NEW STRATEGIES FOR THE RHODIUM-CATALYSED AQUEOUS-BIPHASIC HYDROFORMYLATION OF MEDIUM CHAIN ALKENES

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“New strategies for the rhodium-catalysed aqueous-biphasic hydroformylation of medium chain alkenes”

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For the of the degree of Doctor of Philosophy

15th June 2009

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I, **Simon L. Desset** hereby certify that this thesis, which is approximately **28 000** words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in **February 2005** and as a candidate for the degree of **doctor of philosophy** in **February 2006**; the higher study for which this is a record was carried out in the University of St Andrews between **2005 and 2008**.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of doctor of philosophy in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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To all of you and those I forget, Thank You.

Abstract

Aqueous-biphasic organometallic catalysis is, as illustrated by the industrial hydroformylation of propene and butene, one of the most promising ways to overcome the intrinsic problem of catalyst separation in organometallic catalysis. However, for poorly water-soluble substrates, mass transfer limitations bring the reaction rate below any that could be economically viable, greatly limiting the scope of this elegant technology. We have studied three different strategies to overcome this limitation. We developed additives that speed up the reaction whilst retaining fast phase separation and good metal retention. Evidence suggest that those additives affect the reaction by forming emulsions with poor stability under the reaction conditions These emulsions increase the interfacial surface area but break after settling for a short time. We also developed ligands that allow the catalyst to be reversibly transported between an aqueous and an organic phase upon addition and removal of carbon dioxide. This allows the reaction to be carried out under homogeneous conditions, only limited by intrinsic kinetics, and the catalyst to be separated by aqueous extraction triggered by carbon dioxide. The catalyst can be returned to a fresh organic phase by flushing out the carbon dioxide. By applying this methodology for the hydroformylation of medium chain length alkenes, very high reaction rates were obtained and the catalyst could be recycle three times with excellent retention of activity and low metal leaching. This methodology could also be reversed with the reaction being carried out in an aqueous phase in the presence of carbon dioxide and extracting the catalyst into an organic solvent using nitrogen flushing. Finally, we briefly investigated the use of an oscillatory baffled reactor as a mean for mass transfer improvement for aqueous-biphasic hydroformylation. This new type reactor did not improve the performance of the system under the investigated conditions, but may require less energy input for equivalent agitation and mixing.

Contents

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ONE

Introduction

Parts of this chapter are published in:

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1.1 Catalysis

We are now facing a time where raw materials and energy are growing scarce. Concerns regarding the burden human activity is putting onto the planet are finally turning into actions and a general will for more responsible behaviors can be seen at the different levels of society. A global decrease in consumption and a more equal share of the "end of the pipe" existing goods could offer a rapid and efficient answer to these issues. However, due to the growing earth population, the "ill" need for economic growth and the societal changes required this is not likely to be retained as one of the "applicable" solutions by the political and economical managers. Continuing to support global growth while reducing its environmental consequences requires making the most efficient uses of the available resources at all stages. This range from more efficient motor engines, better building insulation, dry toilets to solar panels.

When considering the chemical industry in particular it translates into making the desired product with the highest efficiency in terms of material incorporation and energy consumption. This has been part of the purpose of the “green chemistry” concept primarily developed by Anastas in the nineties[1]. While the prime concern of green chemistry regarded the impact of chemistry on the environment in terms of emissions, use of noxious substances and generation of wastes; some of its 12 principles pave the way to more efficient chemical transformations (Figure 1. 1)[1b-e]. Especially, it was recognized that maximizing the incorporation of all materials into the final product, avoiding the use of auxiliary substances, minimizing the energy requirements and the use of renewable raw material were of major importance in reducing waste generation. Some 12 years later, those principles are recognized by a vast majority as the basis for the improvement and the development of chemical processes.

A major tool for chemists and engineers to fulfill these principles is catalysis. By its nature, catalysis enables more efficient synthesis since it allows reactions to proceed under milder conditions, hence reducing energy consumption. Maximizing material incorporation into the final products requires the transformations to be as selective as possible and to use simple building blocks as starting material. Organometallic catalysts are especially suited for this purpose.The homogeneous nature of the catalytic system, has allowed a deep understanding of the catalytic cycles through the use of in-situ spectroscopic techniques (NMR, IR), which has led to the development of highly active and selective catalysts. As an example of the level of selectivity achievable with homogeneous catalysts, Figure 1. 2 shows the different products that can be obtained form a mixture containing an alkene, carbon monoxide, hydrogen and methanol. By careful choice of the metal centre, the ligand and the reaction conditions, one out of the many different products can be obtained with selectivities superior to 90 %. It is also worth noticing the simplicity of the starting materials used and that they are fully incorporated into the products.

