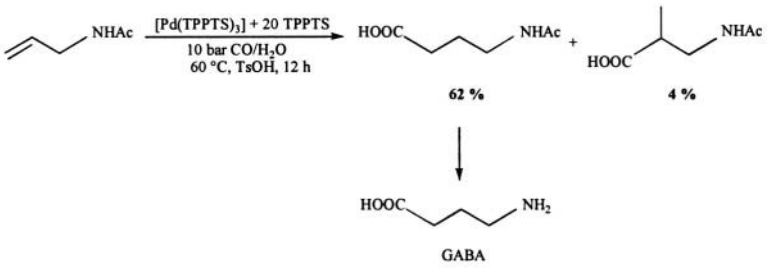


Scheme 5.14

Interestingly, when a water-soluble bisphosphine, a 86/14 mixture of tetra- and trisulfonated 1,3-bis(diphenylphosphino)propane was used as ligand, the rate of carbonylation did not change considerably, however, the selectivity to Ibuprofen was only 22 % and the major product was 3-IPPA (78 %).

Carbonylation of IBPE and other 2-arylethanols with various organosoluble Pd-catalysts was studied in detail with special emphasis on the role of the promoters p-toluenesulfonic acid and LiCl [55]. Some of the catalytic species, such as $[PdCl(PPh_3)_2]^+$ formed from $[Pd(PPh_3)_4]$ or from Pd(II) precursors in aqueous methylethylketone (MEK) under reaction conditions (54 bar CO, 105 °C) were identified by ^{31}P NMR spectroscopy. Ibuprofen was obtained in a fast reaction ($TOF = 850\ h^{-1}$) with 96% yield (3-IPPA 3.9 %), while the carbonylation of l-(6-methoxynaphtyl)ethanol gave 2-(6-methoxynaphtyl)propionic acid (Naproxen) with high selectivity (97.2 %) but with moderate reaction rates ($TOF = 215\ h^{-1}$).

The Pd/TPPTS/p-toluenesulfonic acid (TsOH) catalyst system was found also active in the hydroxycarbonylation of N-allylacetamide. What gives the importance of this process is that de-acetylation of the the linear product affords the important neurotransmitter γ-aminobutyric acid (GABA) (Scheme 5.15). The water solubility of N-allylacetamide allowed the reaction run in water with no organic solvent. Although in aqueous solution carbonylation was accompanied by extensive side reactions (hydrolysis and allylic substitution), under optimized conditions 62 % of N-allylacetamide was converted into 4-acetamidobutyric acid accompanied by a small amount of 3-acetamido-2-methylpropanoic acid (4 % yield). Thus the l/b ratio is much higher (> 15) than what is generally observed with the same catalyst in the hydrocarboxylation of propene (1.3-1.6, see above). Consequently, the amide group should play an active role in determining the regioselectivity, most probably through its coordination to palladium in the intermediate species. When accumulated in sufficient amounts at higher conversions, the by-products of the reaction strongly inhibit the catalysis of hydrocarboxylation, however this can be prevented by a large excess of TPPTS over palladium [56].



Scheme 5.15

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Chapter 6

Carbon-carbon bond formation

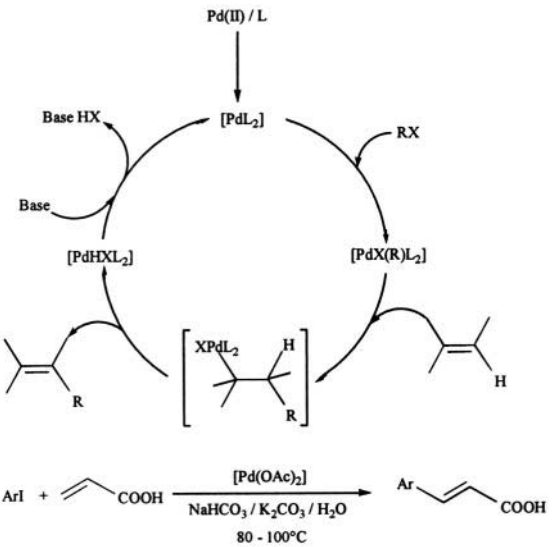
Synthetic organic chemistry is equivalent to systematic making and breaking chemical bonds of which the manipulation of carbon-carbon bonds plays an extraordinary role in construction of an organic molecule. Traditionally this chemistry was carried out in organic solutions, however, water or partially aqueous solvents gain more and more significance in organic synthesis recently. To attempt a comprehensive description of this field would be a hopless venture these days, and this chapter gives only examples of the most important ways of carbon-carbon bond formation in aqueous media. Non-catalytic reactions are discussed in several books and reviews published in the last ten years [1-6] and here we shall focus on *catalysis* of C-C bond formation or rupture *by transition metal complexes.* In most cases, the studies which give the basis of this brief account were motivated by the aims of synthesis and mechanistic details were hardly scrutinized. Consequently, although in several reactions the presence of water was found essential in order to obtain good yields or selectivities explanations of these observations often remain elusive.

Carbon-carbon cross-coupling reactions, such as the Heck, Suzuki, Sonogashira, Tsuji-Trost and Stille couplings are important synthetic methods of organic chemistry and were originally developed for non-aqueous solutions. It has been discovered later that many of the reactions and catalysts do tolerate water or even proceed more favourably in aqueous solvents. The development and applications of these processes in aqueous media is more specifically reviewed in references [7-11]. It is characteristic of this field that the H_2O content of the solvent may vary between wide boundaries, from only a few % to neat water. The other characteristic feauture is in that with a very few exceptions the catalyst is based on palladium with or without tertiary phosphine ligands. Water-soluble phosphines (for example TPPTS and TPPMS) are often used as ligands in

these catalysts. However, in the most popular mixed aqueous-organic solvents (prepared with acetonitrile, butyronitrile or benzonitrile) this may not be necessary since PPh_3 or $[Pd(PPh_3)_4]$ have sufficient solubility in these mixtures.

6.1 Heck reactions in water

Vinylation or arylation of alkenes with the aid of a palladium catalysts is known as the Heck reaction. The reaction is thought to proceed through the oxidative addition of an organic halide, RX onto a zero-valent $[PdL_2]$ species followed by coordination of the olefin, migratory insertion of R, reductive elimination of the coupled product and dehydrohalogenation of the intermediate $[HPdXL_2]$ (Scheme 6.1).



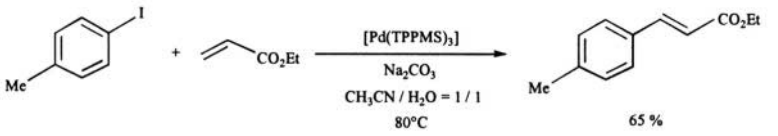
[12]

Scheme 6.1

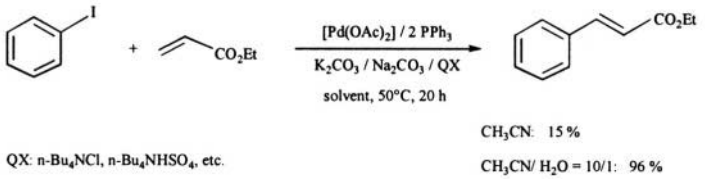
$[Pd(OAc)_2]$ or the complexes formed from it with tertiary phosphines can serve as catalysts (precursors), but $[PdCl_2]$, $[PdCl_2(PPh_3)_2]$, $[Pd(PPh_3)_4]$, $[Pd(DBA)_2]$ (DBA = dibenzylidene acetone) or $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ can also be used. It is well known that in the presence of water phosphines efficiently reduce Pd(II) to Pd(0).

In accordance with the suggested mechanism aryl iodides react easily (Scheme 6.2). At 80-100 °C, iodobenzene and acrylic acid gave cinnamic acid in neat water with $[Pd(OAc)_2]$ as catalyst and a mix of $NaHCO_3$ and K_2CO_3 as base [12]. Similar reactions were run in water/acetonitrile 1/1 with

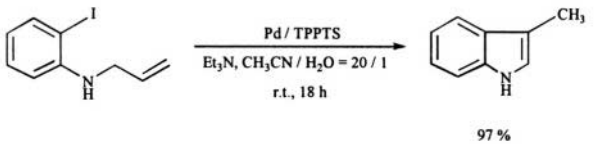
the well-characterized **[Pd(TPPMS)$_3$]** complex [13]. The in situ prepared Pd/TPPTS catalyst was effective for both inter- and intramolecular couplings at room temperature [14]. In the latter case the solvent contained only 5 % water. However, even this limited amount of **H_2O** may be very important for an efficient reaction. It was observed, that in dry acetonitrile the reaction of iodobenzene with methyl acrylate proceeded sluggishly even in the presence of tetrabutylammonium salts, and under given conditions gave only 15 % of methyl cinnamate. In contrast, when a **CH_3CN/H_2O** 10/1 solvent mixture was used the yield of methyl cinnamate exceeded 96 % [15].



[13]



[15]



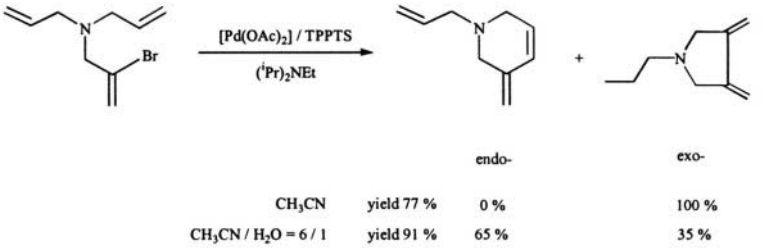
[14]

Scheme 6.2

Despite the fact that aryl bromides are generally less reactive, o- and p-bromotoluenes could be efficiently vinylated with ethene in **DMF/H_2O** with **[Pd(OAc)$_2$] + P(o-tolyl)$_3$** as catalyst and **Et_3N** as base [16]. With careful choice of reaction parameters (90 °C and 6 bar of ethene) all bromotoluene was converted to high purity *ortho*- or *para*-vinyltoluene. Under the conditions used, the reaction mixture forms two phases. In this case the main role of water is probably the dissolution of triethylamine hydrobromide which otherwise precipitates from a purely organic reaction medium and causes mechanical problems with stirring.

Running a Heck reaction in an aqueous phase may substantially change the selectivity of the process as demonstrated by the cyclization of iodo- and

bromodienes [17]. Under non-aqueous conditions such reactions usually afford the exo-product. Indeed, in anhydrous CH_3CN, cyclization of the diallylamine derivative (Scheme 6.3) proceeded with 100% regioselectivity towards the formation of the exo-product. Conversely, in CH_3CN/H_2O 6/1 the same reaction produced a 65/35 mixture of the endo/exo heterocycles.

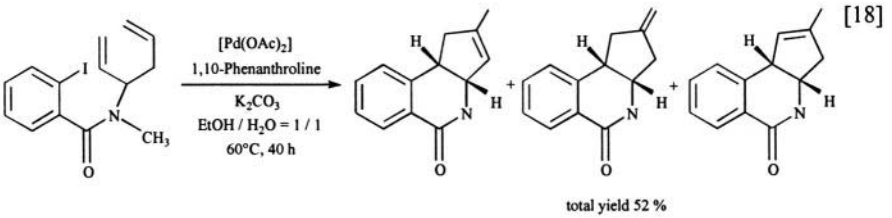


[17]

Scheme 6.3

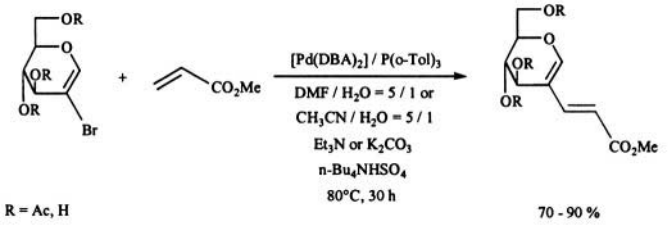
In the cyclization of the (iodoaryl)diene, N-methyl-N-(1,5-hexadiene-3-yl)-2-iodobenzoic acid amide, the combined yield of the tricyclic products arising from a double intramolecular Heck reaction reached 52 % when the catalyst was prepared from $[Pd(OAc)_2]$ and 1,10-phenanthroline and the reaction was run in ethanol/water 1/1 (Scheme 6.4) [18,19]. Interestingly, in CH_3CN the reaction did not proceed at all with this catalyst. It is also noteworthy, that Pd-phenanthroline complexes are rarely used as catalysts in Heck-type reactions.

Unsaturated branched-chain sugars were synthetized with 72-84 % yield from both protected and unprotected 2-bromo-D-glucal with methyl acrylate in CH_3CN/H_2O 5/1 or in DMF/H_2O 5/1 with a catalyst prepared from $[Pd(DBA)_2]$ and P(o-tolyl)$_3$. Et_3N or K_2CO_3 + *n*-Bu_4NHSO_4 could be used as base with similar results.



[18]

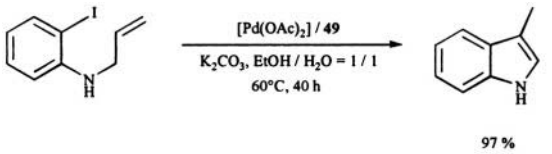
Scheme 6.4



[20]

Scheme 6.5

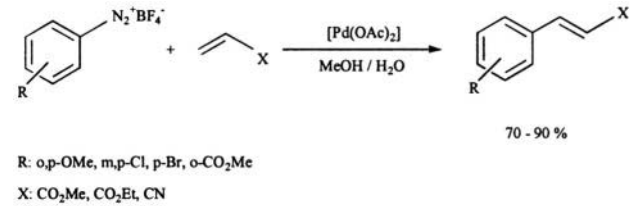
The palladium complex of the dibenzofuran-based water-soluble tertiary phosphine **49** was found catalytically active for the internal Heck reaction of N-allyl-o-iodoaniline in CH_3CN/H_2O 1/1(Scheme 6.6) [21].



[21]

Scheme 6.6

Heck reactions of arenediazonium salts can be conveniently carried out with $[Pd(OAc)_2]$ in ethanol. This method was extended to the one-pot sequential diazotation and allylation of anilines (Scheme 6.7). The latter were converted to the corresponding diazonium salts at 0 °C with $NaNO_2$ + 42 % HBF_4. Ethyl acrylate and $[Pd(OAc)_2]$ were added and the reaction mixture was heated on a water bath for 1 h. The corresponding cinnamate esters were obtained in 65-80 % yield [22].



[22]

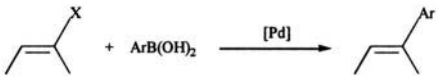
Scheme 6.7

This method of obtaining cinnamate esters directly from anilines has useful features. It is simple and the yields are comparable to those obtained with isolated diazonium salts. However, in this case isolation of the latter is not required, what is most beneficial in case of unstable diazonium salts,

such as the one formed from anthranilic acid. It is to be noted, however, that the reaction is successful only if HBF_4 is used for diazotation; with HCl the aqueous one-pot procedure fails.

6.2 Suzuki couplings in aqueous media

In general terms Suzuki coupling refers to the reaction of organic halides with boronic acids and boronates (Scheme 6.8). These compounds are fairly stable to hydrolysis, so application of aqueous solvents [7-11] is quite straightforward.



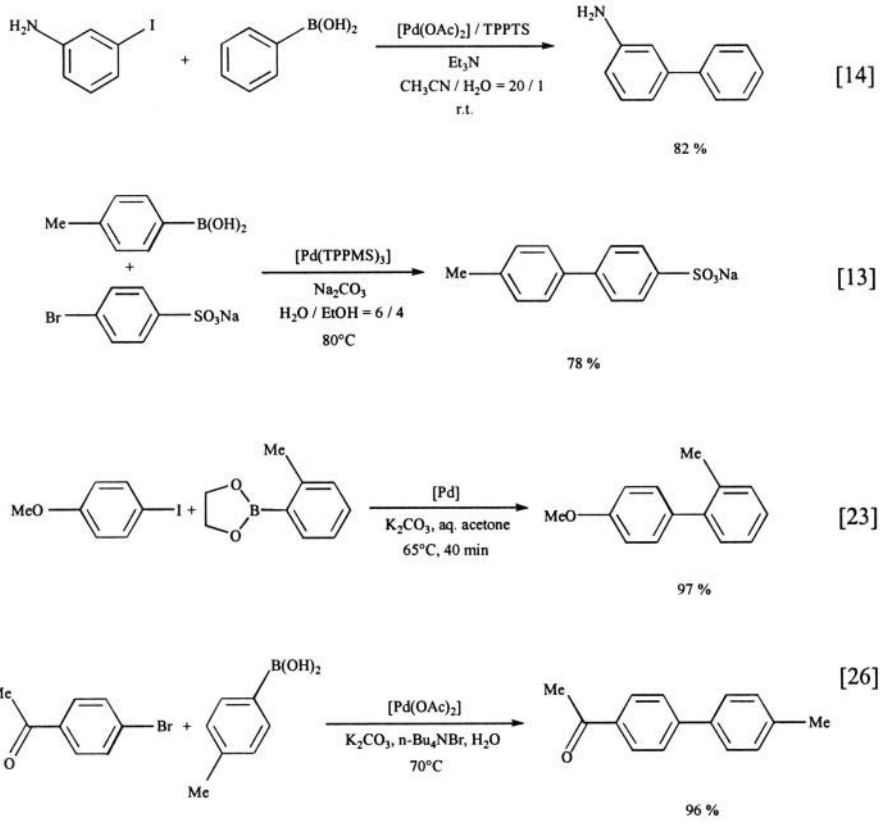
Scheme 6.8

The reaction is catalyzed by palladium complexes either pre-formed, as $[Pd(TPPMS)_3]$ [13], or prepared in situ from (usually) $[Pd(OAc)_2]$ and various phosphines [21,23-27], TPPTS being one of the most frequently used [14]. Other precursors, e.g. $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ and so-called ligand-less (phosphine-free) Pd-catalysts can also be effective. In fact, in several cases a phosphine inhibition was observed [23]. The solvent can be only slightly aqueous (5 % water in CH_3CN, [14]) or neat water [26]. In the latter case a biphasic reaction mixture (e.g. with toluene) facilitates catalyst separation albeit on the expense of the reaction rate. A short selection of the reactions studied in aqueous solvents is shown on Scheme 6.9.

Special mention has to be made of the use of surfactants. Aryl halides are insoluble in water but can be solubilized in the aqueous phase with the aid of detergents. A thorough study [24,25] established that the two-phase reaction of 4-iodoanisole with phenylboronic acid (toluene/ethanol/water 1/1/1 v/v/v), catalyzed by $[PdCl_2\{Ph_2P(CH_2)_4SO_3K\}_2]$, was substantially accelerated by various amphiphiles. Under comparable conditions the use of CTAB led to a 99 % yield of 4-methoxybiphenyl, while 92 % and 88 % yields were observed with SDS and $n\text{-}Bu_4NBr$, respectively (for the amphiphiles see Scheme 3.11). Similar effects were observed with Pd-complexes of other water-soluble phosphines (TPPTS and TPPMS), too.

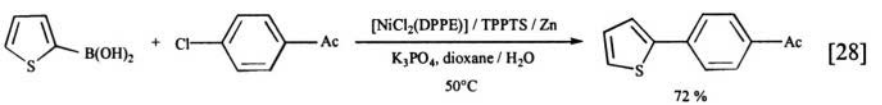
With palladium catalysts aromatic chlorides are rather unreactive, however, nickel is able to catalyze the reactions of these substrates, too. The water-soluble catalyst was generated in situ from the easily available $[NiCl_2(DPPE)]$ and an excess of TPPTS by reduction with Zn in mixtures of 1,4-dioxane and water. Although it had to be used in relatively large quantities (10 mol %), the resulting compound catalysed the cross-coupling

of chloroaromatics with phenylboronic acid (Scheme 6.10) [28]. Sulfur-containing reactants did not poison the catalyst so thienylboronic acid could also be applied.



Scheme 6.9

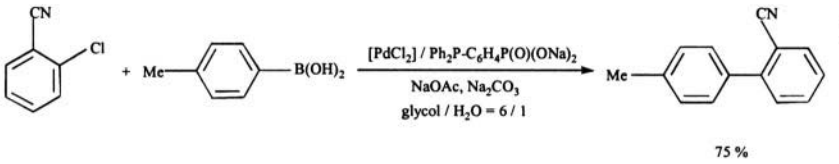
Activated tiophenes were coupled with iodoarenes with phosphine-free Pd-catalysts in CH_3CN/H_2O 9/1 [29].



Scheme 6.10

2-Chlorobenzonitrile was coupled with p-tolylboronic acid affording the important pharmaceutical intermediate 2-(p-tolyl)benzonitrile in good yield

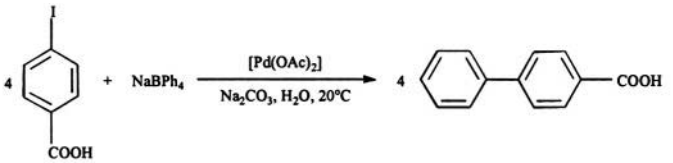
(Scheme 6.11) [30,31]. The catalyst was prepared from $[PdCl_2]$ and the phosphonato-phosphine $Ph_2P\text{-}C_6H_4\text{-}PO(ONa)_2$ in water/ethyleneglycol and a mixture of NaOAc and Na_2CO_3 served as base. Similar results were obtained with the Pd/TPPTS catalyst in a biphasic reaction mixture.



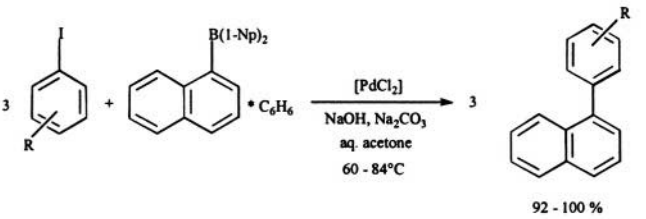
[30]

Scheme 6.11

In a modified version of the Suzuki reaction arylboronates or boranes are utilized instead of arylboronic acid. Under the action of phosphine-free palladium catalysts $NaBPh_4$ and *tris*(1-naphtyl)borane were found suitable phenyl-sources for arylation of haloaromatics in fully or partially aqueous solutions at 20-80 °C with good to excellent yields (Scheme 6.12) [32-34]. Aryl halides can be replaced by water-soluble diaryliodonium salts, Ar_2IX ($X = HSO_4$, BF_4, CF_3COO); in the presence of a base both Ar groups take part in the coupling [35].

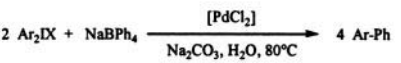


[32]



[34]

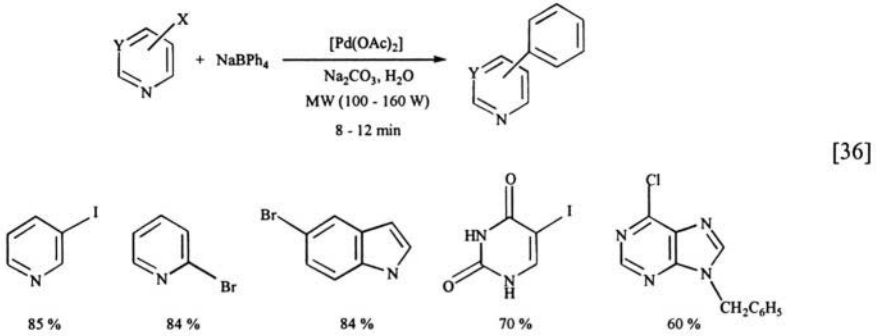
R: p-MeO, m-CO_2H, p-Cl, m-NO_2, p-NH_2, p-OH, p-CN



[35]

Scheme 6.12

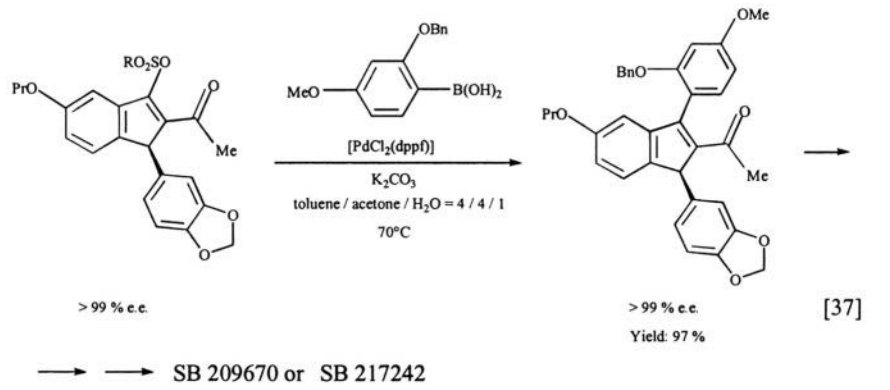
Due to its stability and water-solubility sodium tetraphenylborate is a particularly convenient starting material for such reactions. Several halogenated heterocycles were phenylated with $NaBPh_4$ in aqueous solution with $[Pd(OAc)_2]$ catalyst under *microwave irradiation* (Scheme 6.13) [36]. All reactions were run under argon in Teflon-closed pressure tubes. It is not easy to compare these results to those of thermal reactions, since the temperature of the irradiated samples is not known precisely. Nevertheless, the microwave method is certainly very effective since 8-12 min irradiation at 100-160 W power allowed the isolation of 60-85 % phenylated products.



[36]

Scheme 6.13

Palladium catalyzed cross coupling of arylboronic acid to nonracemic trifluoromethylsulfonyl and fluorosulfonyl enol ethers is one of the key steps in the synthesis two endothelin receptor antagonists, SB 209670 and SB 217242, which have been clinically evaluated for several illnesses including hypertension, ischemia, stroke and others [37] (Scheme 6.14).

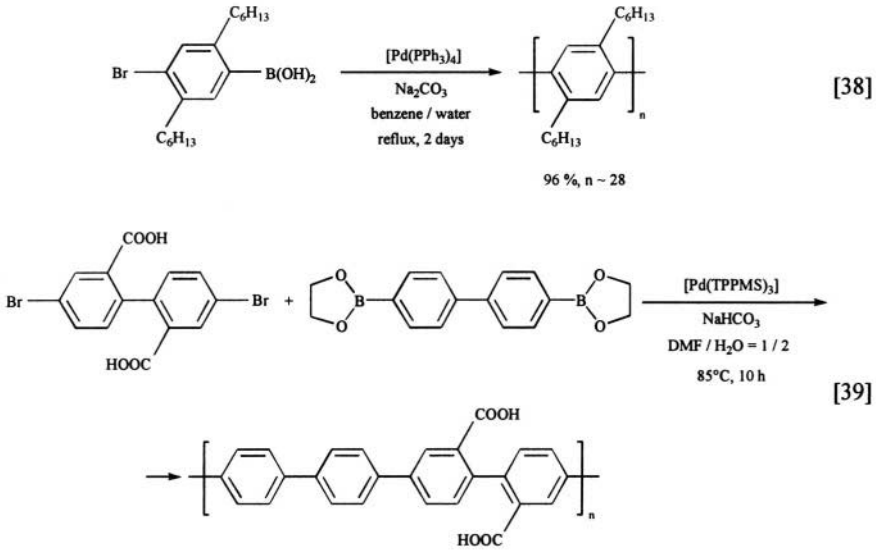


[37]

Scheme 6.14

The reactions were run in toluene/acetone/water 4/4/1 in the presence of K_2CO_3 (strong bases had to be avoided due to the sensitivity of the starting compounds). A Pd-complex of 1,1`-bis(diphenylphosphino)ferrocene, **[$PdCl_2$(dppf)]** proved to be the most efficient catalyst providing the arylated products in excellent yield (up to 98.6%) with complete retention of configuration i.e. with no loss of enantiopurity (Scheme 6.14).

Suzuki cross-coupling has found applications in the preparation of specialty polymers, too. Rigid rod polymers may have very useful properties (the well-known Kevlar, poly(p-phenyleneterephtalamide) belongs to this family, too) but they are typically difficult to synthetize, characterize and process. Such materials with good solubility in organic solvents [38] or in water [39] were obtained in the reactions of bifunctional starting compounds under conventional Suzuki conditions with **[$Pd(PPh_3)_4$]** and **[$Pd(TPPMS)_3$]** catalysts, respectively (Scheme 6.15).

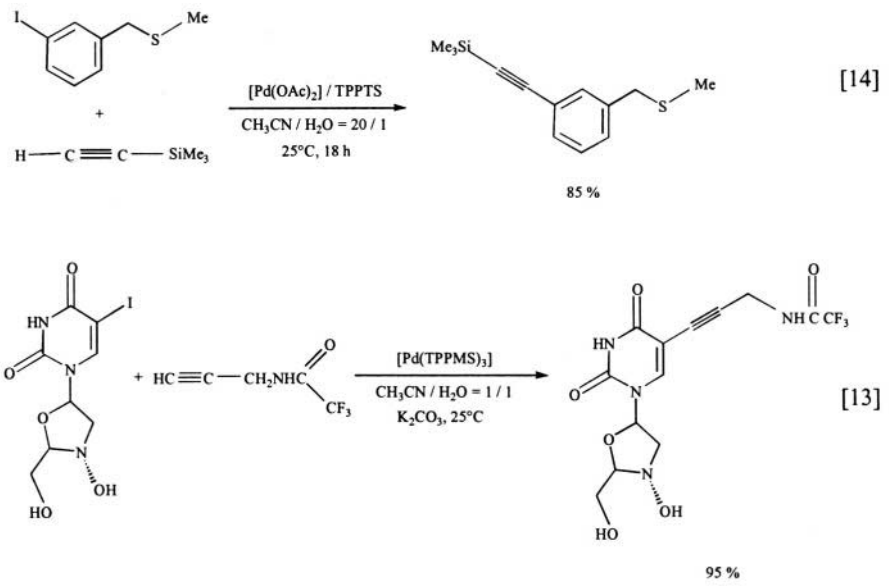


Scheme 6.15

6.3 Sonogashira couplings in aqueous media

Cross-coupling of terminal alkynes with aryl and vinyl halides are usually carried out in organic solvents, such as benzene, dimethylformamide or chloroform with a palladium-based catalyst and a base scavenger for the hydrogen halide. Copper(I) iodide is a particularly effective co-catalyst allowing the reaction to proceed under mild conditions.

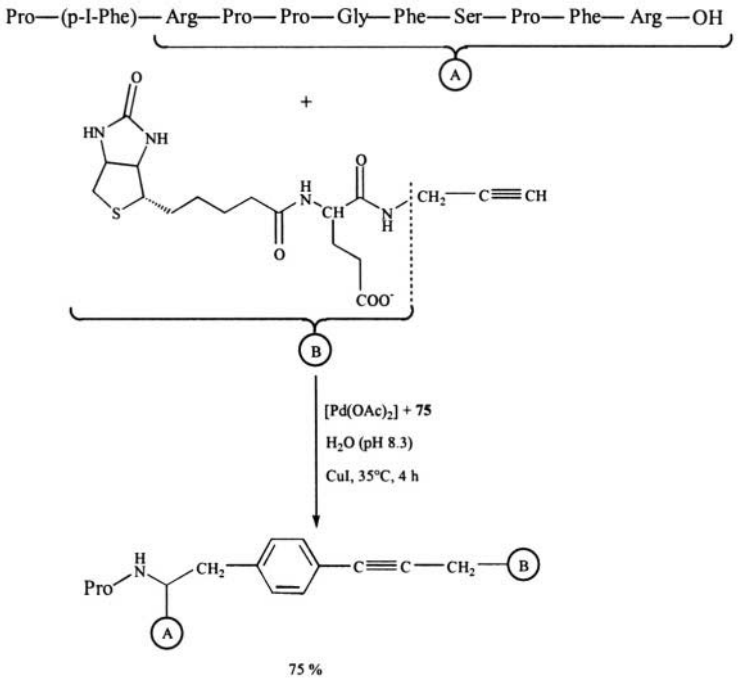
This methodology has been successfully applied in the reactions of biologically interesting compounds, such as nucleosides (e.g. 5-iodo-2`-deoxyuridine) and amino acids [13]. The reactions were generally conducted in aqueous acetonitrile (1/1) with a $[Pd(TPPMS)_3]$ catalyst and a CuI promoter. Similarly, phenylacetylene underwent cross-coupling with various iodobenzenes catalyzed by $[PdCl_2(PPh_3)_2]$ + CuI, using neat water as solvent and n-$Bu_3N + K_2CO_3$ as base [40]. However, it was also observed [14], that a variety of iodoaromatics or vinyl halides reacted with propargyl alcohol, phenylacetylene or ethynyltrimethylsilane without any CuI. Some of these reactions are depicted on Scheme 6.16.



Scheme 6.16

Palladium catalysts containing phosphine ligands with m-guanidinium-phenyl moieties (type **75** and **76**) were found active in the cross-coupling of 4-iodobenzoic acid and (trifluoracetyl)propargylamine [41], as well as in that of 4-iodobenzoic acid and 4-carboxyphenylacetylene [42]. The reactions could also be conducted in water, however, they were considerably faster in aqueous acetonitrile (50 or 70 % H_2O). In addition to their good catalytic activity, the cationic Pd-complexes of guanidinium phosphines are much more stable towards oxidation in aqueous solution than complexes with the TPPTS ligand. The cationic nature of these catalysts is advantageous also in the modification of proteins which carry a net negative charge under conditions required for Sonogashira couplings. It can be

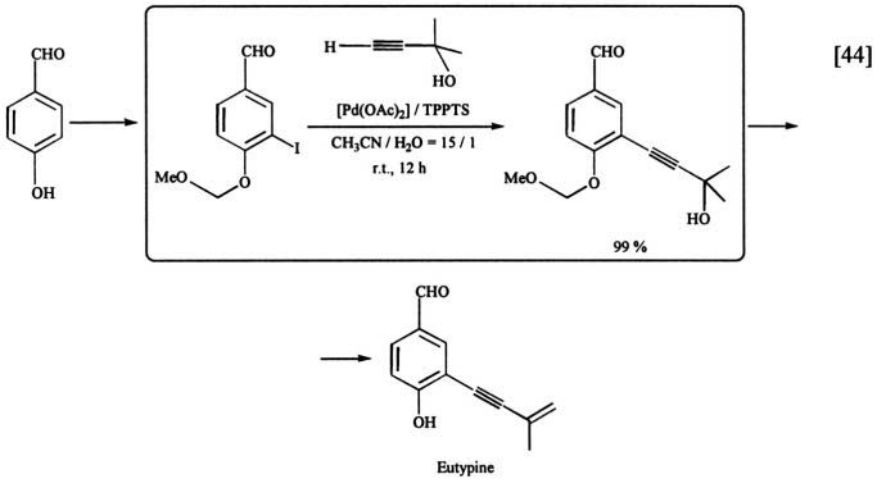
anticipated that in comparison with **[Pd(TPPTS)$_3$]** (overall nine negative charges due to the anionic ligand) the catalyst prepared from **[Pd(OAc)$_2$]** and **75** or **76** will experience no electrostatic barrier in the interaction with proteins. Indeed, it was found, that biotinylglutamoylpropargylamide could be smoothly coupled with an oligopeptide containing a p-iodophenylalanine unit (Scheme 6.17) [43]. The importance of these studies is in that they demonstrate the possibility of protein modification in their natural aqueous environment, furthermore, the reactions provide access to biotinylated oligo- and polypeptides which can be readily bound to avidin (see also 3.1.3) and utilized further in biological chemistry.



[43]

Scheme 6.17

A detailed study on the catalytic use of Pd/TPPTS catalyst in aqueous Sonogashira couplings revealed, that it is possible to obtain unsymmetrical diynes with moderate to good yields in aqueous methanol, with CuI as promoter and **Et$_2$NH** as base (Scheme 6.18) [44]. The same authors describe a short synthesis of Eutypine, which is an antibacterial substance isolated from the culture medium of *Eutypa lata.* The fungus *E. lata* is held responsible for a vinyard disease known as eutyposis, so obviously this synthesis is of great interest.



Scheme 6.18

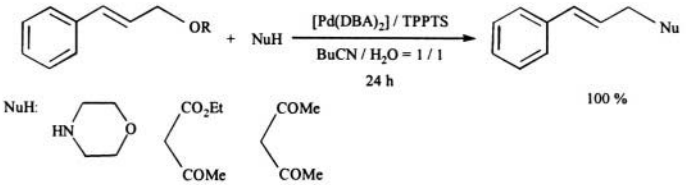
Aqueous palladium-catalyzed Sonogashira coupling reactions were also applied for the preparation of polymers (see Chapter 7).

6.4 Allylic alkylations in aqueous media

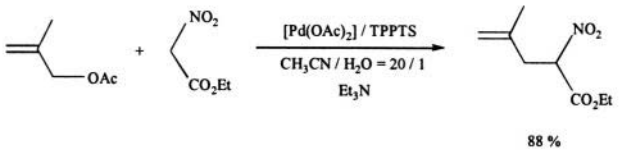
Palladium-catalyzed nucleophilic substitution of allylic substrates (Tsuji-Trost coupling) is a most important methodology in organic synthesis and therefore it is no wonder that such reactions have been developed also in aqueous systems. Carbo- and heteronucleophiles have been found to react with allylic acetates or carbonates in aqueous acetonitrile or DMSO, in water or in biphasic mixtures of the latter with butyronitrile or benzonitrile, affording the products of substitution in excellent yields (Scheme 6.19) [7-11,14,45,46]. Generally, K_2CO_3 or amines are used as additives, however in some cases the hindered strong base diazabicycloundecene (DBU) proved superior to other bases.

One distinct advantage of using water as solvent is in that it dissolves polar substances, the reactions of which would otherwise require highly polar organic solvents and high temperatures. Uracils and thiouracils are hardly soluble in organic media, although they can be alkylated with cinnamyl acetate or ethyl carbonate with a Pd/TPPTS catalyst and DBU as base in DMSO at 105 °C or in refluxing dioxane [47]. Such reactions afford both N-1 and N-3 alkylated products together with the disubstituted derivate. The regioselectivity was substantially changed, however, when a water/acetonitrile 17/2 mixture was used as solvent. With the same catalyst and base, but at much milder conditions (60 °C) the sole product was the

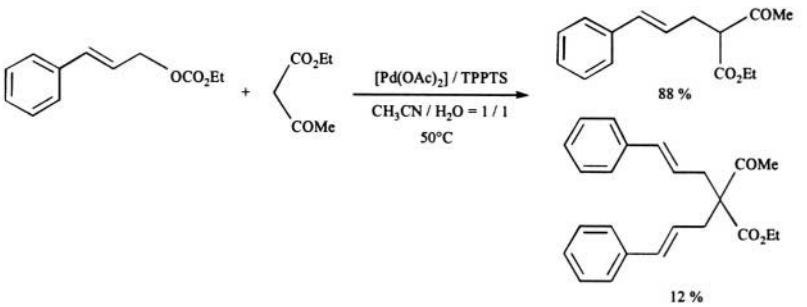
N-1-cinnamyluracil isolated in 80 % yield (Scheme 6.20). Similar changes in regioselectivity were also observed in reactions of various carbonucleophiles with allylic acetates or carbonates [48].



[45]

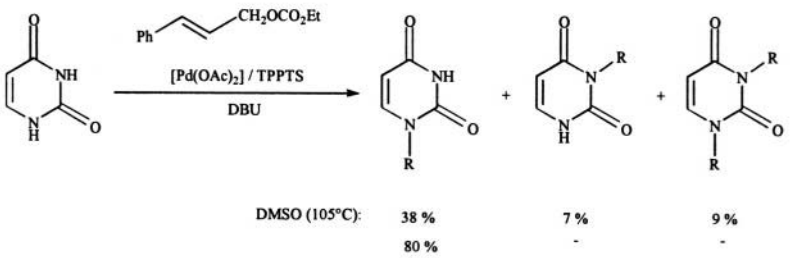


[14]



[46]

Scheme 6.19

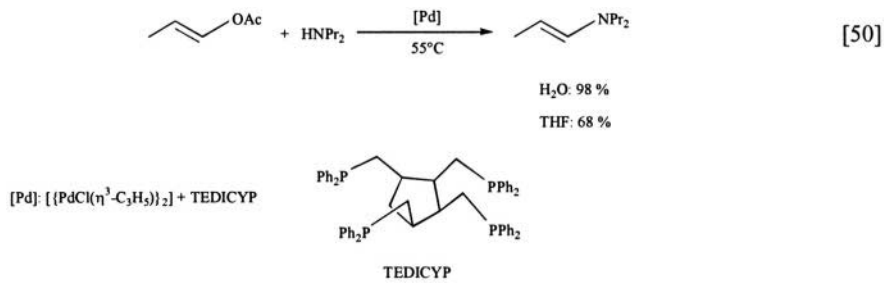


[48]

Scheme 6.20

Although the most frequently used catalysts contain the TPPTS or PPh_3 ligands (probably due to their easy availability and low price) variation of the phosphine in these catalysts may bring unexpected benefits. *Cis,cis,cis-*

1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (TEDICYP), a tetradentate phosphine ligand, in combination with $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ provided an extraordinarily active catalyst of allylic alkylations. In the reaction of dipropylamine and allyl acetate in water at 55 °C, a substrate/catalyst ratio of 1.000.000 could be used and 98% yield was achieved in 240 h, which corresponds to an average turnover frequency $TOF = 4100\ h^{-1}$ (Scheme 6.21) [50]. Several other amines were alkylated with similar efficiency. Such a catalyst activity allows using as low as 0.0001 mol % of the catalyst which is a distinct advantage from environmental aspects, too.

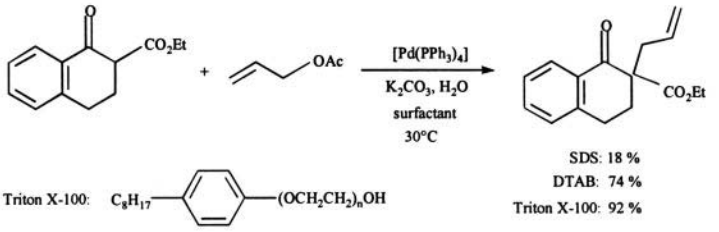


Scheme 6.21

Similar to the case of Suzuki couplings (6.1.2), allylic alkylations can also be run in neat water as solvent in the presence of surfactants. In addition to the general solubilization effect, the amphiphiles may also have a specific influence on the reaction rate. For example, the reaction of the β-ketoester substrate on Scheme 6.22 with allyl acetate, catalyzed by $[Pd(PPh_3)_4]$ was only slightly accelerated by the anionic SDS (1.5 h, 18 % yield), however, the reaction rate dramatically increased in the presence of the cationic CTAB and the neutral Triton X-100 detergents, leading to 74 % and 92% yields in 1.5 h and 5 min (!), respectively [51]. Several other carbonucleophiles were alkylated in such emulsions with excellent yields.

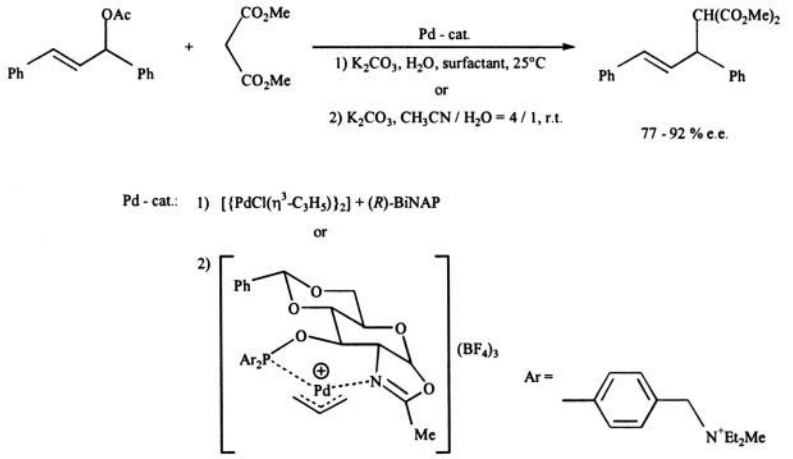
As shown by the previous example, in the presence of surfactants the catalyst need not be water-soluble. This made it possible that Pd-catalysts prepared from $[\{PdCl(\eta^3\text{-}C_3H_5)\}_2]$ and the well known chiral diphosphines, (*R*)-BINAP, (*R*)-MeOBIPHEP and others could be used for the allylation of the prochiral substrate, 1,3-diphenyl-2-propenyl acetate with malonate (Scheme 6.23). Interestingly, there was no reaction with (*S,S*)-CHIRAPHOS. The reactions were conducted in neat water at 25 °C, and –depending on the surfactant– gave good conversions in 0.5-4 hours. Cetyltrimethylammonium hydrogen sulfate, $CTAHSO_4$ provided the fastest reactions (conversions up

to 100 %) and highest enantioselectivities (up to 92 % e.e.). Conversely, in the presence of SDS this reaction did not proceed at all [52].