Despite its success, organometallic catalysis is racked by a major dilemma. The homogeneous nature of the catalyst made the success of organometallic catalysis by enabling understanding, control and tuning of the catalytic cycles but at the same time it greatly complicates the separation and subsequent reuse of the catalyst.

1. It is better to prevent waste than to treat or clean up after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy or function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used.
6. Energy requirement should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical /chemical processes) should be avoided.
9. Catalytic reagents (as selective as possible) are superior to stoechiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Figure 1. 1 *The twelve principles of green chemistry*[1b-e].

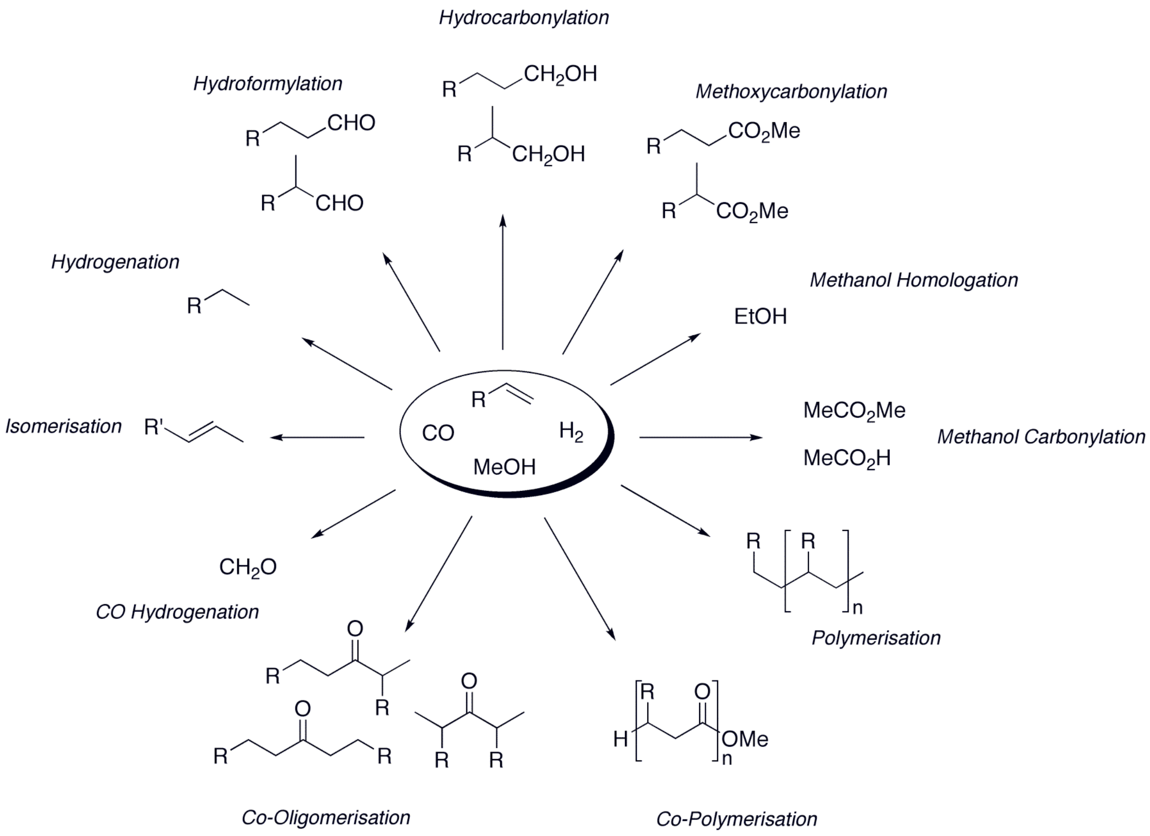
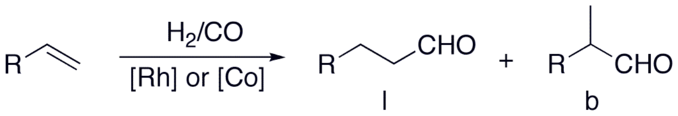