[51]

Scheme 6.22



[52]

[53]

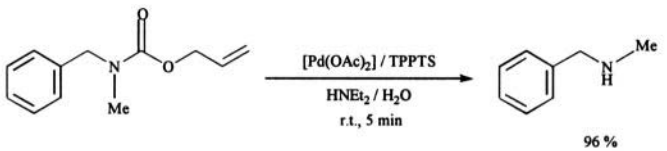
Scheme 6.23

Reactions of the same substrate with several nucleophiles were also catalyzed by the water-soluble Pd-complex of a phosphinite-oxazoline ligand which was prepared from natural D-glucosamine (Scheme 6.23) [53]. The catalyst dissolves well both in water and in CH_3CN but not in diethyl ether. Therefore the reactions could be run either in water/toluene biphasic systems or in homogeneous water/CH_3CN solutions. In the latter case, phase separation could be induced by addition of diethyl ether upon which the catalyst moved quantitatively to the aqueous phase. The product was obtained from the organic phase by evaporation of the solvent(s) and the aqueous solution of the Pd-complex was recycled. In aqueous systems the

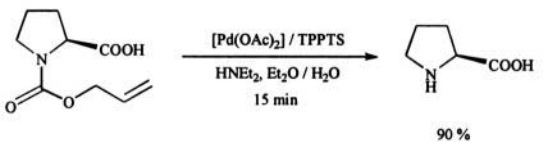
enantiomeric excess varied between 77 and 85 %, somewhat less than the 92 % e.e. obtained in pure acetonitrile.

6.5 Catalytic removal of allylic protecting groups

Smooth and selective removal of protecting groups is of paramount importance in organic synthesis involving sensitive molecules with several functional groups. Allyl and allyloxycarbonyl (Alloc) groups are often used for protection of amino, hydroxy and carboxylic functions, not the least because there are efficient catalytic methods for their removal [7,54-58]. In aqueous media the catalyst of choice is the Pd/TPPTS combination together with diethylamine as scavenger of the allyl moiety (Scheme 6.24). These reactions are usually fast and clean and allow the isolation of the deprotected compounds in high yields. The by-products (CO_2 and diethylallylamine) can be removed by vacuum, which further drives the reaction towards completion.



[54]

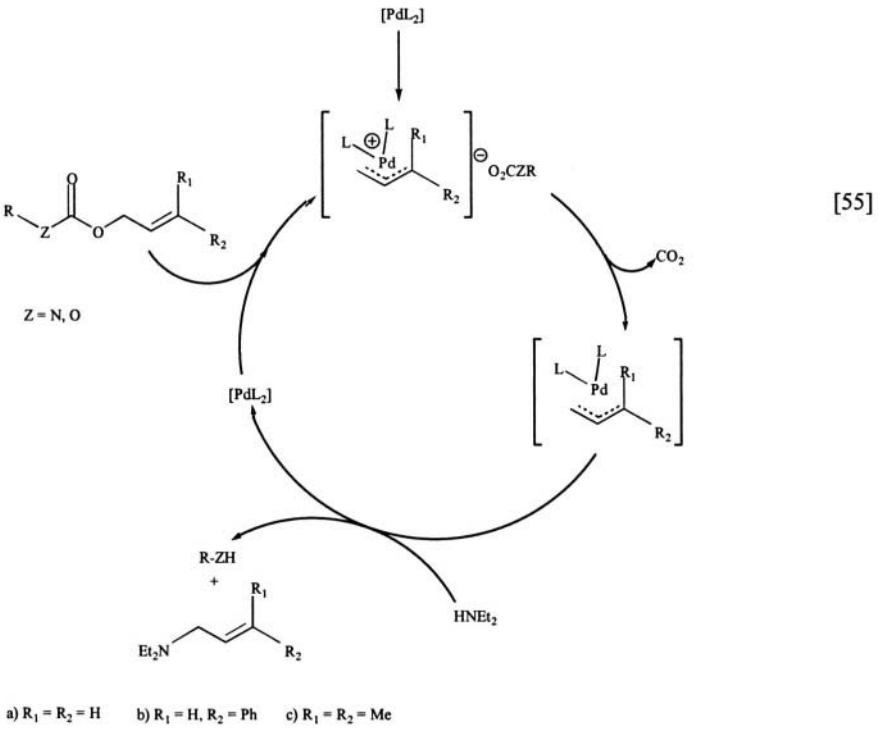


[54]

Scheme 6.24

The reaction mechanism (Scheme 6.25) involves formation of a cationic π-allylpalladium complex by the oxidative addition of the substrate onto the catalyst. In case of a dimethylallyloxycarbonyl protecting group this step is disfavoured compared to Alloc and therefore the removal of dimethylallyl groups is slower or requires more catalyst. Accordingly, in homogeneous CH_3CN/H_2O solutions deprotection of (allyl)phenylacetate proceeded instantaneously with 2 mol % $[Pd(OAc)_2]$/TPPTS while it took 85 min to remove the dimethylallyl group (cinnamyl is an intermediate case with 20 min required for complete deprotection). The reactivity differences are

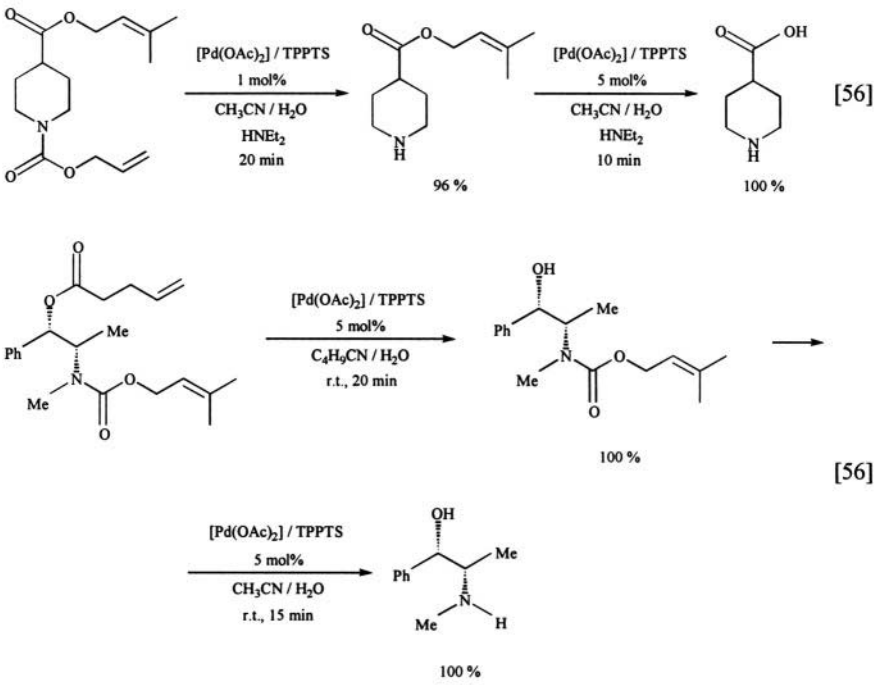
even more pronounced in biphasic mixtures: in ***n*-BuCN/H_2O 5/1**, even with 5 mol % Pd-catalyst, (dimethylallyl)- and (cinnamyl)phenylacetates did not react at all, while it was still possible to cleave the allyl ester [55].



[55]

Scheme 6.25

This gives a possibility for selective removal of allyl and dimethylallyl protecting groups by the proper choice of the amount of the catalyst or by variation of the solvent composition. For example, the allyloxycarbamate of isonipecotic acid was selectively cleaved in the presence of 1 % of Pd, without effecting the dimethylallyl carbonate. However, increasing the amount of the catalyst to 5 % led to a smooth deprotection of the carboxylate group, too (Scheme 6.26). In the doubly protected (1*R*,2*S*)-(–)-ephedrine the allyloxycarbonyl group was selectively cleaved from the oxygen with 5 % Pd/TPPTS in a biphasic butyronitrile/water mixture. Under these conditions the dimethylallylcarbamate moiety did not react. Deprotection of the secondary amine part of the molecule, however, could be easily achieved with the same amount of catalyst in homogeneous solutions made with **CH_3CN/H_2O** (Scheme 6.26).



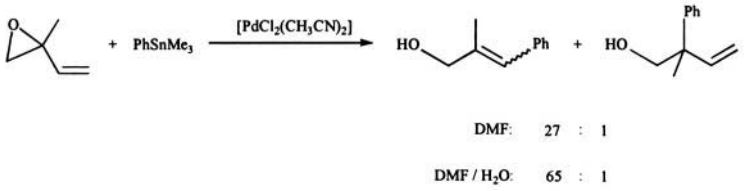
Scheme 6.26

Chemically modified **β-cyclodextrins** were successfully used to accelerate the deprotection of various water insoluble allylic carbonates in genuine two-phase systems without organic cosolvents. The cyclodextrins act not only as reverse phase transfer agents but may increase the selectivity of the reactions through molecular recognition [59-60] (see also Chapter 10).

6.6 Stille couplings in aqueous media

The palladium-catalyzed coupling of aryl and vinyl halides to organotin compounds, known as Stille coupling, is one of the most important catalytic methods of carbon-carbon bond formation. The reaction is generally conducted in polar organic solvents, such as dimethylformamide, with tertiary phosphine complexes of palladium, although phosphine-free complexes or simple Pd-salts are also frequently used as catalysts [8].

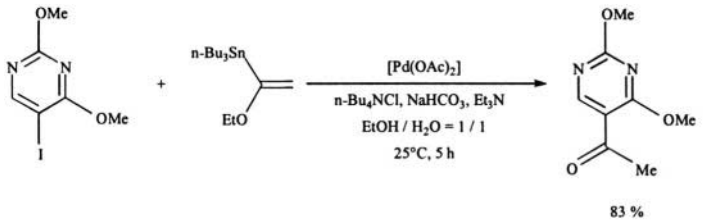
It has been observed quite long ago, that small amounts of water improved the selectivity of the phenylation of 1-methyl-1-vinyloxirane (Scheme 6.27) [61]. Both the relative amount of the rearranged product and the E/Z ratio were increased in aqueous DMF.



[61]

Scheme 6.27

It is mentioned in an early paper on the effect of water on Heck vinylations [62] that 2,4-dimethoxy-5-iodopyrimidine reacted with 1-(ethoxyethenyl)-tri-*n*-butylstannane to afford an acylated pyrimidine derivative in 83 % yield (via in situ hydrolysis of the intermediate enol ether) (Scheme 6.28).



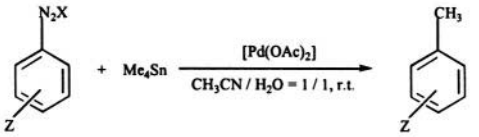
[62]

Scheme 6.28

Arenediazonium salts reacted with tetramethyltin under very mild conditions in acetonitrile yielding the corresponding toluenes [63] and this reaction could be carried out in aqueous media, as well [64] (Scheme 6.29). Similar to the Heck reactions discussed in 6.1.1, a one-pot procedure could be devised starting from anilines, with no need for the isolation of the intermediate diazonium salts. The pH of the solutions should always be kept below 7 in order to avoid side reactions of the diazonium salts, however, unlike with the Heck reactions, HCl or H_2SO_4 can also be used. Since organotin compounds are easily hydrolysed in acidic solutions, a careful choice of the actual pH is required to ensure fast and clean reactions. Diaryliodonium salts are hydrolytically stable and also react smoothly with various organotin compounds (Scheme 6.29) [65].

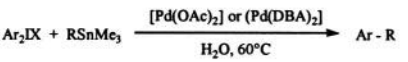
In addition to all the good features of the Stille couplings, there are a few problems with the use of $RSnMe_3$ or $RSn(n\text{-}Bu)_3$ in aqueous solutions. These compounds are rather volatile and water-insoluble but this can be overcome with the aid of co-solvents. However, the products of the reaction still contain alkyltin species which are toxic and environmentally unacceptable. Furthermore, only one of the four Sn-C units take active part in the

susbtitution which is a waste of the organotin reagent. These problems can be partially eliminated by the use of the readily available monosubstituted organotin compounds $RSnX_3$ [66,67]. In the presence of KOH these compounds dissolve in water as various hydroxotin species and are suitable for reaction with aryl and vinyl halides (Scheme 6.30). The reactions are effectively catalyzed by phosphine-free palladium salt, too, but in several cases improvement of the yields could be achieved by addition of TPPMS or TPPDS. This is one of the scarce applications of disulfonated triphenylphosphine in catalysis [67].



[64]

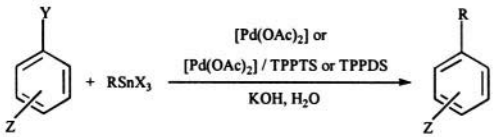
X = Cl, HSO_4 Z = o-, p-NO_2, p-I, p-Br, p-MeO, p-Me



[65]

Ar = C_6H_5, C_6H_4-m-NO_2 R = Me, C_6H_4-m-Me

Scheme 6.29

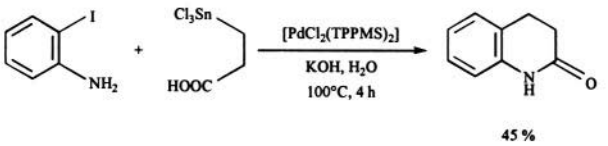


[66, 67]

Y = Br, I X = Cl, Br

Z = p-Me, p-OH, p-COMe, p-OCH_2COOH, m-COOH, o-NH_2

R = Ph, Me, i-Pr, n-Bu, CH_2CH_2COOH, $CH_2=CH$, cis-HOOC−CH=CH



[66]

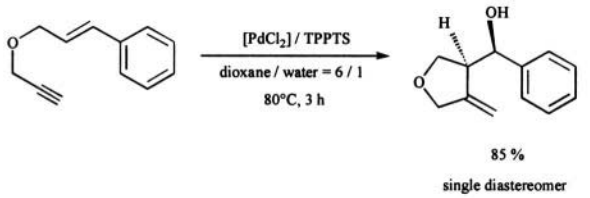
45 %

Scheme 6.30

6.7 Other catalytic C-C bond formations

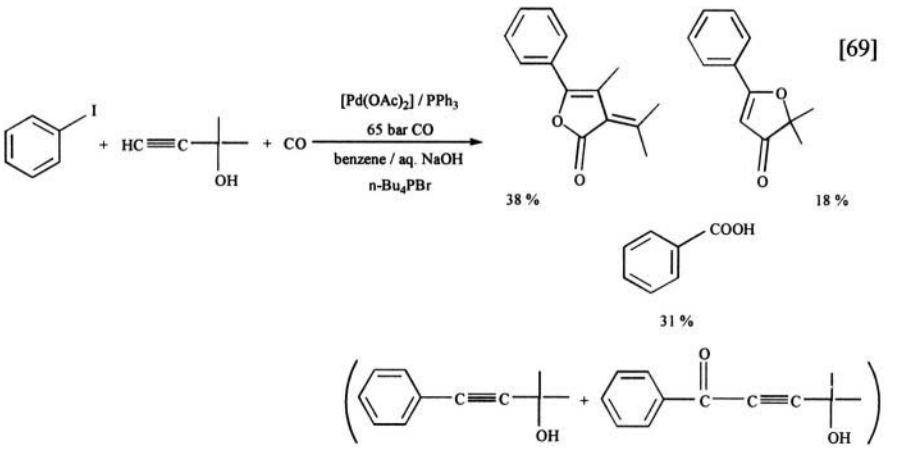
6.7.1 Miscellaneous reactions

Intramolecular *hydroxypalladation* of 1,6-enynes is catalyzed by the $[PdCl_2]$/TPPTS catalyst in aqueous media. Such hydroxylations/cyclizations yielded (hydroxyaryl)tetrahydrofurans or (hydroxyaryl)cyclopentanes with good to moderate yields (Scheme 6.31) [68]. Although the reactions work well with no added base, an active role of a $[Pd(H)(OH)L_2]$ species is supposed.



[68]

Scheme 6.31

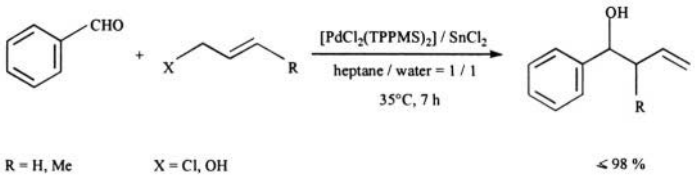


[69]

Scheme 6.32

Carbonylative coupling of iodobenzene with 2-methyl-3-butyn-2-ol under 65 bar carbon monoxide afforded phenylfuranones (double carbonylation) in reasonable yields (Scheme 6.32) [69]. The reaction is thought to proceed through the formation of a benzoylpalladium intermediate which either reacts with the alkynol or liberates benzoic acid; hence the formation of considerable amounts of the latter.

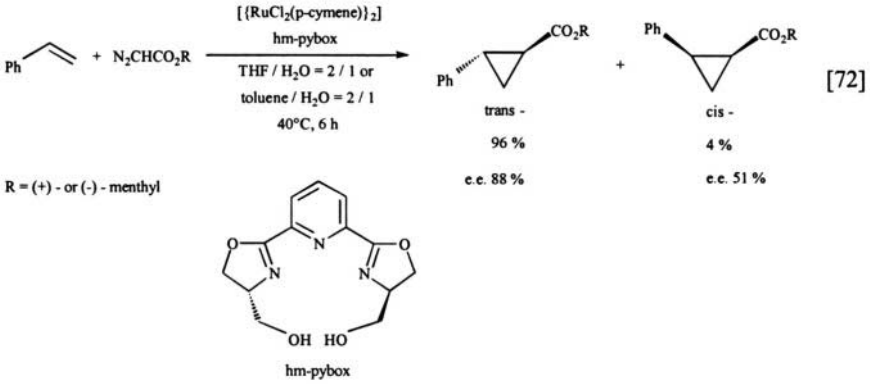
Stoichiometric *Barbier-Grignard type reactions*, mediated by tin, zinc, indium or other metals proceed readily in aqueous solutions [70]. *Catalytic* reactions of this kind are more scarce to find. Benzaldehyde and sulfonated benzaldehyde were readily allylated with allyl and cinnamyl halides in the presence of $SnCl_2$ and a $[PdCl_2(TPPMS)_2]$ catalyst in heptane/water biphasic systems (Scheme 6.33). The amphiphilic palladium complex acted as a phase transfer agent, too, carrying the coordinated allyl moiety into the aqueous phase where the reactions with $SnCl_2$ (or rather with its hydrolysis products) took place. Several other aromatic aldehydes reacted similarly, affording the carbonyl-allylated products in high yields (generally close to 100 %).



[71]

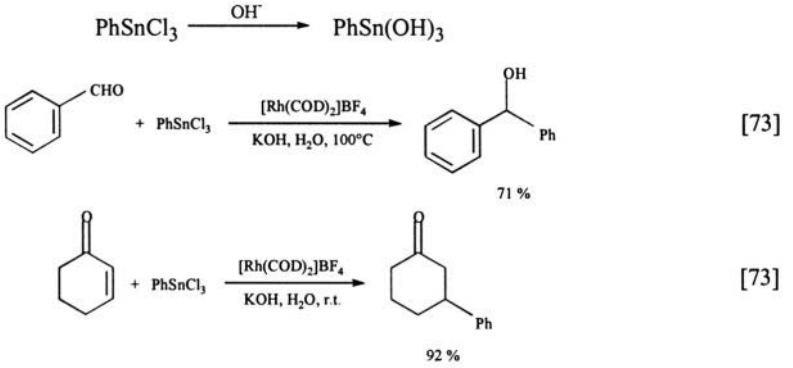
Scheme 6.33

Cyclopropanation is an important synthetic method, and enantioselective catalytic reactions of olefins and diazoacetates provide access to valuable products with biological activity. In general, these reactions are conducted in anhydrous solvents and in several cases water was found to diminish the rate or selectivity (or both) of a given process. Therefore it came as a surprise, that the Cyclopropanation of styrene with (+)- or (–)-menthyl diazoacetates, catalyzed by a water-soluble Ru-complex with a chiral bis(hydroxymethyldihydrooxazolyl)pyridine (hm-pybox) ligand proceeded not only faster but with much higher enantioselectivity (up to 97 % e.e.) than the analogous reactions in neat THF or toluene(8-28 % e.e.) (Scheme 6.34) [72]. The fine yields and enantioselectivities may be the results of an accidental favourable match of the steric and electronic properties of *hm-pybox* and those of the menthyl-dizaoacetates, since the hydroxyethyl or isopropyl derivatives of the ligand proved to be inferior to the hydroxymethyl compound. Nevertheless, this is the first catalytic aqueous cyclopropanation which may open the way to other similar reactions in aqueous media.



Scheme 6.34

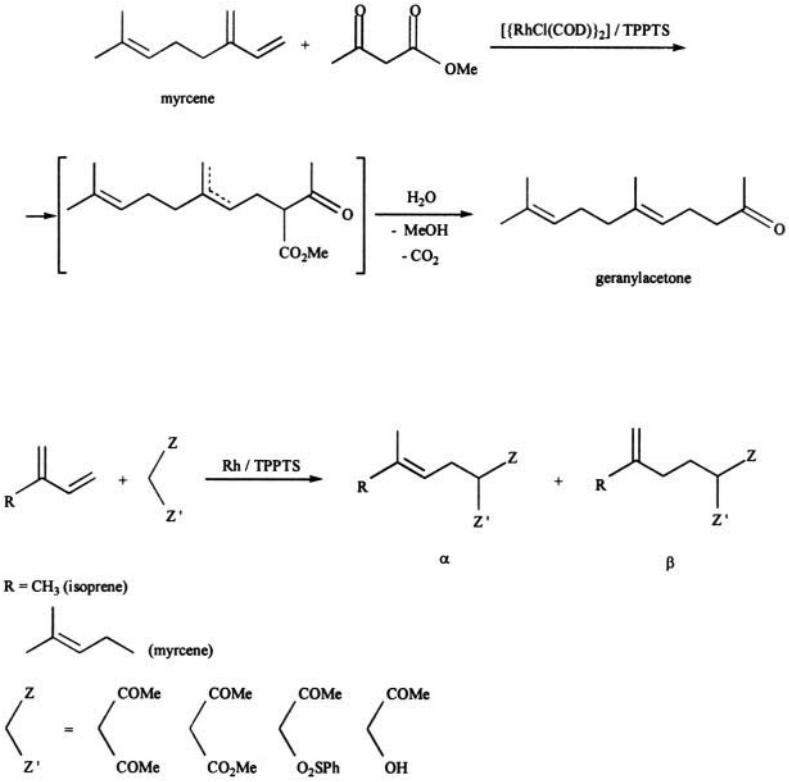
In basic aqueous solutions with a $[Rh(COD)_2]BF_4$ catalyst, *phenyltin trichloride* was found to react with *aromatic aldehydes or unsaturated ketones.* In the presence of a strong aqueous alkali (KOH) $PhSnCl_3$ is readily hydrolysed and the products of this reaction, such as e.g. $PhSn(OH)_3$ add to the carbonyl function of aldehydes or undergo conjugate addition to unsaturated ketones (Scheme 6.35). In the absence of KOH no reaction takes place at all. Yields are generally high [73].



Scheme 6.35

6.7.2 Nucleophilic additions to 1,3-dienes; the synthesis of geranylacetone

In the presence of Rh(I)-catalysts, conjugated dienes react with active methylene compounds (or with heteronucleophiles) both in organic and in aqueous solutions (Scheme 6.36). This general reaction [74,75] has been developed by Rhône Poulenc into a new industrial process for manufacturing geranylacetone (Scheme 6.36) [76,77], required for the production of Vitamin E. Easily available technical grade myrcene is reacted with methyl acetoacetate using a catalyst prepared either from rhodium sulfate and excess TPPTS or (on a laboratory scale) from $[\{RhCl(COD)\}_2]$ and sulfonated phosphine(s). In this particular case the aqueous system with TPPTS leads to 1:1 addition with high regioselectivity (> 99%) in contrast to organic solutions with PPh_3 where only 1:2 addition products are obtained. This advantageous difference is probably due to the protection of the 1:1 adduct against further nucleophilic addition by separation into the organic phase.



Scheme 6.36

The industrial process requires a large phosphine excess ([P]/[Rh] = 21:1) which can be easily provided by the extremely water-soluble TPPTS. However, the reactants are insoluble in such an aqueous phase, therefore the reaction is run in the presence of co-solvents, usually alcohols. (Less soluble TPPMS performs better at [P]/[Rh] = 3, probably its surfactant properties help in solubilizing the diene and methyl acetoacetate.) The organic products are easily separated from the aqueous catalyst solution which can be recycled.

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Chapter 7

Dimerization, oligomerization and polymerization of alkenes and alkynes

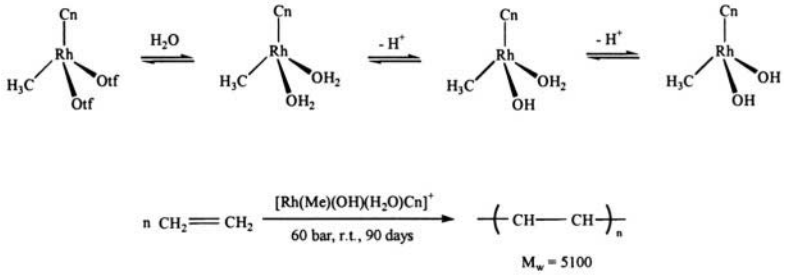
The annual production of various polymers can be measured only in billion tons of which polyolefins alone figure around 100 million tons per year. In addition to radical and ionic polymerization, a large part of this huge amount is manufactured by coordination polymerization technology. The most important Ziegler-Natta, chromium- and metallocene-based catalysts, however, contain early transition metals which are too oxophilic to be used in aqueous media. Nevertheless, with the late transition metals there is some room for coordination polymerization in aqueous systems [1,2] and the number of studies published on this topic is steadily growing.

7.1 Dimerization and polymerization of ethylene

Coordination polymerization of ethylene by late transition metals is a rather slow process especially when the catalyst is dissolved in water. In a study of the interaction of $CH_2=CH_2$ and $[Ru(H_2O)_6](tos)_2$ (tos = tosylate), both $[Ru(CH_2=CH_2)(H_2O)_5](tos)_2$ and $[Ru(CH_2=CH_2)_2(H_2O)_4](tos)_2$ were isolated by evaporation of the aqueous phase which had been previously pressurized with 60 bar ethylene at room temperature for 6 and 18 hours, respectively. Longer reaction times (72 h) led to the formation of butenes with no further oligomerization. This aqueous catalytic dimerization was not selective, the product mixture contained Z-2-butene, E-2-butene and 1-butene in a 1/2.2/2.2 ratio [3].

The facially coordinating 1,4,7-trimethyl-1,4,7-triazacyclononane (Cn) ligand forms stable methylrhodium(III) complexes, such as $[Rh(Me)_3Cn]$, $[Rh(Me)_2Cn]OTf$ and $[Rh(Me)Cn](OTf)_2$ (OTf=trifluoromethanesulfonate) and the latter two have rich aqueous chemistry. When dissolved in water, $[Rh(Me)Cn]^{2+}$ readily coordinates two water molecules to form the

octahedral $[Rh(Me)(H_2O)_2Cn]^{2+}$ in which the aqua ligands undergo sequential deprotonation in basic solutions with $pK_{a,1} = 8.6$ and $pK_{a,2} = 10.7$ (Scheme 7.1) [4].

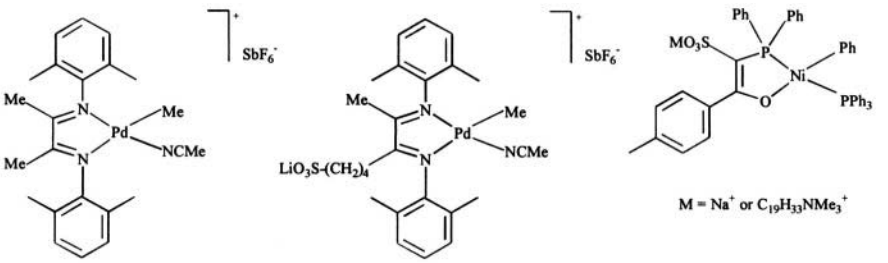


Scheme 7.1

At 24 °C and 15-60 bar ethylene, $[Rh(Me)(OH)(H_2O)Cn]^+$ catalyzed the slow polymerization of ethylene [4]. Propylene, methyl acrylate and methyl methacrylate did not react. After 90 days under 60 bar $CH_2=CH_2$ (the pressure was held constant throughout) the product was low molecular weight polyethylene with $M_w = 5100$ and a polydispersity index of 1.6. This is certainly not a practical catalyst for ethylene polymerization ($TOF \approx 1$ in a day), nevertheless the formation and further reactions of the various intermediates can be followed conveniently which may provide ideas for further catalyst design. For example, during such investigations it was established, that only the monohydroxo-monoaqua complex was a catalyst for this reaction, both $[Rh(Me)_3Cn]$ and $[Rh(Me)(H_2O)_2Cn]^{2+}$ were found completely ineffective. The lack of catalytic activity of $[Rh(Me)_3Cn]$ is understandable since there is no free coordination site for ethylene. Such a coordination site can be provided by water dissociation from $[Rh(Me)(OH)(H_2O)Cn]^+$ and $[Rh(Me)(H_2O)_2Cn]^{2+}$ and the rate of this exchange is probably the lowest step of the overall reaction.The hydroxy ligand facilitates the dissociation of H_2O and this leads to a slow catalysis of ethene polymerization.

Cationic Pd- and neutral Ni-complexes of chelating N-N or P-O ligands catalyze the polymerization of ethylene in aqueous media with reasonably high acitivity (Scheme 7.2) [5,6,61,62]. In fact, the turnover frequencies are close to those obtained with the same catalysts in CH_2Cl_2 (TOF-s 450 vs. 600 h^{-1} at room temperature). On the other hand, aqueous polymerizations provided polymers with much higher molecular mass (e.g. 77700 compared to 14500, obtained in CH_2Cl_2). The same kind of branching was found in these polymers, nevertheless the higher molecular mass was manifested in the physical apperance - the polymers obtained in the aqueous reactions

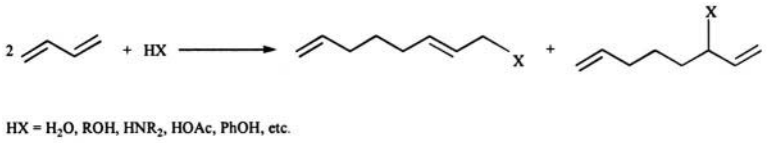
were rubbery solids while polymerizations in CH_2Cl_2 afforded viscous oils. Very importantly, the active Pd- and Ni-catalysts are water-*insoluble*, consequently these aqueous polymerizations were catalyzed by solid particles of the catalysts suspended in the aqueous phase rather than by homogeneously dissolved metal complexes. When a palladium catalyst was made water-soluble by using a sulfoalkyl-modified diimine ligand no activity whatsoever was observed. The catalytic activity was similarly lost upon dissolution of the catalysts in the aqueous phase by co-solvents, such as acetone.



Scheme 7.2

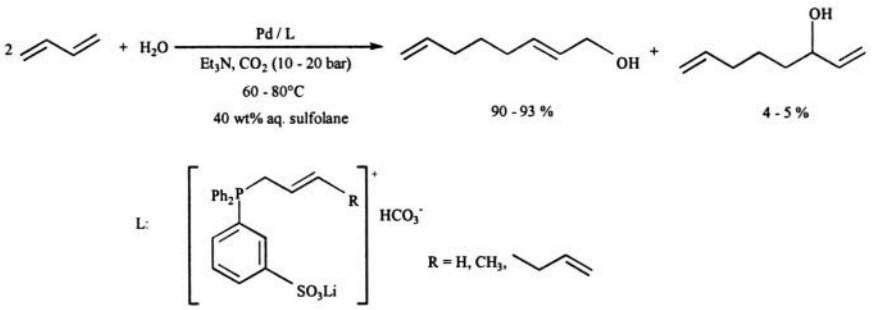
7.2 Telomerization of dienes

The linear telomerization reaction of dienes was one of the very first processes catalyzed by water soluble phosphine complexes in aqueous media [7,8]. The reaction itself is the dimerization of a diene coupled with a simultaneous nucleophilic addition of HX (water, alcohols, amines, carboxylic acids, active methylene compounds, etc.) (Scheme 7.3). It is catalyzed by nickel- and palladium complexes of which palladium catalysts are substantially more active. In organic solutions $[Pd(OAc)_2] + PPh_3$ gives the simplest catalyst combination and Ni/TPPTS and Pd/TPPTS were suggested for running the telomerizations in aqueous/organic biphasic systems [7]. An aqueous solvent would seem a straightforward choice for telomerization of dienes with *water* (the so-called hydrodimerization). In fact, the possibility of separation of the products and the catalyst without a need for distillation is a more important reason in this case, too.



Scheme 7.3

The most important aqueous catalytic telomerization reaction is that of butadiene with water affording octadienols. 2,7-Octadien-1-ol can be easily hydrogenated to yield 1-octanol, which is used as a raw material for obtaining phtalate plasticizers for PVC. With Pd/PPh_3 or with Pd/TPPTS this reaction could not be developed into a commercial process due to the rapid degradation of the catalyst. Such a degradation can be retarded with a large excess of the respective triarylphosphine, unfortunately this leads to an almost complete loss of catalytic activity [9]. This problem was solved by researchers of Kuraray who introduced the phosphonium salt depicted on Scheme 7.4 in place of PPh_3 [9-11]. The water-solubility of this Pd/phosphonium salt catalyst allows to run the hydrodimerization of butadiene in aqueous/organic two-phase systems. For industrial applications an aqueous phase containing 40 wt% sulfolane was found the most advantageous for good reaction rates, easy phase separation during workup and excellent retainment of the Pd-catalyst.



Scheme 7.4

In the industrial process [12] 1,3-butadiene and water are reacted at 60-80 °C in an aqueous sulfolane solvent in the presence of triethylamine hydrogencarbonate under 10-20 bar CO_2 pressure. The reaction yields linear telomers mainly, with a 90-93 % selectivity to 2,7-octadien-1-ol together with 4-5 % 1,7-octadien-3-ol. Most of the products are removed from the reaction mixture by extraction with hexane, and the aqueous sulfolane phase with the rest of the products, the catalyst and the ammonium bicarbonate is

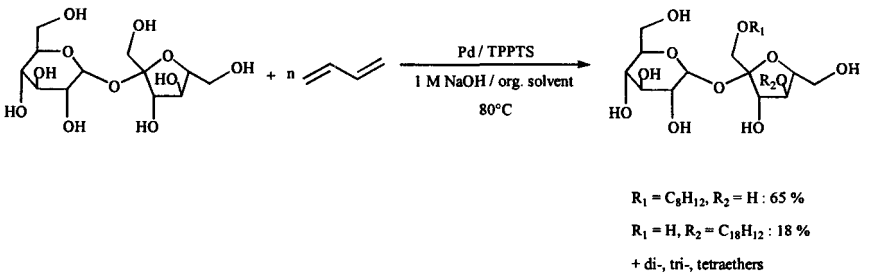
recycled. The loss of the catalyst is in the range of a few ppm. Based on this process, Kuraray operates a plant with a capacity of approximately 5000 t/y.

Interestingly, various phosphonium salts have been applied [13] as constituents of palladium catalysts for hydrodimerization of butadiene and isoprene about the same time when the results of Kuraray were disclosed. These were obtained by quaternization of aminoalkylphosphines with methyl iodide or HCl (Ph_2P-R-NH_2 type compounds are known to yield phosphonium salts with these reagents). Although the catalysts prepared in situ from [$PdCl_2$] were reasonably active (TOF-s of 10-20 h^{-1}) the reactions always yielded complex product mixtures with insufficient selectivity towards the desired 1,7-octadienyl derivatives.

Aqueous/organic biphasic reaction systems with no co-solvents (such as the sulfolane above) would be desirable for simplified technologies of diene telomerization. It was found that with the use of amines which possess one long alkyl chain, such as dodecyldimethylamine good yields of 2,7-octadien-1-ol could be obtained in water alone, under CO_2 pressure. The Pd/TPPTS catalyst showed high activity with TOF-s up to 270 h^{-1} [14,15]. The main byproducts were octatrienes and 4-vinylcyclohexene. Amines, which do not form micelles ($EtNMe_2$, $BuNMe_2$) proved much less useful (TOF = 80 h^{-1}). The beneficial role of the micelle-forming amines may be in the solubilization of butadiene in the aqueous phase, furthermore, the hydrogencarbonate salts formed under CO_2 pressure may also act as phase transfer catalysts. This reaction also shows the kinetic complexities of the telomerization of butadiene with water, the outcome of which greatly depends on the reaction variables [20].

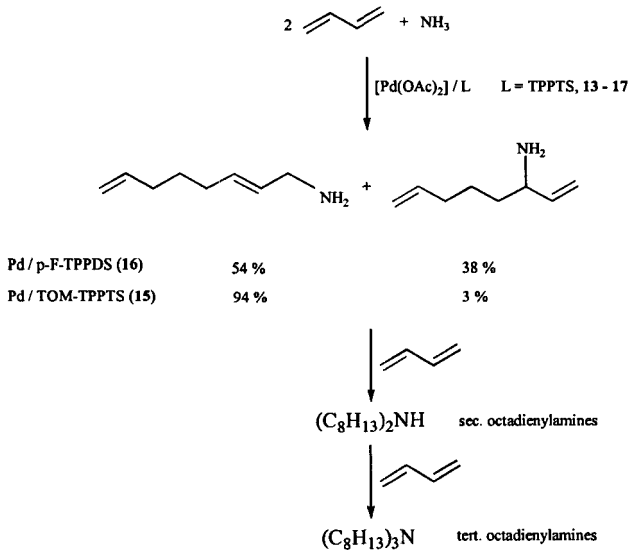
An interesting application of the palladium-catalyzed telomerizations is the reaction of butadiene with sucrose (Scheme 7.5) and other carbohydrates. These substrates are water-soluble therefore it is straightforward to use an aqueous solvent. The products of this reaction (mono- and dioctadienylethers) are hydrophobic alkyl glucosides which are biodegradable, have good surfactant properties and can be used as emulsifiers in various products. From this respect monoalkylated carbohydrates are more valuable. The reactions were run in water/organic solvent (methylisobutylketone, methylethylketone, isopropanol) with a Pd/TPPTS catalyst in the presence of NaOH. Although selective monoalkylation could not be achieved, the average number of alkadienyl chains per carbohydrate unit could be made as low as 1.3 [16]. The products with an average degree of substitution of 4.7-5.3 are clear, almost clourless viscous liquids, practically insoluble in water [60]. It is worth mentioning, that this reaction employs (in part) a renewable raw material and provides a

biodegradable product - both features are important from environmental aspects.



Scheme 7.5

Solutions of the nickel(0) and palladium(0) complexes of 1,3,5-triaza-7-phosphaadamantane, PTA (**82**) and tris(hydroxymethyl)phosphine (**98**) in water catalyze the oligomerization and telomerization of 1,3-butadiene at 80 °C. Although high yields and good selectivities to octadienyl products (87 %) were obtained, the complexes (or the intermediate species formed in the reaction) dissolve sufficiently in the organic phase of the monomer and the products to cause substantial metal leaching [17].



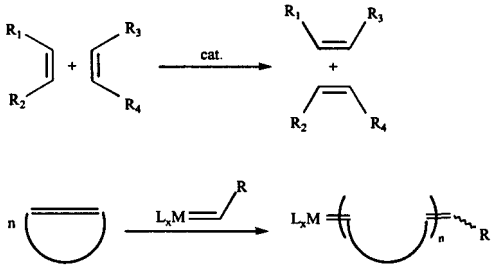
Scheme 7.6

Telomerization of butadiene with ammonia is of great industrial interest. Albeit primary and secondary amines would also be valuable, in single phase organic solutions this reaction yields tertiary octadienylamines as main products. The reason for this result is in that primary and secondary amines are more nucleophilic than NH_3 and in the presence of a catalyst their further reactions cannot be prevented. However, the use of water-soluble Pd-complexes in aqueous/organic biphasic media provides a solution for this problem [18,19]. The first-formed organophilic primary (and secondary) amines collect in the organic phase and thus become unable to compete with NH_3 dissolved in the aqueous phase ("protection by phase separation"). Selective monoalkylation of NH_3 was made possible this way. The reaction was conducted at 80 °C with catalysts prepared from $[Pd(OAc)_2]$ and TPPTS or other sulfonated triarylphosphines, **13-17**. The highest rate ($TOF = 357\ h^{-1}$) was obtained with p-F-TPPDS, **16**, but on the expense of regioselectivity (Scheme 7.6). Conversely, the reactions catalyzed by Pd/TOM-TPPTS (**15**) were slow ($TOF = 47\ h^{-1}$) but provided 2,7-octadienylamine almost exclusively (94 %).

Although not a telomerization, it is mentioned here, that syndiotactic 1,2-polybutadienes were prepared in aqueous emulsions with a π-allyl-cobalt catalyst [33]. Similarly, chloroprenes were polymerized using aqueous solutions of $[PdCl_2(TPPMS)_2]$ and $[RhCl(TPPMS)_3]$ as catalysts at 40 °C in the presence of an emulsifier and a chain growth regulator (R-SH, $R=C_{10}$-C_{18}) [35]. Despite the usual low reactivity of chlorinated dienes, these reactions proceeded surprisingly fast, leading to quantitative conversion of 10 g chloroprene in 2 hours with only 50 mg of catalyst (approximate $TOF = 3500\ h^{-1}$).

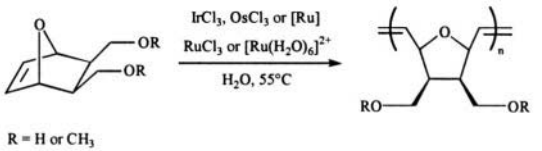
7.3 Ring-opening metathesis polymerizations in aqueous media

Olefin metathesis (olefin disproportionation) is the reaction of two alkenes in which the redistribution of the olefinic bonds takes place with the aid of transition metal catalysts (Scheme 7.7). The reaction proceeds with an intermediate formation of a metallacyclobutene. This may either break down to provide two new olefins, or open up to generate a metal alkylidene species which –by multiple alkene insertion– may lead to formation of alkylidenes with a polymeric moiety [21]. Ring-opening metathesis polymerization (ROMP) is the reaction of cyclic olefins in which backbone-unsaturated polymers are obtained. The driving force of this process is obviously in the relief of the ring strain of the monomers.



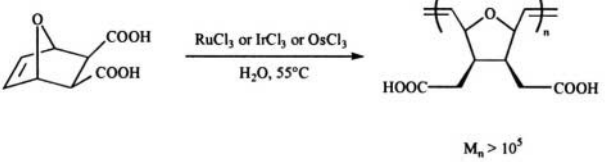
Scheme 7.7

Traditionally, olefin metathesis is catalyzed by complexes of early transition metals which do not tolerate polar functionalities let alone polar or aqueous solvents. However, with the application of late transition metal complexes this situation has been changed substantially [21]. In fact, some of these catalysts worked better in water or in a largely aqueous environment than in meticulously dried organic solvents [22]. A case in the point is the aqueous polymerization of 7-oxanorbornene derivatives (Scheme 7.8) [22-26] catalyzed by $RuCl_3$ or by $[Ru(H_2O)_6]^{2+}$ yielding nearly quantitative yields of the ROMP polymer. It has also been established, that a probable intermediate of the reaction is a $[Ru(H_2O)_5(olefin)]$ complex [25] which may rearrange to an alkylidene species, although this step could not be directly investigated. Water-soluble ROMP polymers were also prepared this way from 7-oxanorbornene dicarboxylates [23].



[21-26]

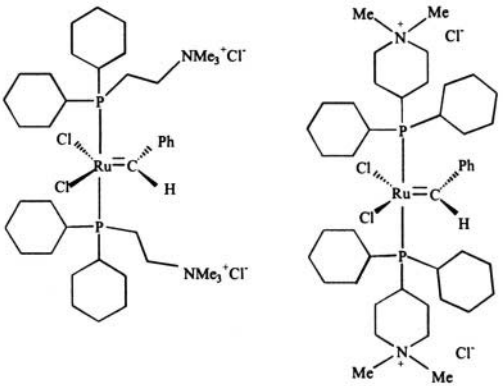
[25]



[23]

Scheme 7.8

These observations led to the catalytic application of well-defined ruthenium alkylidenes, some of them freely soluble and sufficiently stable in water (Scheme 7.9) although their stability was found somewhat less in aqueous solutions than in methanol [21,27,28]. With these catalysts a real living ROMP of water-soluble monomers could be achieved, i.e. addition of a suitable monomer to a final solution of a quantitative reaction resulted in further polymerization activity of the catalyst [28]. This is particularly important in the preparation of block copolymers.

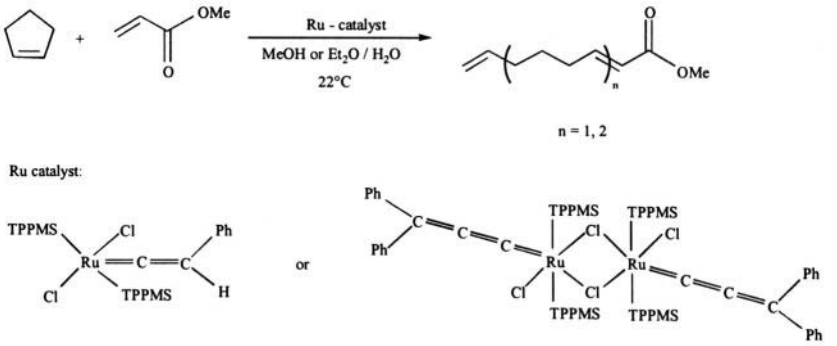


Scheme 7.9

Water-soluble ruthenium vinylidene and allenylidene complexes were also synthetized in the reaction of $[\{RuCl_2(TPPMS)_2\}_2]$ and phenylacetylene or diphenylpropargyl alcohol [29]. The mononuclear Ru-vinylidene complex $[RuCl_2\{C=C(H)Ph\}(TPPMS)_2]$ and the dinuclear Ru-allylidene derivative $[\{RuCl(\mu\text{-}Cl)(C=C=CPh_2)(TPPMS)_2\}_2]$ both catalyzed the cross-olefin metathesis of cyclopentene with methyl acrylate to give polyunsaturated esters under mild conditions (Scheme 7.10).

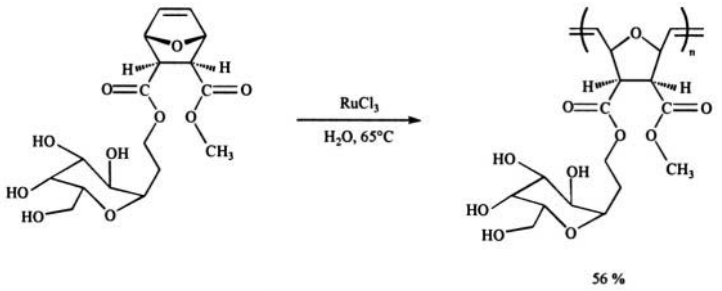
A specific application of aqueous ROMP is the preparation of carbohydrate-substituted polymers from suitably modified 7-oxanorbornene derivatives (Scheme 7.11) [30-32]. The target molecules find application in the study of the role of carbohydrates in cell-agglutination. Carbohydrate receptors often bind weakly to target saccharide ligands and multiplication of this weak binding is essential in cellular recognition. An artificial polymer, containing several identical pendant carbohydrate units may experience a strong binding and, in turn, the precise engineering of such polymers may produce models which allow conclusions with regard to the

cell surface receptors. In addition, such polymers themselves may have unique biological properties.



Scheme 7.10

Several polymers were prepared in water from glucose- or mannose-containing 7-oxanorbornenes, using $RuCl_3.aq$ as catalyst, of which Scheme 7.11 shows only one example. In line with the general observations of aqueous ROMP, high molecular mass polymers were obtained ($M \sim 10^6$). The cell agglutination effect of the carbohydrate-binding protein, concanavalin A, was efficiently inhibited by these polymers, especially when a fine match of the protein receptor units and the polymer carbohydate content (density) could be struck on [32]. In other words, the carbohydrate-containing ROMP polymer mimicked the cell surface carbohydrate distribution and blocked the concanavalin A binding sites before it could induce cell agglutination.

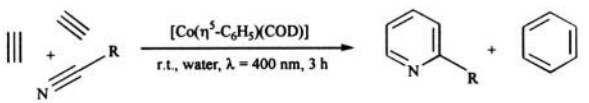


Scheme 7.11

7.4 Alkyne reactions

Oligomerization and polymerization of terminal alkynes may provide materials with interesting conductivity and (nonlinear) optical properties. Phenylacetylene and 4-ethynyltoluene were polymerized in water/methanol homogeneous solutions and in water/chloroform biphasic systems using **[RhCl(CO)(TPPTS)$_2$]** and **[IrCl(CO)(TPPTS)$_2$]** as catalysts [37]. The complexes themselves were rather inefficient, however, the catalytic activity could be substantially increased by addition of **Me_3NO** in order to remove the carbonyl ligand from the coordination sphere of the metals. The polymers obtained had an average molecular mass of **M_w = 3150-16300.** The rhodium catalyst worked at room temperature providing polymers with *cis*-transoid structure, while **[IrCl(CO)(TPPTS)$_2$]** required 80 °C and led to the formation of *trans*-polymers.

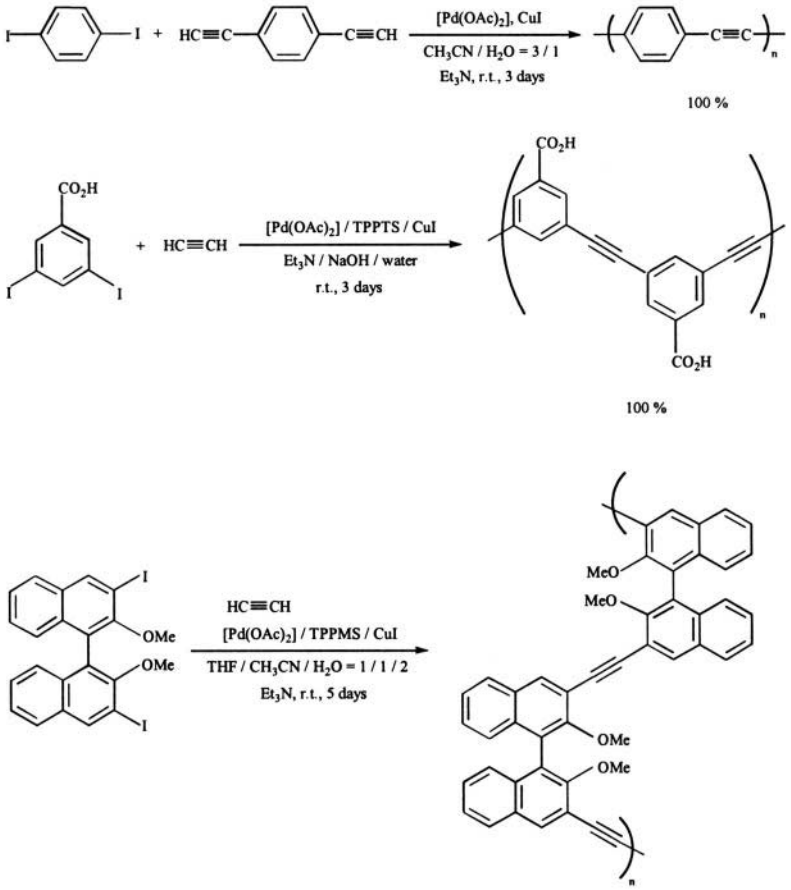
Six water-soluble rhodium compounds, **$RhCl_3$.aq, [RhCl(TPPMS)$_3$],** [RhCl(COD)(TPPMS)], **[{Rh(μ-TPPMS)(COD)}$_2$], [{Rh(μ-SPh)(CO)(Ph$_2$P-C$_6$H$_4$-m-COOH)}$_2$]** and **[Rh$_3$O(OAc)$_6$(H$_2$O)$_3$]OAc** were applied as catalysts for the polymerization of terminal alkynes under homogeneous and aqueous/organic biphasic conditions [38]. In homogeneous solutions propynoic acid was trimerized by all six catalysts to trimellitic and trimesic acids **[1,2,4-C$_6$H$_3$(COOH)$_3$** and **1,3,5-C$_6$H$_3$(COOH)$_3$,** respectively], while phenylacetylenes were found to undergo dimerization, trimerization and steroregular polymerization.



Scheme 7.12

In the presence of Co(I)-catalysts alkynes and nitriles can be co-trimerized in organic solvents to yield substituted pyridines under rather harsh conditions. The reaction is biased by formation of large quantities of benzene derivatives and with acetylene gas as much as 30 % of all products may arise from homotrimerization. It has been found recently, that with cobalt(I) catalysts heterotrimerization of various nitriles and **C_2H_2** could be achieved under ambient conditions using aqueous/organic biphasic systems and irradiating the reaction mixture with visible light (Scheme 7.12) [39,40].

$[Co(\eta^5\text{-}C_5H_5)(COD)]$, $[Co(\eta^5\text{-}C_5H_4COMe)(COD)]$ and $[Co(\eta^5\text{-}C_9H_7)(COD)]$ all showed good catalytic activity. For example, in the reaction of acetylene with benzonitrile, catalyzed by $[Co(\eta^5\text{-}C_5H_5)(COD)]$ at a nitrile/catalyst ratio of 300, 2-phenylpyridine was produced in 75 % yield in 3 hours. Very importantly, only 0.5 % benzene was detected in the same reaction. The beneficial role of the aqueous environment can be rationalized by assuming, that the catalyst and the nitrile can strongly interact in the aqueous solution or emulsion, while the steady-state concentration of the hydrophobic ethyne is low which prevents self-trimerization.

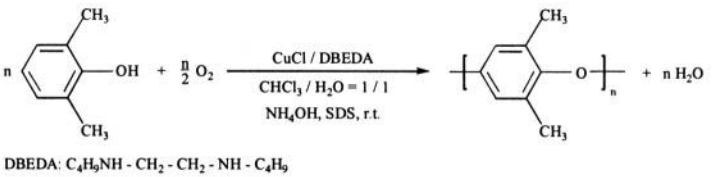


Scheme 7.13

Areneethynylene polymers can be prepared in the palladium-catalysed copolymerization of diiodoarenes and acetylene gas in an aqueous medium

[41,42]. In fact, this is a multiple Sonogashira coupling (see Chapter 6) conducted in CH_3CN/H_2O with $[Pd(OAc)_2]$ + CuI in the presence of Et_3N (Scheme 7.13). Depending on the aryl iodide (1,4- or 1,3-diiodo derivatives) the resulting polymers have different structural properties. The polymer, prepared from 3,5-diiodobenzoic acid is soluble in basic aqueous solvents but reversibly swithes to a hydrogel by lowering the pH of the solution [42]. The product of the reaction of the binaphtyl derivative on Scheme 7.13 shows a strong fluorescence at 435 nm when excited at 324 nm. Such a behaviour promises a potential application in light emitting diodes (LED-s) [41].

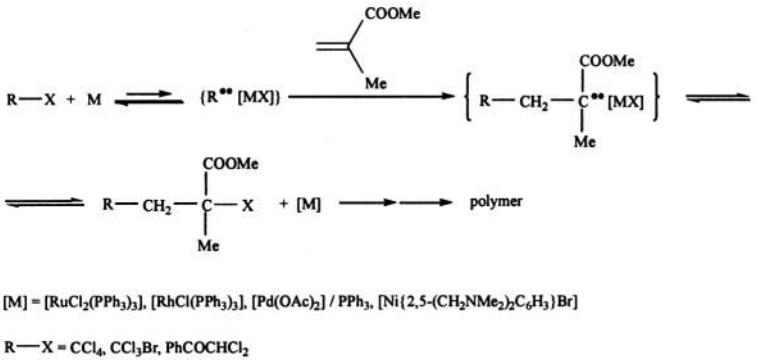
Oxidative coupling polymerization of 2,6-dimethylphenol to poly(2,6-dimethyl-l,4-phenylene oxide), PPO was carried out in water/chloroform biphasic systems using a catalyst prepared from CuCl and a surface active diamine ligand, typically N,N-dibutylethylenediamine [43,44]. The reaction (Scheme 7.14) proceeds in basic media (NH_4OH) and addition of other surface active agents, such as SDS is also beneficial. PPO is an important thermoplastic resin used in the manufacture of filter devices, food trays, surgical instruments etc. [44]. The biphasic technique allows easier product separation and catalyst recovery than the processes using homogeneous organic solutions or micellar aqueous emulsions.



Scheme 7.14

Free radical polymerizations can be readily performed in bulk, aqueous emulsion or suspension. However, chain growth is difficult to control due to the high reactivity of free radicals. A very important kinetic feature is that chain termination is a second order reaction while propagation is first order in active centers therefore termination becomes more and more probable with increasing concentration of growing chains. Such radical processes are not well suited to obtain specialty polymers with high molecular weight and precisely engineered microstructure. However, controlled radical polymerization was demonstrated in the reaction of methyl methacrylate with the participation of $[Pd(OAc)_2]/PPh_3$ [46], $[RhCl(PPh_3)_3]$ [47], $[RuCl_2(PPh_3)_3]$ [48], or $[Ni\{(2,5\text{-}(CH_2NMe_2)_2C_6H_3\}Br]$, an arylnickel(II)

complex [45] (Scheme 7.15), in some cases under aqueous/organic biphasic conditions [47,48]. The reactions were intitiated by $PhCOCHCl_2$, CCl_4 or CCl_3Br. In the initiation step the metal complex reversibly forms an organometallic radical pair with the halide which subsequently inserts a methyl methacrylate into its metal-carbon bond and this process is repeated until a high molecular weight polymer is obtained (usually until the monomer is consumed). The metal centered radical continuously interacts with the radical end of the growing polymer chain and prevents termination. Thus way "pseudoliving" polymerizations can be carried out in which the properties of the polymer can be controlled more precisely than in traditional free radical reactions. For example, the poly(methyl methacrylates) obtained by controlled radical polymerization had high molecular weigth (10^5 g mol^{-1}) and were characterized by narrow molecular weigth distribution (M_w/M_n = 1.1-1.3).



Scheme 7.15

The role of water in these reactions is not completely clear since the applied metal complexes are not water-soluble. One reason for using aqueous systems is the possibility of producing aqueous emulsion directly which is a distinct technological benefit. Nevertheless, in polymerizations of methyl methacrylate with $[RuCl_2(PPh_3)_3]$ and $PhCOCHCl_2$, consistently higher reaction rates were observed in the presence of water than in dry toluene [48].

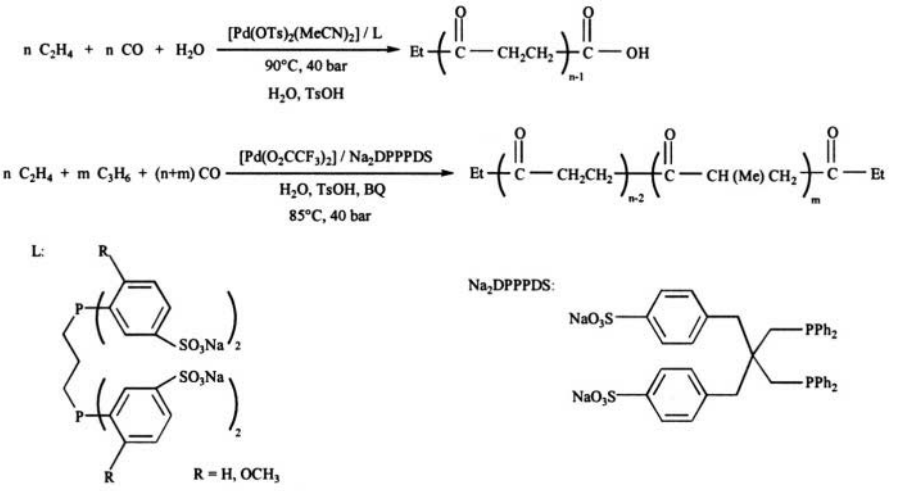
7.5 Alternating copolymerization of alkenes and carbon monoxide

Reppe and Magin disclosed in 1951 that an olefinic compound, typically ethene reacted with carbon monoxide at 190 bar (C_2H_4:CO = 1:1) in the

presence of an aqueous solution of $K_2[Ni(CN)_4]$ to produce polyketones which precipitated from the reaction mixture. The use of such products as "plasticizers, textile assistants or tanning agents" was envisaged [52]. Later it was discovered, that similar reactions were actively catalyzed by cationic palladium-bisphosphine complexes in methanol [49-51]. Optimum catalyst performance is provided by bis(diphenylphosphino)propane, DPPP, and the productivity of the Pd/DPPP catalyst is > 6 kg polymer $(g\ Pd)^{-1}\ h^{-1}$. The copolymers obtained this way have a perfectly alternating CO/C_2H_4 structure. These materials have high crystallinity, high mechanical strength, good chemical and solvent resistance and impermability for gases and fluids, all the good properties which attract considerable practical interest. The ethene/carbon monoxide copolymers melt around 260-270 °C, however, above this temperature there is extensive degradation and cross-linking so that melt-processing is only possible in a limited temperature window. This problem can be counteracted by incorporating higher olefins into the polymer and, indeed, the CO/ethene/propene termonomers are superior to the CO/ethene copolymer in this respect. The termonomer with 5-8 % CO/propene content is produced commercially by Shell (Carilon®).

The water-soluble palladium complex prepared from $[Pd(MeCN)_4](BF_4)_2$ and tetrasulfonated DPPP (**34**, n=3, m=0) catalyzed the copolymerization of CO and ethene in neutral aqueous solutions with much lower activity [21 g copolymer $(g\ Pd)^{-1}\ h^{-1}$] [53] than the organosoluble analogue in methanol. Addition of strong Brønsted acids with weakly coordinating anions substantially accelerated the reaction, and with a catalyst obtained from the same ligand and from $[Pd(OTs)_2(MeCN)_2]$ but in the presence of p-toluenesulfonic acid (TsOH) 4 kg copolymer was produced per g Pd in one hour [54-56] (Scheme 7.16). Other tetrasulfonated diphosphines (**34**, n=2, 4 or 5, m=0) were also tried in place of the DPPP derivative, but only the sulfonated DPPB (n=4) gave a catalyst with considerably higher activity [56]. Albeit with lower productivity, these Pd-complexes also catalyze the CO/ethene/propene terpolymerization.

One of the major problems with these palladium-phosphine catalysts is in that they are rather unstable under the process conditions and gradual loss of the catalytic activity and precipitation of palladium black can often be observed. The introduction of appropriately substituted DPPP derivatives (Scheme 7.16) not only increased the activity over all previous values but largely improved the stability of the catalysts, as well [57].

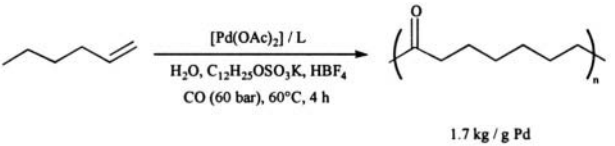


Scheme 7.16

The palladium complex containing the 1,3-bis(di(2-methoxyphenyl)phosphino)propane tetrasulfonate ligand produced 32.2 kg copolymer per g Pd per hour. Very active catalyst were also prepared from $[Pd(O_2CCF_3)_2]$ and $Na_2DPPPDS$, (Scheme 7.16) with a productivity exceeding 7 kg polymer $(g\ Pd)^{-1}\ h^{-1}$. However, in this case a large excess of the Brønsted acid (TsOH) and a reoxidant (benzoquinone) had to be used in order to obtain stable catalyst solutions [58]. On the other hand, this latter system provided polymers containing exclusively ketone groups and no acid end groups were detected which could arise from the hydrolysis of the intermediate [Pd-C(O)R] species.

Water-soluble 1,3-bis(di(hydroxyalkyl)phosphino)propane derivatives were thoroughly studied as components of Pd-catalysts for CO/ethene (or other α-olefins) copolymerization and for the terpolymerization of CO and ethene with various α-olefins in aqueous solution (Scheme 7.17) [59]. The ligands with long hydroxyalkyl chains consistently gave catalysts with higher activity than sulfonated DPPP and this was even more expressed in copolymerization of CO with α-olefins other than ethene (e.g. propene or 1-hexene). Addition of anionic surfactants, such as dodecyl sulfate (potassium salt) resulted in about doubling the productivity of the CO/ethene copolymerization in a water/methanol (30/2) solvent (1.7 kg vs. 0.9 kg copolymer $(g\ Pd)^{-1}\ h^{-1}$ under conditions of [59]) probably due to the concentration of the cationic Pd-catalyst at the interphase region or around the micelles which solubilize the reactants and products. Unfortunately under such conditions stable emulsions are formed which prevent the re-use

of the aqueous phase. The same catalysts were suitable for terpolymerization of CO, propene and the the water-soluble termonomer N-vinyl formamide.



Scheme 7.17

It is interesting to note, that the Pd-bisphosphine complexes do not catalyze hydrocarboxylation of the olefins used in these co- and terpolymerization reactions, although the related compounds with monomeric phosphine ligands, such as **[Pd(TPPTS)$_3$]** are very active for that reaction (see Chapter 5). One reason may be in that the catalyst attached to the end of the growing polymer chain effectively works in a non-aqueous environment and can be approached by C_2H_4 and CO but not by H_2O. This is supported by the observation that with the aqueous phase, obtained at the end of the reaction after filtering out the polyketone product, only traces of copolymer was obtained in a second run [57]. It seems, that bulky bisphosphines, especially with ortho-substituents provide the same protection against chain termination or catalyst degradation by hydrolysis. The low steady-state concentration of CO and ethene is also favorable for chain growth and indeed, formation of CO/ethene copolymers with very high molecular mass **(50-125 kg mol^{-1})** has often been observed. (One noteworthy practical consequence of the fast formation of high-weight polymers is in that stirring in the reactor can be slowed down or even stopped by the precipitating product.)

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Chapter 8

Catalytic oxidations in aqueous media - recent developments

Catalytic oxidation of organic compounds is an extremely important field of chemistry, spanning the range from biological oxidations to large scale industrial production of commodity chemicals. However, many of these transformations can hardly be classified as organometallic reactions, since the catalysts (often simple metal salts) and the intermediates can be rather regarded as coordination complexes than organometallic compounds. Therefore our discussion will be limited to a few specific examples, despite the fact that oxidations have an inherent connection to aqueous systems - after all in many cases (except e.g. epoxidations or hydrogen transfer oxidations) water is produced as byproduct. Even the truly organometallic activation of hydrocarbons by platinum complexes is excluded from this discussion, the simple reason being in that a monumental treatise [1] of this fundamentally important problem has appeared quite recently. Other books and reviews describe the field from the aspects of industry [2,3], basic catalysis research [4,5,6], activation of dioxygen [7] or hydrogen peroxide [8] and from that of organic synthesis [9] - and the list is far from being complete.

8.1 Wacker-type oxidations

This is a genuine organometallic reaction in which ethene is oxidized by Pd(II) to yield acetaldehyde (eq. 8.1) [3]:

$$C_2H_4 + H_2O + [PdCl_2] = CH_3CHO + [Pd^0] + 2\ HCl \qquad (8.1)$$

Similar oxidations of longer chain olefins provide methyl ketones, however, the reaction is accompanied by olefin isomerization and

subsequent oxidation so usually a rather complex product mixture is formed. $[Pd^0]$ is prone to aggregate into palladium black, however, this can be prevented by reoxidation by $[CuCl_2]$ (eq. 8.2) followed by aerobic oxidation of $[Cu_2Cl_2]$ to $[CuCl_2]$ in an excess of HC1 (eq. 8.3). With ethene as substrate the overall process is described by eq. 8.4.

$$[Pd^0] + 2\,[CuCl_2] + 4\,Cl^- = [PdCl_4]^{2-} + 2\,[CuCl_2]^- \qquad (8.2)$$

$$2\,[CuCl_2]^- + 2\,H^+ + \tfrac{1}{2}\,O_2 = 2\,[CuCl_2] + H_2O \qquad (8.3)$$

$$C_2H_4 + \tfrac{1}{2}\,O_2 = CH_3CHO \qquad (8.4)$$

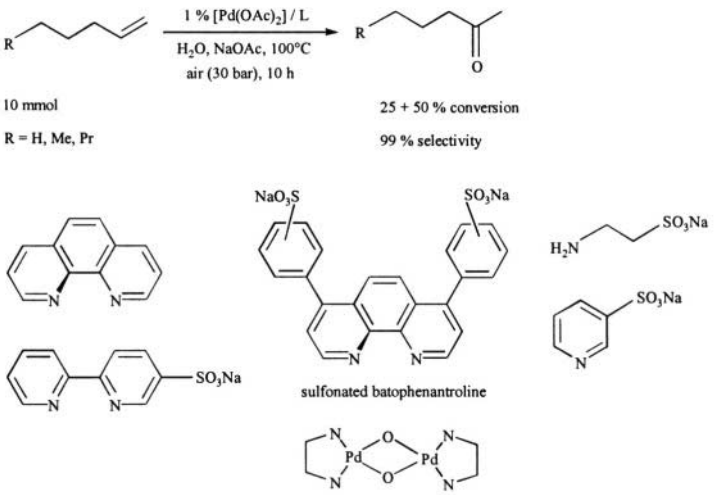
The reaction has been developed into an industrial process which has been in production for about 40 years now. Although eq. 8.4 does not tell about it, the process suffers from the need of a highly corrosive reaction mixture containing large amounts of copper chlorides - a rather nasty situation from environmental aspects.

In a quest for a more environment-friendly process it has been found that reaction 8.4 can be catalyzed by Pd(II) complexes of various nitrogen-donor ligands (Scheme 8.1) under not too harsh conditions (100 °C, air) without the need of copper chlorides [10, 11]. Of the investigated ligands, sulfonated batophenanthroline proved to be the best. Higher olefins, such as 1-hexene or cyclooctene were similarly transformed by this catalyst. Very importantly, there was no isomerization to internal olefins and 2-hexanone was formed with higher than 99 % selectivity. This outstanding selectivity is probably due to the absence of acid and Cu-chlorides.

In contrast to the usual Wacker-conditions, optimum rates and catalyst stability in the Pd/batophenanthroline-catalyzed olefin oxidations was observed in the presence of NaOAc (pH ≅ 11.5). Under such conditions, the catalyst-containing aqueous phase could be recycled with about 2-3 % loss of activity in each cycle. In the absence of NaOAc precipitation of Pd-black was observed after the second and third cycles. Nevertheless, kinetic data refer to the role of a hidroxo-bridged dimer (Scheme 8.1) rather than the so-called giant palladium clusters which could easily aggregate to metallic palladium.

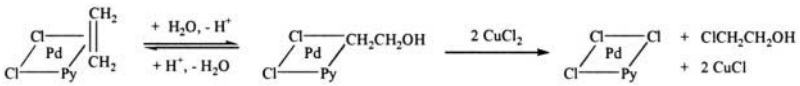
Poly(ethylene oxide) polymers and poly(ethylene oxide/propylene oxide) copolymers with iminodipropionitrile (**139**) or iminodiacetonitrile end groups were used as ligands in the palladium-catalyzed oxidation of higher olefins (1-octene to 1-hexadecene) at 50-70 °C with atmospheric air or 1-3 bar O_2. In an ethanol/water mixture 88 % yield of 2-hexanone and 92 % yield of 2-hexadecanone was obtained in 4 and 2 h, respectively, with a

substrate/catalyst ratio of 65. The aqueous-alcoholic catalyst solutions could be recycled with no loss of activity after phase separation [12].



Scheme 8.1

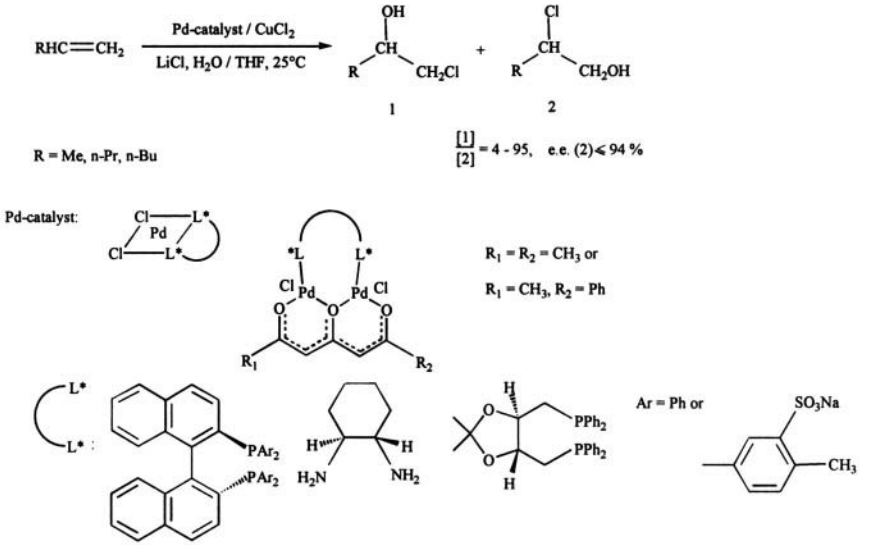
It is known of the Wacker reaction, that at low chloride concentration (< 1 M) it yields exclusively acetaldehyde. However, at $[Cl^-] \geq 2.5$ M, chloroethanol is produced in appreciable quantities. In a detailed kinetic study it was established, that when a chloride ligand in $[PdCl_2]^{2-}$ is replaced by pyridine, the intermediate hydroxyethylpalladium complex is stable enough to undergo reaction with $[CuCl_2]$ with the formation of chloroethanol up to a yield of 98 % in 8 M chloride solutions (Scheme 8.2) [13].



Scheme 8.2

With olefins other than ethene two isomeric chlorohydrins can be obtained, one of them being chiral. When pyridine was replaced by monodentate chiral amines in $[PdCl_3(pyridine)]^-$, the enantioselectivities were low (8-12%) (Scheme 8.3) [14]. The mononuclear $[PdCl_2(L_2)]$ complexes (L_2 = sulfonated p-tolyl-BINAP) performed better providing the chiral chlorohydrin in 46-76% e.e. Even better activities and

enantioselectivities were achived with the dinuclear, mixed β-triketonato/chiral (bisphosphine or diamine) catalysts (Scheme 8.3) which allowed enantioselective production of chlorohydrins with several olefins. The highest optical purities were 94% e.e. for propene and 93 % e.e. for allylphenyl ether [15]. The reactions can be conducted under mild conditions, although the environmental concerns with regard to the use of concentrated $[CuCl_2]$ solutions still prevail.



Scheme 8.3

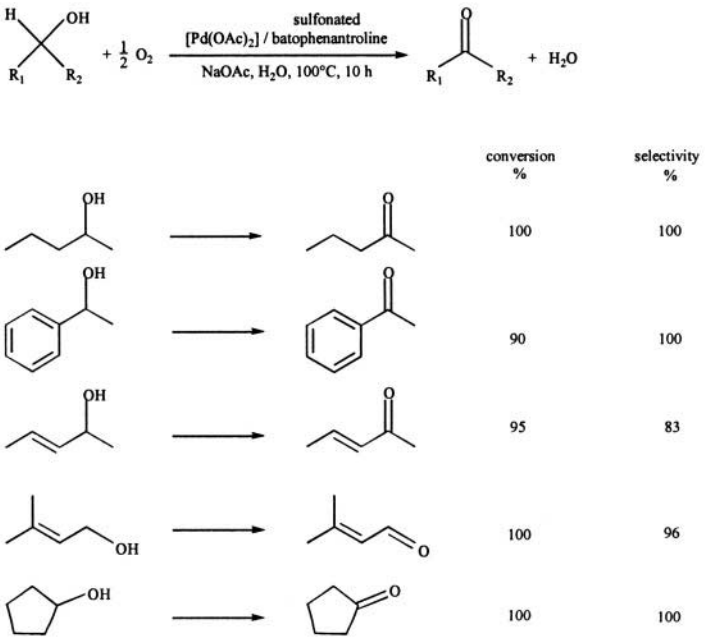
8.2 Oxidations with O_2 and H_2O_2

An important trend in oxidations is the use of O_2 or H_2O_2 in place of inorganic or organic oxidants, allowing the development of green processes with no toxic by-products or wastes. In the special case of alcohols one preferred oxidant is chromium(VI) causing obvious problems. An other method consists of running the oxidations in the presence of reactive aldehydes, for example butyraldehyde (usually in the presence of a metal-containing catalyst). In fact, the immediate oxidants for alcohols are the peracids which form in situ from the aldehydes and O_2 (Mukaiyama oxidations, see e.g. [17]). This reaction, however, also yields one mol of an acid byproduct for each mol of the target compound. An attractive way for such reactions would be the use of O_2 or H_2O_2 as oxidants in a biphasic

catalytic process, preferably with water as one of the phases, for easy product isolation and catalyst recovery.

In the presence of a **$[RuCl_2(PPh_3)_3]$** catalyst N-methylmorpholine-N-oxide (MMO) reacts with alcohols in dichloroethane or 1,2-dichloroethylene to afford mostly aldehydes together with carboxylic acids. Instead of the rather expensive MMO as reagent, a combination of N-methylmorpholine and aqueous **H_2O_2** (35 w%) could be used with similar results for the oxidation of long chain alcohols (1-octanol to 1-hexadecanol) [16]. At the end of the reaction the aqueous phase, containing the ruthenium catalyst and methylmorpholine could be recycled with no apparent loss of activity.

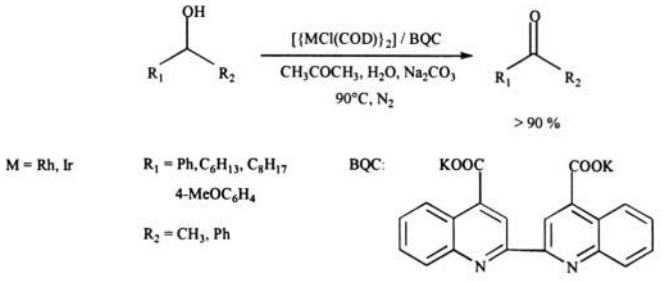
Perhaps the most important recent discovery in catalytic oxidation of alcohols is the use of a catalyst prepared from **$[Pd(OAc)_2]$** and sulfonated batophenanthroline (see Scheme 8.1 above). This catalyst was found to oxidize primary and secondary, as well as benzylic and allylic alcohols with close to quantitative yields and 90-100 % selectivities to the corresponding aldehydes or ketones (Scheme 8.4) [18]. The easy oxidation of non-activated secondary alcohols is particularly noteworthy since in general these are rather unreactive towards **O_2**.



Scheme 8.4

The reactions can be carried out in aqueous solutions or biphasic mixtures of the substrates with no additional solvent, in the presence of NaOAc (pH ≅ 11.5) at 100 °C. At this pH the resting state of the catalyst is probably the dinuclear species depicted on Scheme 8.1, which falls apart upon coordination of the substrate alcohol. In this respect the catalyst system as very similar to that for the oxidation of terminal olefins [10,11]. Good results were obtained with 30 bar of air, however, an 8 % O_2/N_2 mixture can also be used, which further improves the safety of the process. Recycling of the aqueous catalyst solution is possible and is especially easy in case of biphasic reaction mixtures. Taking all these features, this Pd-catalyzed oxidation of alcohols is a green process, indeed.

Oppenauer-type oxidation of secondary alcohols can be a convenient procedure for obtaining the corresponding carbonyl compounds. It was found recently [19], that Ir(I)- and Rh(I)-complexes of 2,2'-biquinoline-4,4'-dicarboxylic acid dipotassium salt (BQC) efficiently catalyze the oxidation of secondary alcohols with acetone in water/acetone 2/1 mixtures (Scheme 8.5). The reaction proceeds in the presence of Na_2CO_3 and affords medium to excellent yields of the isolated ketones. The process is much faster in largely aqueous solutions, such as above, than in wet organic solvents; in acetone, containing only 0.5 % water, low yields were observed (15 % vs. 76 % in case of cyclohexanol).



Scheme 8.5

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Chapter 9

Miscellaneous catalytic reactions in aqueous media

The realm of aqueous organometallic catalysis incorporates many more reactions and catalysts than discussed in the preceeding chapters. However, these were not investigated in so much detail as, for instance, hydrogenation or hydroformylation; some of them are mentioned only here and there. An attempt is made to give a representative sample of these studies. At the end of this chapter, a few findings will be briefly mentioned, which do have some connection to aqueous organometallic catalysis in the sense we used this term throughout this book, but which perhaps could be best categorized as emerging techniques.

9.1 Aqueous organometallic catalysis under traditional conditions

In this part of the chapter we shall look at examples of catalytic isomerization, hydration, cyanation, hydrocyanation, hydrophosphination and animation reactions. "Traditional conditions" refer to ranges of temperature and pressure within which water behaves as we are used to it normally, i.e it forms a highly polar liquid phase, capable of dissolving electrolytes and polar substances. Under such conditions water is a poor solvent for nonpolar organic compounds which –with appropriate organic solvents– allows the use of aqueous-organic biphasic media for organometallic catalysis. A guide to the literature of these studies is found in Table 9.1.

Isomerization is a frequent side-reaction of catalytic transformations of olefins, however, it can be a very useful synthetic method, as well. One of the best-known examples is the enantioselective allylamine → enamine isomerization catalyzed by **[Rh{(*R*)-** or **(*S*)-BINAP}(COD)]$^+$** which is the crucial step in the industrial synthesis of L-menthol by Takasago [42]

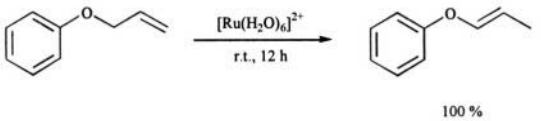
(performed under unhydrous conditions). Especially valuable feature of isomerizations is in that all atoms of the starting compound are incorporated into the product, respresenting a 100 % atom economy.

Table 9.1. Miscellaneous catalytic reactions in aqueous media

Substrates	Products	Catalyst	Ref.
Isomerization			
Olefins	Isomerized olefins	$[Ru(H_2O)_6]^{2+}$	[1-3]
Allylbenzene	Propenylbenzene	$[\{RuCl_2(TPPMS)_2\}_2]$	[4]
Eugenol, allylbenzene, 2-butene-1-ol	Ioseugenol, propenylbenzene, butanal	$[Ni(TPPTS)_3]/CN^-$	[5]
Allylbenzene	Propenylbenzene	Ni/TPPTS, Ni/ **34** (n=2,m=0)	[6,7]
Homoallyl alcohols	Repositioned (!) allylic alcohols	$[RuCl_2(PPh_3)_3]$	[8,9]
Allylic alcohols	Carbonyl compounds	Ru, Rh or Pd with TPPTS or **34** (n=3, m=0)	[10]
H-D exchange			
C-H (alkynes)	C-D (alkynes)	$[RhCl(PMe_3)_4$	[11]
C-H (methyl)	C-D (methyl)	$[Mo(OH)(H_2O)(MeCp)_2]^+$	[12]
C-H (alkylidenes)	C-D (alkylidenes)	$[RuCl_2(\mathbf{P})_2(CHPh)]$, **P=173,175**	[13]
H_2O	HOD, D_2O	Ru and Rh with TPPMS, TPPTS and PTA (**82**)	[14]
Hydration			
1,1-Difluoroethylene	Acetic acid	Ru(II) chlorides	[15]
Allylalcohol	Propyleneglycol	$[\{Pd(OH)(H_2O)(PhPC_6H_4\text{-}SO_3Na)\}_2]$	[16]
Diethyl maleate	Diethyl malate	$[\{Pd(\mu\text{-}OH)(DPPE)\}_2]^{2+}$	[17]
Conjugated dienes	Ketones	$[Ru(acac)_3]$ + 2,2'-bipyridyl or 1,10-phenanthroline	[18] [19]
$RCHCH_2$ (R=H,Me,Et)	Carbonyl compounds	$[RuCl_n(H_2O)_{6-n}]^{(n+3)+}$	[20]
Acetylene	Acetaldehyde	$[RhCl_n(H_2O)_{6-n}]^{(n+3)+}$	[21]
Acetylene	Acetaldehyde	Ru and Rh/TPPMS	[22]
Terminal alkynes	Ketones	$[IrCl(CO)(TPPTS)_2]$	[23]
Terminal alkynes	Ketones	$RhCl_3 + R_4QX$	[24]
Alkynes	Carbonyl compounds	$[PtCl_4]$ + CO	[25]
Conjugated alkynones	1,3-Diketones	$[H_2PtCl_6]$	[26]
Terminal alkynes	Aldehydes (anti-Markovnikov addn.)	$[\{RuCl_2(C_6H_6)\}_2] + PPh_2(C_6F_5)$ or TPPTS	[27]
Acrylonitrile	Acrylamide	$[PdCl(OH)(H_2O)(1,10\text{-phen})]$	[28]
Sat. and unsat. nitriles	Sat. and unsat. amides	$[IrH(CO)(TPPTS)_3]$	[29]
Aceto- and benzonitrile	Amides	Rh, Ir, Pd, Pt with TPPTS, PMe_3 or 2,2'-bipyridyl	[30]
Cyanation, hydrocyanation			
Allylbenzene	4-Phenylbutyronitrile	$[Ni(TPPTS)_3]/CN^-$	[5]
Dienes	Dinitriles	$[Ni(TPPTS)_3]$	[31]
Alkenes	Nitriles	$[Ni(TPPTS)_3]$	[32]

Substrates	Products	Catalyst	Ref.
Alkenes, cyanoalkenes	Nitriles	$[Ni(COD)_2]$ + **37** (m=0)	[33]
Acetylenes	Nitriles	$[Ni(CN)_4]^{2-}$+ $NaBH_4$ or Zn	[34]
α-Ketoalkynes	Unsat.hydroxylactams	$[Ni(CN)_2]$, CO , KCN, NaOH:	[35]
		$[Ni(CN)_4]^{4-}$	[36]
Aryl halides	Nitriles	Pd-phosphines + NaCN	[37]
Hydrophosphination			
$CH_2O + PH_3$	$P(CH_2OH)_3$	$[M\{P(CH_2OH)_3\}_4]$,	[38]
		M=Pt,Pd,Ni	[39]
Acrylonitrile + PH_3	$P(CH_2CH_2CN)_3$	$[Pt\{P(CH_2CH_2CN)_3\}_3]$	[40]
Amination, amine exchange			
Ar-X	N-substituted anilines	$[Pd(OAc)_2]$ + **44** (sulfonated	[41]
X=Cl, Br, I, CF_3OSO_2		BINAS)	
Anilines + allyl-ammonium chlorides	Quinolines	$[RuCl_2(PPh_3)_3]$ + $SnCl_2.2H_2O$	[46]

$[Ru(H_2O)_6]^{2+}$, which is a precursor of ROM polymerization of cyclic dienes has also been found to possess good alkene isomerization activity [1]. Among others it catalyzed the isomerization of allylphenyl ether to a vinylphenyl ether (Scheme 9.1) at room temperature. Allyl ethers are stable to acids and bases, while vinyl ethers are easily cleaved in acidic solutions. Therefore this isomerization gives a mild method for removal of protecting allyl groups under exceedingly mild conditions.

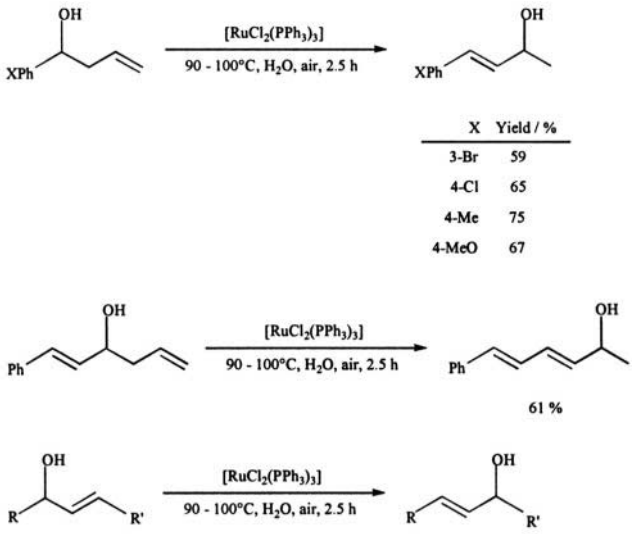


Scheme 9.1

In an interesting reaction, reshuffling of functional groups can be achieved in the $[RuCl_2(PPh_3)_3]$-catalyzed rearrangement of homoallylic alcohols (Scheme 9.2) [8,9]. Allylic alcohols also react the same manner, however, when both kind of olefinic bonds are present in the same molecule, than it is the homoallylic moiety which reacts exclusively.

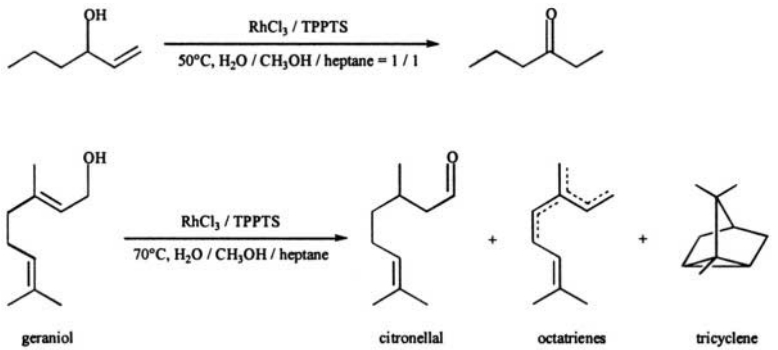
In water-heptane biphasic systems, allylic alcohols underwent rearrangement to the corresponding carbonyl compounds with a catalyst prepared in situ from $RhCl_3.aq$ and TPPTS. The reactions proceeded very fast (TOF up to **2500** h^{-1}) and in most cases provided the carbonyl products quantitatively. The industrially interesting geraniol was isomerized mostly to citronellal, albeit octatrienes and tricyclene were also produced. With an increase of the pH of the aqueous phase the yield of isomerization decreased somewhat (from 48 % to 40 %), however the selectivity towards the

formation of citronellal was found to increase from 50 % to 70 % (Scheme 9.3) [10].



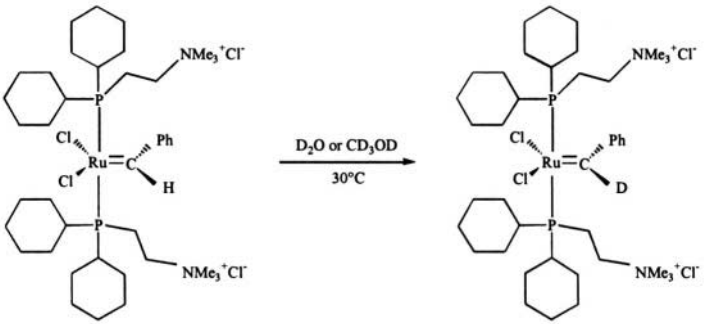
Scheme 9.2

Isomerization processes have been used as test reactions in developing microreactors for dynamic, high throughput screening of fluid/liquid molecular catalysis [45].



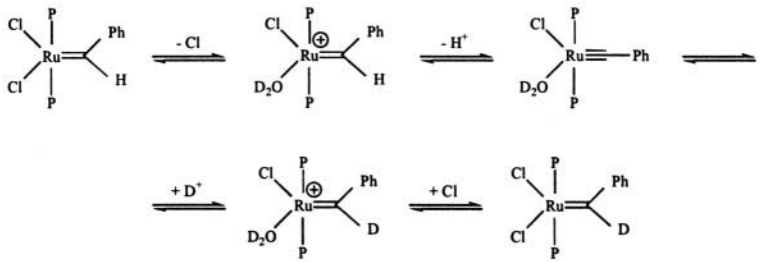
Scheme 9.3

The stable ruthenium alkylidenes, used for catalysis of ring opening metathesis polymerizations, were found to exchange the alkylidene proton for a deuteron in D_2O or in CD_3OD (Scheme 9.4) [13].



Scheme 9.4

The reaction is thought to proceed with the dissociation of Cl^- followed by release of the extra charge of the ruthenium complex by dissociating a proton from the alkylidene ligand. Such an exchange in itself does not lead to the decomposition of the alkylidene complex. Nevertheless, both the formation of the charged species, both the intermediate existence of the carbyne complex (Scheme 9.5) may open new ways to the deterioration of the ROMP catalysts.



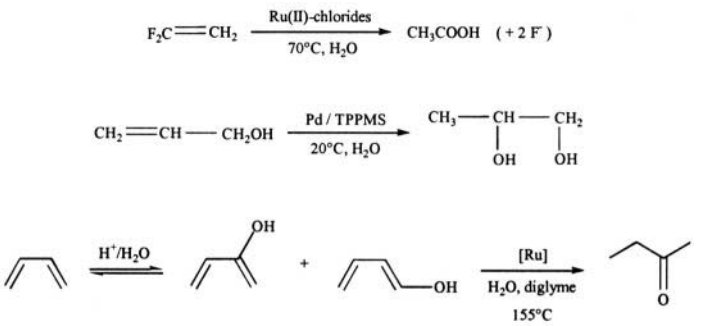
Scheme 9.5

Isotope exchange methods are useful tools for labeling important compounds, such as drugs, and for mechanistic investigations in reaction kinetics. During catalytic hydrogenations in homogeneous aqueous solutions or in aqueous-organic biphasic systems there is ample possibility for H/D exchange between hydrogen in the gas phase and the solvent (e.g. reaction 9.1) if D_2 or D_2O is used.

$$H_2 + D_2O \rightleftharpoons HD + HDO \quad (9.1)$$
$$D_2 + H_2O \rightleftharpoons HD + HDO \quad (9.2)$$

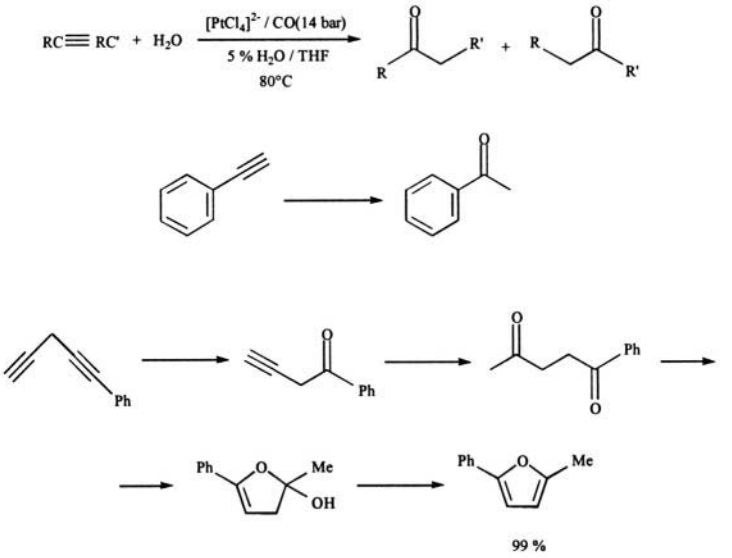
The reactions can be conveniently followed by ^1H or ^2H NMR in a high-pressure sapphire NMR tube. Our detailed studies have shown that water-soluble phosphine complexes of ruthenium and rhodium with TPPMS, TPPTS or PTA ligands are able to catalyze this exchange with outstanding activity [14]. In fact, some of the reactions were surprisingly fast. For example, in the pH-range of 2.0-5.0, a $TOF = 1250\ h^{-1}$ was observed with $[\{RuCl_2(TPPMS)_2\}_2]$ as catalyst at 25 °C and 20 bar H_2 pressure. Such a fast exchange may play a considerable role in the deuteriation of products of hydrogenation reactions (see also 3.1.3 and 3.1.4).

Hydration of olefins, alkynes and nitriles calls explicitely for the use of aqueous solvents. Indeed, one of the earliest investigations originates from 1969, when hydration of fluoroalkenes were studied with Ru(II)-chloride catalysts (Scheme 9.6). The reaction has no synthetic value but the studies helped to clarify the mechanism of the interaction of olefins with Ru(II) [15]. Similarly, it remained an isolated example that $[Pd(OAc)_2]$/TPPMS systems yielded 1,2-propyleneglycol when heated in aqueous allyl-alcohol [16]. More synthetic interest is generated by the potentially very useful hydration of dienes. As shown on Scheme 9.6, methylethylketone (MEK) can be produced from the relatively cheap and easily available 1,3-butadiene with combined catalysis by an acid and a transition metal catalyst. Ruthenium complexes of several N-N chelating ligands (mostly of the phenanthroline and bipyridine type) were found active for this transformation in the presence of Bronsted acids with weakly coordinating anions, typically p-toluenesulfonic acid, TsOH [18,19]. In favourable cases 90 % yield of MEK, based on butadiene, could be obtained.



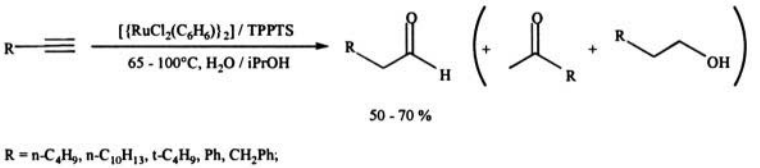
Scheme 9.6

By the example of 34 different alkynes, it was convincingly demonstrated that the product of the treatment of $[PtCl_4]$ with CO at 40-110 °C is a very powerful *alkyne hydration* catalyst; some of the reactions are shown on Scheme 9.7 [25]. The best medium for this transformation is THF containing 5 % H_2O. The reaction can also be performed in a water-organic solvent two-phase system (e.g. with 1,2-dichloroethane), however in this case addition of a tetralkylammonium salt, such as Aliquat 336, is required to facilitate mass transfer between the phases. After the reaction with CO, the major part of platinum is present as $H_2[\{Pt_3(CO)_6\}_n]$, but the catalytic effect was assigned to a putative mononuclear Pt-hydride, $[PtHCl(CO)_2]$, presumably formed from the cluster and some HC1 (supplied by the reduction of $[PtCl_4]$). The hydration of terminal acetylenes follows Markovnikov's rule leading exclusively to aldehyde-free ketones.



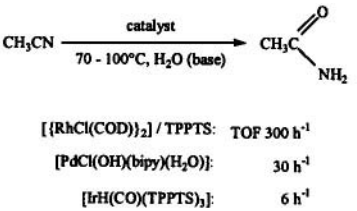
Scheme 9.7

The first *anti-Markovnikov hydration of terminal acetylenes*, catalyzed by ruthenium(II)-phosphine complexes, has been described in 1998 [27]. As shown on Scheme 9.8, the major products were aldehydes, accompanied by some ketone and alcohol. In addition to TPPTS, the fluorinated phosphine, $PPh_2(C_6F_5)$ also formed catalytically active Ru-complexes in reaction with $[\{RuCl_2(C_6H_6)\}_2]$.

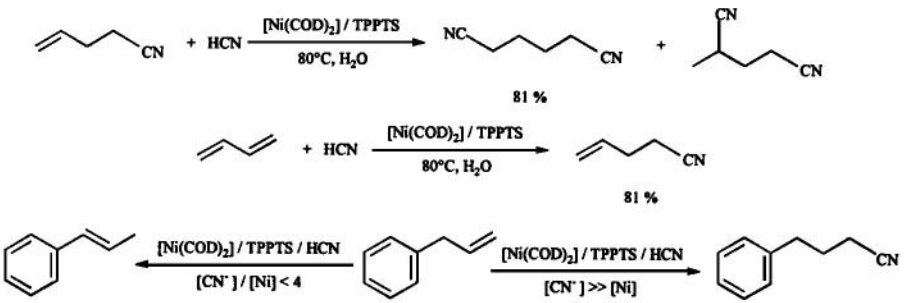


Scheme 9.8

Hydration of nitriles providing carboxamides is usually carried out in strongly basic or acidic aqueous media - these reactions require rather harsh conditions and suffer from incomplete selectivity to the desired amide product. A few papers in the literature deal with the possibility of transition metal catalysis of this reaction [28-30]. According to a recent report [30], acetonitrile can be hydrated into acetamide with water-soluble rhodium(I) complexes (such as the one obtained from $[\{RhCl(COD)\}_2]$ and TPPTS) under reasonably mild conditions with unprecedently high rate ($TOF = 300\ h^{-1}$).



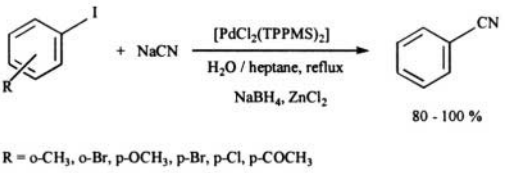
Scheme 9.9



Scheme 9.10

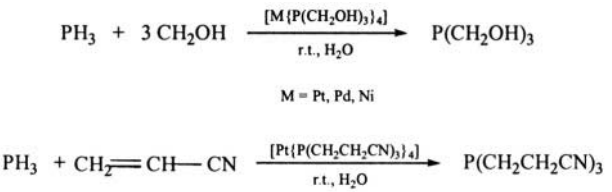
Hydrocyanation of olefins and dienes is an extremely important reaction [32] (about 75 % of the world's adiponitrile production is based on the hydrocyanation of 1,3-butediene). Not surprisingly, already one of the first Rhone Poluenc patents on the use of water soluble complexes of TPPTS described the Ni-catalyzed hydration of butadiene and 3-pentenenitrile (Scheme 9.10). The aqueous phase with the catalyst could be recycled, however the reaction was found not sufficiently selective.

In the presence of a large excess of cyanide, the catalyst prepared from **[Ni(COD)$_2$]** and TPPTS was also active in the hydrocyanation of allylbenzene; however, at low cyanide/nickel ratios isomerization to propenylbenzene became the main reaction path (Scheme 9.9) [5].



Scheme 9.11

Cyanation of iodoarenes with NaCN was catalyzed by **[PdCl$_2$(TPPMS)$_2$]** in the presence of **NaBH$_4$** and **ZnCl$_2$** in water/heptane, toluene or anisole biphasic systems (Scheme 9.11) [37]. Lipophilic catalysts prepared with **P(p-tolyl)$_3$** or **PPh$_3$** showed negligible activities for the biphasic cyanation, due to the lack of **CN$^-$** in the organic phase. The reaction provided good to excellent yields of the respective benzonitriles with several substituted iodoarenes.



Scheme 9.12

Hydrophosphination is the addition of a P-H unit onto a double bond which can be catalyzed by transition metal phosphine complexes. In fact this reaction has been known for long [22,43]: addition of **PH$_3$** onto formaldehyde serves as a basis for production of **P(CH$_2$OH)$_3$,** a flame resisiting agent for wood and textiles. The details of this reaction have been recently scrutinized [38, 40], besides that the first hydrophosphination of an

alkene, catalyzed by $[Pt\{P(CH_2CH_2CN)_3\}_4]$ in aqueous solution has also been described (Scheme 9.12). The product of this latter reaction, tris(cyanoethyl)phosphine finds use in the photographic industry [39].

9.2 Emerging techniques

Concentrated aqueous salt solutions were used for dehydration of carbohydrates catalyzed by $RuCl_3 + Ag_2SO_4$ ('$RuSO_4$') [47]. Such solvents may also help in constructing aqueous-organic biphasic media with good phase separation properties. Selective dehydroxylation of polyols and sugars was achieved in aqueous solutions with the use of anionic ruthenium carbonyls, as well [48].

Several reactions were described in aqueous media, which –depending on the temperature and pressure– were referred to as "high temperature", "superheated", "near-critical", "sub-supercritical" and "supercritical" water; attempts are already known from the early 1990-ies [49]. The critical point of water is at 374 °C and 221 bar, which makes it less attractive as solvent of general use, than supercritical carbon dioxide (30.9 °C and 73.75 bar). Nevertheless, there are some unique properties of near and supercritical water, scH_2O [44]. Namely, as the critical point is passed, the ion product (K_w) decerases dramatically, and it is 9 orders of magnitude less at 600 °C and 250 bar than at ambient conditions. In other words, this kind of water is not the one we are used to, instead it becomes non-polar and a good solvent for organic compounds. This allows reactions in water without the need of organic (co-)solvents or phase transfer agents - important goals of green organic synthesis [53,54,60,61]. Organic chemistry in supercritical water is well reviewed [50,51].

The decrease of polarity starts well under the critical point and the dielectric constant of water is approximately 31 at 225 °C and 100 bar; such systems are referred to as high temperature water (HTW). Moreover, the polarity can be adjusted by changing the temperature and pressure in order to dissolve certain organic components of a catalytic reaction mixture. Under such conditions Heck reaction of iodobenzene and various cyclic alkenes, catalyzed by $[Pd(OAc)_2]$ afforded coupled products in 17-54% yield [52].

Supercritical water was recently used as solvent of cyclotrimerization of acetylenes catalyzed by $[CpCo(CO)_2]$ [59]; the reaction has some early precedents [55-57].

All these results show that it is possible to conduct catalytic aqueous organometallic reactions even under the harsh conditions met in HTW and supercritical water. However, the need for unique apparatus with utmost

corrosion-resistant properties will make this technique suitable only for very specialized applications.

Supercritical carbon dioxide and water are not freely miscible, and there are several examples in the literature of the use of H_2O - $scCO_2$ biphasic liquid mixtures as media for catalysis with water-soluble Rh and Pd catalysts with TPPDS or TPPTS ligands [62-65]. Hydrogenation of styrene [62] and cinnamaldehyde [64], as well as the Heck vinylation of iodobenzene with butyl acrylate and styrene [65] served as model reactions. The advantage of such systems over other variations of biphasic catalysis is in that after separating the two phases the aqueous catalyst phase can be reused, while the product can be easily and cleanly isolated from the $scCO_2$ phase. For simultaneous dissolution of both water-soluble and organic-soluble components in relatively large concentrations, microemulsions can be formed with the aid specific surfactants designed for water - $scCO_2$ mixtures [62,63].

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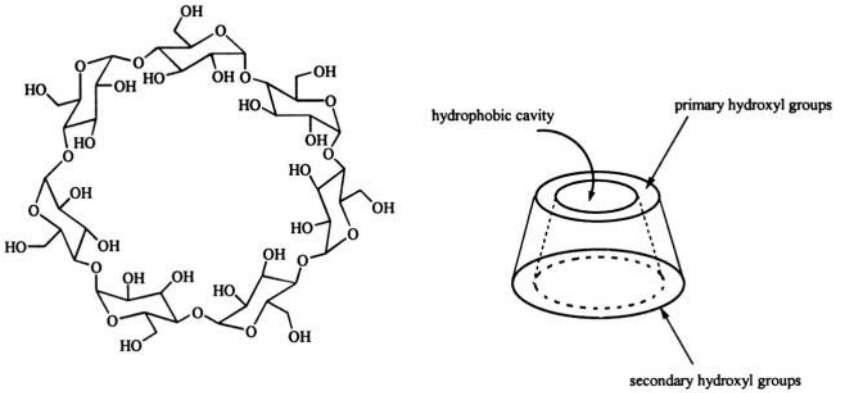
Chapter 10

Host-guest chemistry in aqueous organometallic catalysis

10.1 Cyclodextrins and the formation of inclusion compounds

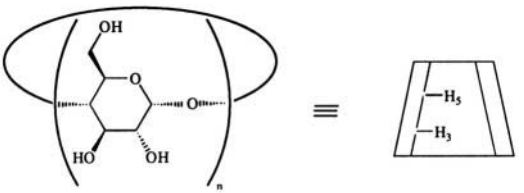
Host-guest complexation relies on interactions of molecules through secondary chemical bonds. Such complexation can lead to formation of loose associations, as well as to that of very stable adducts. In formation of these addition compounds, important roles are played by hydrogen-bonding and hydrophobic interactions. In certain cases one of the reacting partners will wind up in a relatively enclosed space, embraced by the other reactant - this is when the host-guest description is most appropriate. In general, any such interaction between host and guest is expected to change the properties of both molecules but it is the host molecule which is looked at with anticipation of its reactivity being changed in a favourable manner.

Among the best known and most versatile hosts are the various cyclodextrins [1,2] of which α-, β- and γ-cyclodextrins are the most available. These are cyclic oligosaccharides built up of six, seven, or eight glucopyranose units, respectively. These compounds can be prepared by enzymatic hydrolysis of starch. The undoubtedly most important member of the cyclodextrin family is β-cyclodextrin (β-CD) which has become a cheap and easily available chemical, suitable for large scale applications. Schemes 10.1 and 10.2 show the common representations of the cyclodextrin structure(s), emphasizing the topological difference between the polar outer surface and the hydrophobic inner face of the molecules. It is worth mentioning, that while β-cyclodextrin has a rather rigid structure due to internal hydrogen bonding, α- and γ-cyclodextrins are structurally more flexible.



Scheme 10.1

The most important property of cyclodextrins is in their ability to accommodate guest molecules within their cavity, which has a volume of **262 Å^3** per molecule or 157 mL per mol of **β-CD** (cavity diameter 6.0-6.5 Å). In aqueous solution, this cavity is filled with molecules of water the displacement of which by a less polar guest leads to an overall decrease in free energy. Stability constants and thermodynamic parameters for complexation of a vast number of guest molecules can be found in ref. [3].



Scheme 10.2

Chemical modification of cyclodextrins is achieved through reactions of their hydroxyl groups. Of the 21 hydroxyls of **β-CD,** the seven primary ones (C-6) can easily be reacted. In addition, the C-2 secondary hydroxyl groups are also fairly reactive while the ones at C-3 resist modification (e.g. by methylation). Several CD derivatives are available commercially in large quantities including –among others– randomly methylated **β-cylodextrin** and **hydroxypropyl-β-cylodextrin** [2]. Chemical modifications substantially alter the solubility of cyclodextrins in water. For example, the solubility of **β-CD**

is **18.5 g L^{-1}** at room temperature, while that of **heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DiOMe-β-CD)** is much higher (allowing preparation of even a 50 % solution). Very interestingly, on heating a clear 10 % aqueous solution of **DiOMe-β-CD,** a sudden crystallization occurs at about 55 °C within a range of 0.5 °C [1]. This phenomenon may be worth of keeping in mind when applying methylated **β-cyclodextrins** in reactions at high temperatures.

The chemical reactivity of a guest molecule may be influenced by complexation to a very large extent. One major application of cyclodextrins is based on their ability to protect their guests against oxidation which is of paramount importance for formulation of oxidation-sensitive drugs or flavour substances. On the other hand, reactions of certain compounds can be largely accelerated by inclusion into the cyclodextrin cavity - generally this results from proper positioning of the substrate (guest) towards a catalytic entity, which may be one of the CD hydroxyls or even a metal ion attached to a functionalized cyclodextrin molecule. This is this latter property which is the most attractive from the aspects of aqueous organometallic chemistry. Finally, being water soluble, cyclodextrins can serve as (reverse) phase transfer agents transporting organosoluble substrates into the aqueous phase for further reactions.

It would be unfair to leave unmentioned other host molecules, capable of promoting catalytic reactions in aqueous media. Appropriately modified calixarenes and crown ethers have been used sporadically for such purposes. Although the potential of very specific applications of these host molecules cannot be denied, from the practical view of availability and price, however, these are a far cry behind cyclodextrins.

10.2 Application of cyclodextrins and other host molecules in aqueous organometallic catalysis

An overview of the literature on the application of host-guest interactions in aqueous organometallic catalysis reveals the following:

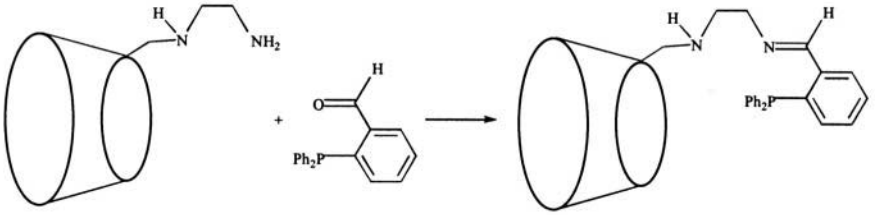
- in most cases (almost exclusively) cyclodextrins were used as hosts,
- majority of the reactions in such systems were catalyzed by complexes bearing a sulfonated phosphine ligand, and
- majority of the above reactions involved higher olefins or aromatics.

In principle, cyclodextrins can interact with both the substrate, the product and the catalyst of a catlytic reaction mixture. Indeed, this is what happens.

The interaction of TPPTS with **β-CD** has been investigated in detail by uv-vis, circular dichorism, ^{1}**H** and ^{31}**P** NMR and electrospray mass spectroscopy [4,5]. The main conclusion of these studies is that one of the

sulfonated phenyl rings of TPPTS is included into the cavity of β-CD and that the complex formation constant at 298 K is approximately 1200 M^{-1}. Most probably 2:1 and 3:1 CD:TPPTS complexes are also formed in a small extent but their stability constants could not be quantitatively established. Nevertheless, this means that in a catalytic application there is a competition for β-CD between the substrate and catalyst molecules although substrates can win this competition owing to the their (usually) large excess over the catalyst. In addition, the product can also take part in this competition and if an organic solvent is used it should obviously be chosen carefully in order to avoid its strong interaction with the cyclodextrin.

Attachment of a catalytic unit to the cyclodextrin torus can be achieved by several modifications. One recent example is shown on Scheme 10.3 (although no catalytic application of complexes with this ligand have been disclosed yet), other modified cyclodextrins (**126-128**) are depicted in Chapter 2.

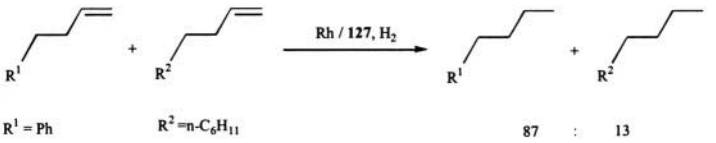


Scheme 10.3

Hydrogenation of unsaturated carboxylic acids, such as acrylic, methacrylic, maleic, fumaric, cinnamic etc. acids was studied in aqueous solutions with a $RhCl_3$/TPPTS catalyst in the presence of β-CD and permethylated β-cyclodextrin [7]. In general, cyclodextrins caused an acceleration of these reactions. It is hard to make firm conclusions with regard the nature of this effect, since the catalyst itself is rather undefined (probably a phosphine-stabilized colloidal rhodium suspension, see 3.1.2) moreover the interaction of the substrates with the cyclodextrins was not studied separately.

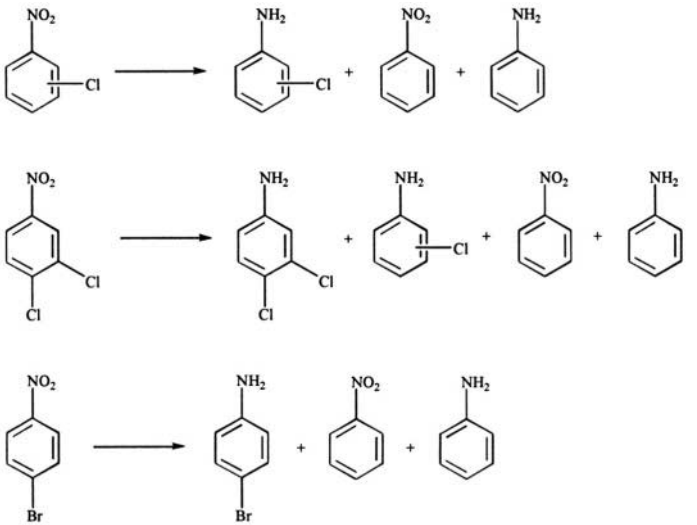
β-Cyclodextrin was modified by attaching 2-(diphenylphosphinoethyl)-thio- (**127**) and 2-bis(diphenylphosphinoethyl)amino- (**126**) moieties at the C-6 position [8-11]. The resulting macroligands were reacted with $[\{RhCl(NBD)\}_2]$ to provide the corresponding cationic rhodium-bisphosphine complexes. These catalysts showed pronounced selectivity due to complexation of the substrate by the CD unit adjacent to the catalytically active metal center. For example, in competitive *hydrogenation* of similarly substituted terminal olefins (Scheme 10.4), 4-phenyl-but-1-ene was

preferentially hydrogenated over 1-decene, up to the ratio of 87/13 [11]. Since these rhodium complexes are highly water soluble, these reactions could be carried out in aqueous/organic biphasic systems, too. Note, that no selectivity was obtained with the analogous complexes lacking the cyclodextrin substituent in their ligands.



Scheme 10.4

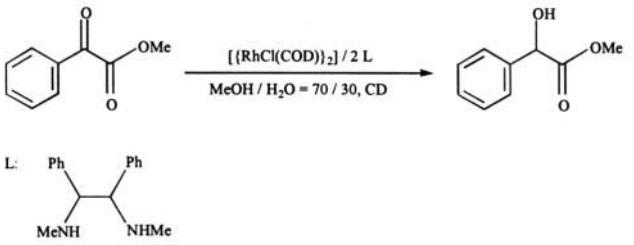
Complexes of Rh, Pt, and Pd with the same ligands were active in the biphasic *hydrogenation* of chloro- and bromonitrobenzenes. At 80-100 °C and 20 bar H_2 pressure the main products were the corresponding chloro- and bromoanilines, up to 99.8 % yield (Scheme 10.5) [12]. The selectivity of similar reactions catalyzed by a Rh/TPPTS was only about 90 %, i.e. the attached cyclodextrin moiety further decreased the extent of hydrodehalogenation, probably by complexation of the halonitroaromatic substrate.



Scheme 10.5

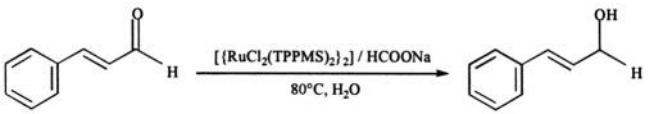
The rhodium complex prepared from $[\{RhCl(COD)\}_2]$ and (1*R*,2*R*)-N,N'-dimethyldiphenylethylenediamine was found to be a catalyst for the

enantioselective hydrogenation of methyl phenylglyoxylate in methanol with a maximum e.e. of 50 % (Scheme 10.6) which decreased substantially when an aqueous solvent was used. However, when cyclodextrin was added in methanol/water 70/30, the enantioselectivity was restored to the value observed in neat MeOH. No enantioselectivity was observed with a diamine-functionalized cyclodextrin [11].



Scheme 10.6

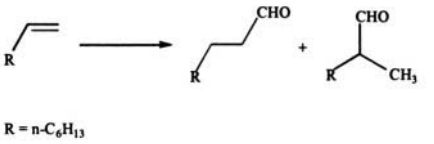
In a water/chlorobenzene biphasic system, reduction of aromatic aldehydes by *hydrogen transfer* from aqueous sodium formate catalyzed by $[\{RuCl_2(TPPMS)_2\}_2]$ provided unsaturated alcohols exclusively (Scheme 10.7). Addition of β-CD slightly inhibited the reaction [13]. It was speculated that this inhibition was probably due to complexation of the catalyst by inclusion of one of the non-sulfonated phenyl rings of the TPPMS ligand, however, no evidence was offered.



Scheme 10.7

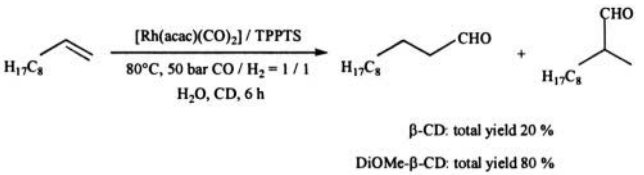
Similar to the above case, *hydroformylation* of 1-hexene using a water-soluble rhodium catalyst $[RhH(CO)(TPPMS)_3]$ gave lower yields when α-cyclodextrin was added to the biphasic reaction system [14]. Again, the reason was suspected in the interaction between the cyclodextrin and the rhodium catalyst.

The cationic rhodium catalysts with bisphosphine-modified CD-s were highly active in the biphasic *hydroformylation* of 1-octene (Scheme 10.8) [9,11]. In a two-phase system of 1-octene/30 % DMF in water, quantitative conversion was obtained with 0.03 mol % of the catalyst at 80 °C and 100 bar syngas within 18 h ($TOF = 180\ h^{-1}$). Selectivity to aldehydes was higher than 99 % with 76 % regioselectivity in favour of the straight-chain product.



Scheme 10.8

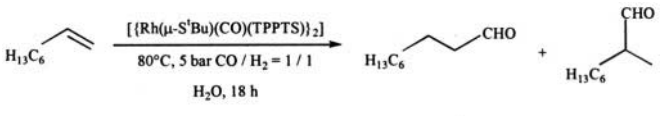
In addition to the natural cyclodextrins, several chemically modified CD-s were also applied as phase transfer agents in the *hydroformylation* of 1-decene (Scheme 10.9). Outstandingly high catalytic activity was observed with **DiOMe-β-CD** which is partially soluble also in the organic phase [15-18]. Selectivity towards the formation of aldehydes was better than 95 %, and the n/i ratio was approximately 2.5 (70 % linear aldehyde). Taking the extremely low solubility of 1-decene in water and the almost complete lack of hydroformylation in the absence of cyclodextrins, the promoting effect of CD-s is really remarkable. A series of olefins bearing aliphatic and aromatic substituents showed similarly good reactivity affording the corresponding aldehydes in close to 100 % yield [16].



Scheme 10.9

Hydroformylation of higher olefins in aqueous/organic biphasic systems with the dinuclear rhodium-thiolato catalyst **[{Rh(μ-S^{t}Bu)(CO)(TPPTS)}$_2$]** afforded the corresponding aldehydes in a rather slow process under mild conditions (Scheme 10.10). Although the TOF of 1-octene hydroformylation was only **0.6 h^{-1}**, selectivity was 98 % towards the linear aldehyde, as usually observed in aqueous media (see also 4.1.4). Addition of **β-cyclodextrin** substantially accelerated the reaction **(TOF = 9.0 h^{-1}** at **[CD]/[Rh] = 18)**, however, the selectivity dropped to 87.5 %, which is characteristic for reactions with this catalyst in non-aqueous surroundings. An acceptable compromise between activity and selectivity can be achieved with a cyclodextrin/rhodium ratio of 7-10. What is even more interesting, the activity of the Rh-catalyst/ **DiOMe-β-CD** combination steadily increased upon each recycling. In the fourth run with the recycled aqueous catalyst phase a **TOF = 27.2 h^{-1}** was obtained, an almost 50 % increase compared to the activity shown in the first run **(TOF = 19.7 h^{-1})**. It is suggested, that the

cyclodextrin, the Rh-catalyst, the organic substrate (or solvent) and water are gradually organized into a rather stable assembly (may be also regarded as a microreactor) in which mass transfer is facilitated and the reaction of the olefin takes place with less restriction [19].

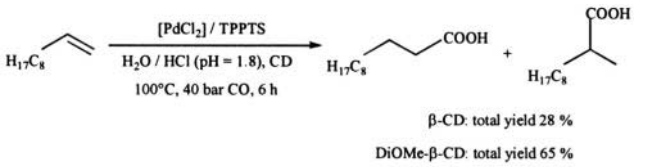


	Yield %		
β-CD	26.2	88.5	: 11.5
DiOMe-β-CD	59.1	88.7	: 11.3

Scheme 10.10

Calix[4]arenes form an interesting class of macrocycles possessing a cone-shaped cavity defined by four symmetrically situated phenoxy rings. Much attention has been devoted to the use of such molecules in host-guest chemistry and several phosphine-substituted calixarenes, prepared with the aim of complexing transition metals, are also known [20]. Water-soluble sulfonated phosphine-modified calix[4]arenes (**197**) were prepared and their rhodium-complexes were used for the hydroformylation of 1-octene in aqueous biphasic media. The reactions were run at 100 °C with 40 bar syngas and with a substrate/catalyst ratio of 125. Under such conditions, use of the calixarene-phosphine led to 95-98 % conversion with approximately 80 % aldehyde yield and a n/i ratio of approximately 2. In comparable experiments, the conversion achieved with a Rh-TPPTS catalyst was close to zero, and the same catalyst together with DiOMe-β-CD gave only 26 % conversion and 21 % yield of aldehydes. Recycling of the calix[4]arene-based catalyst dissolved in the aqueous phase resulted in no loss of activity (in fact, a very slight increase was observed).

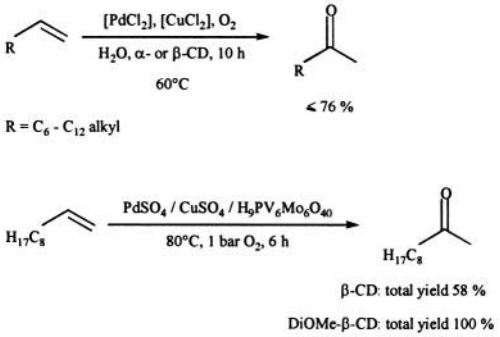
1-Decene was *hydrocarboxylated* with a $[PdCl_2]$/TPPTS catalyst in acidic aqueous solutions (pH adjusted to 1.8) in the presence of various chemically modified cyclodextrins (Scheme 10.11) [18]. As in most cases, the best results were obtained with DiOMe-β-CD. In an interesting series of reactions 1-decene was hydrocarboxylated in 50:50 mixtures with other compounds. Although all additives decreased somewhat the rate of 1-decene hydroformylation, the order of this inhibitory effect was 1,3,5-trimethylbenzene < cumene < undecanoic acid, which corresponds to the order of the increasing stability of the inclusion complexes of additives with β-CD, at least for 1,3,5-trimethylbenzene ($60\ M^{-1}$) and cumene ($1200\ M^{-1}$). These results clearly show the possible effect of competition of the various components in the reaction mixture for the cyclodextrin.



Scheme 10.11

One of the earliest use of cyclodextrins as inverse phase transfer agents was in the *Wacker oxidation* of higher olefins to methyl ketones [22] with $[PdCl_2] + [CuCl_2]$ catalyst (Scheme 10.12). Already at that time it was discovered, that cyclodextrins not only transported the olefins into the aqueous phase but imposed a substrate-selectivity, too: with C_{10+} olefins the yields decreased dramatically and 1-tetradecene was only slightly oxidized.

Similar results were obtained in the biphasic *Wacker oxidation* of 1-decene, catalyzed by $PdSO_4$, $CuSO_4$ and a heteropolyacid $H_9PV_6Mo_6O_{40}$ in the presence of chemically modified **β-cyclodextrins** (methyl, methoxy, hydroxypropyl derivatives). The reactions yielded 2-decanone in rather high yield (up to 58 %) accompanied by extensive isomerization of 1-decene to internal decenes. Nevertheless, these latter apparently did not react, since the ratio of 2-decanone among the oxodecenes exceeded 99 % (Scheme 10.12).

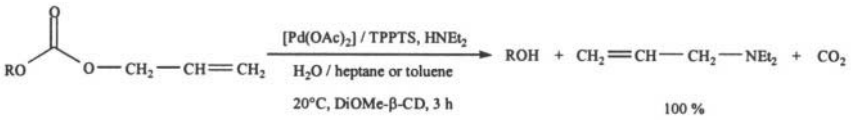


Scheme 10.12

Cyclodextrines, modified with 2-cyanoethyl and with bis(2-cyanoethyl)amino groups were used as ligands in the $[PdCl_2] + [CuCl_2]$-catalyzed Wacker-oxidation of 1-octene. Without the modified cyclodextrins the yield of 2-octanone was less than 1 %, which could be raised to 73 % by the addition of nitrile-modified **β-cyclodextrin** ligands (60 °C, 2 h).

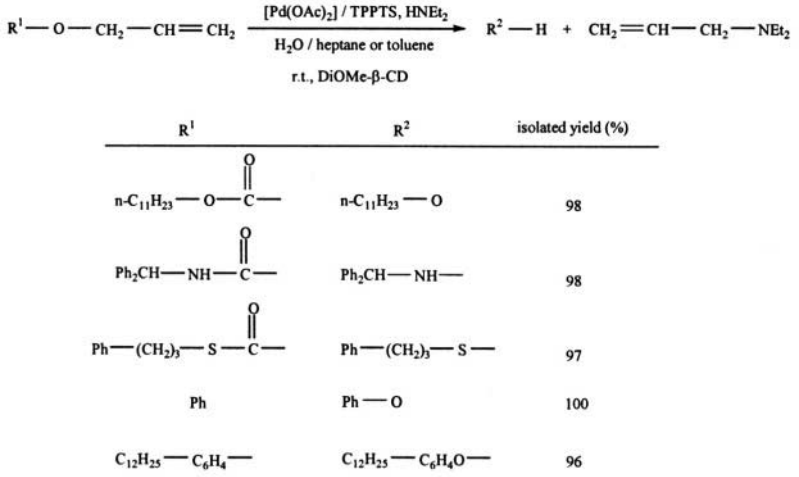
In the presence of **DiOMe-β-CD,** both *allyl carbonates* (Scheme 13) [25] and various *allylic substrates* (Scheme 14) [26] were *cleaved* smoothly in

aqueous-organic biphasic media with Pd/TPPTS catalyst in the presence of $HNEt_2$ under very mild conditions. Conversions are usually quantitative and isolated yields are generally also in excess of 95 %.



Scheme 10.13

The advantage of biphasic systems over the more common CH_3CN/H_2O mixtures (see 6.5) is in the easier and cleaner product isolation. However, practically useful rates can be achieved only in the presence of such reverse phase transfer agents like the various chemically modified cyclodextrins, of which **2,6-di-OMe-β-CD** proved the best.



Scheme 10.14

This short compilation of the recent literature results convincingly demonstrates the usefulness of water-soluble supramolecular complexing agents in biphasic aqueous organometallic catalysis. Due to their availability, cyclodextrins play a major role in this field. Thinking of the relatively low price of these chemicals (a few $ per kg in 1998 [2]) their use on a larger scale can also be envisaged in fine chemicals production.

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KEY TO THE ABBREVIATIONS

acacH = 2,4-pentanedione (acetylacetone)
Aliquat 336 = trioctylmethylammonium chloride
Alizarin red = sodium 1,2-dihydroxy-9,10-anthraquinone-3-sulfonate
amphos = 2-diphenylphosphinoethylammonium ion
AOC = aqueous organometallic catalysis
AOT = see p.78
BDPB = 1,4-bis(diphenylphosphino)butane
BDPBzPSO$_3$ = 3-benzyl(p-sulfonate)-2,4-bis(diphenylphosphino)-pentane
BDPP = 2,4-bis(diphenylphosphino)pentane
BDPPTS = tetrasulfonated BDPP
BIFAPS = **50,** see p. 18
BINAP = 2,2' -bis(diphenylphosphino)-1,1' -binaphtyl
BINAS = **52**, see p. 18
BIPHLOPHOS = **43**, see p. 18
bipy = 2,2'-bipyridine
BISBIS = **46**, see p. 18
BPPM = (2*S*,4*S*)-*N*-*t*-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl)pyrrolidine
Brij = see p.78
BSA = bovine serum albumin
Bu = butyl
CBDTS = tetrasulfonated cyclobutane-DIOP, **37**, see p. 17
CD = cyclodextrin
CHIRAPHOS = 2,3-bis(diphenylphosphino)butane
Cn = 1,4,7-trimethyl-1,4,7-triazacyclononane
COD = 1,5-cyclooctadiene
Cp = η^5-cyclopentadienyl
Cp* = η^5-C_5Me_5, η^5-pentamethylcyclopentadienyl
CTAB = hexadecyltrimethylammonium bromide
DBA = 1,5-diphenyl-1,4,-pentadiene-3-one (dibenzylideneacetone)
DDAPS = see p.78
diam-BINAP = **160**, see p.35
DIOP = *trans*-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolan
DMF = dimethylformamide

DMSO = dimethylsulfoxide
DOPC = dioleoylphosphatidylcholine
DPPC = dipalmitoylphosphatidylcholine
DPPE = 1,2-bis(diphenylphosphino)ethane
DPPP = 1,3-bis(diphenylphosphino)propane
DPUP = ω-diphenylphosphinoundecylphosphate
EDTA = ethylenediaminetetraacetic acid
Et = ethyl
FBS = fluorous biphase systems
HSA = humane serum albumin
HLB = hydrophilic-lipophilic-balance
hm-pybox = see p. 232
^{i}Pr = isopropyl
Me = methyl
Na_2DPPPDS = **182**, see p. 36
NADH = nicotinamide adenine dinucleotide
NBD = bicyclo[2.2.1]hepta-2,5-diene (norbornadiene)
NORBOP = **96**, see p.26
PAA = poly(acrylic acid)
PCy_3 = tricyclohexylphosphine
PEG = poly(ethylene glycol)
PEO = poly(ethylene oxide)
Ph = phenyl
phophos = **159**, see p. 34
PPh_3 = triphenylphosphine
PPO = poly(phenylene oxide)
Pr = propyl
PTA = 1,3,5-triaza-7-phosphaadamantane
PVP = poly(*N*-vinylpyrrolidone)
SAPC = supported aqueous phase catalysis
SDS = sodium dodecylsulfonate
SKEWPHOS, see BDPP
Span 40 = sorbitan monopalmitate
SULPHOS = **31**, see p. 15
TEDICYP = *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)-cyclopentane
TfOH = trifluoromethylsulfonic acid
THF = tetrahydrofuran
TPPDS = disulfonated triphenylphosphine, **2**, see p. 14
TPPMS = monosulfonated triphenylphosphine, **1**, see p. 14
TPPTS = trisulfonated triphenylphosphine, **3**, see p. 14
Triton X-100 = see p. 224

Tween = see p. 78
WGSR = water gas shift reaction
XANTHPHOS, sulfonated
= **48**, see p. 18

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