Figure 1. 2 *Some of the products that can be obtained from a mixture of alkene, carbon monoxide, hydrogen and methanol. Adapted from*[2]*.*

This explains why, while more than 90 % of the chemicals are produced via catalyzed processes[3], only *ca*. 50 processes employ homogeneous organometallic catalysts. Separation from the reaction product is only made simple for light products, which can be evaporated continuously from the reactor. Most of the time, part of the crude reaction medium, containing the (sensitive) catalyst, is continuously removed from the reactor to a separation unit, usually a distillation system. To be efficient, this operation must often be carried out under conditions that promote catalyst degradation *i.e.* low pressure and high temperature. Nowadays, many efforts are devoted to develop innovative and efficient ways to separate and reuse homogeneous catalyst. The present thesis is part of this effort.

1.2 Hydroformylation

When considering catalyst separation and reuse, the industrial hydroformylation of alkenes constitutes a relevant example of the different techniques used and their evolution. In this reaction, an alkene reacts with hydrogen and carbon monoxide in the presence of a transition metal catalyst, usually a rhodium or a cobalt complex, to yield the two corresponding aldehydes, the linear (l) and the branched (b) (1).



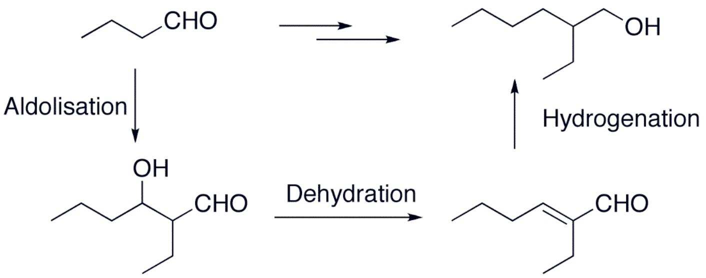
(1)

Since the branched product finds fewer uses, a high linear to branched ratio (l/b) is usually aimed for. In terms of production volume, the hydroformylation of alkenes is nowadays the largest industrial application of homogeneous catalysis with an annual production of aldehydes of 9.2 million tons in 2002[4]. The production capacities for the different aldehydes are uneven with butanal being by far the most produced aldehyde via hydrofomylation (Table 1. 1). This uneven distribution is mainly due to two factors, the availability of the starting alkenes and more importantly the discrepancy in process efficiency for the hydroformylation of the different alkenes, which is strongly related to the ease of catalyst recycle.

It is worth noticing that 60 % of the butanal is used to produce 2-ethyl-hexanol via an aldolisation – dehydration - hydrogenation sequence (2). This C_8 alcohol is then used in

Table 1. 1 *Production capacities of aldehydes by hydroformylation in 1993.*[5]

Aldehydes	C_3	C_4	C_5-C_{13}	$>C_{13}$	Total	2-EthylHexanol
Capacity (10^3 t)	100	4515	1180	385	6180	2420
%	2	73	19	6	100	



(2)

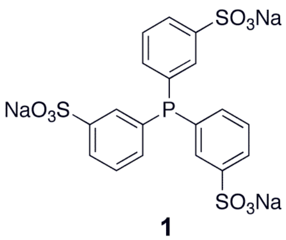
the production of the plasticiser dioctyl phtalate. Plasticiser alcohols of similar performance can be obtained in fewer steps by a hydroformylation-hydrogenation sequence of C_6-C_8 alkenes. However, due to more complicated catalyst recycling (*vide infra*), this route is not widely industrially used despite its inherent simplicity.

One of the main defining parameters of the hydroformylation process is the nature of the metal center used. The first generation of processes exclusively use cobalt carbonyl complexes, modified (Shell) or not (ICI, BASF, Kuhlmann and Ruhrchemie) by phosphine ligands. Such catalysts typically display high activity for internal olefins and for hydrogenation to alcohols. They constitute the catalysts of choice for hydroformylation of medium to long chain alkenes. Mixtures of internal and terminal alkenes can be used as a cheap feedstock and plasticizers or surfactant alcohols can be obtained in a single operation. For processes, employing unmodified cobalt carbonyl complexes, separation of the catalyst is carried out by chemical decobaltation. In the BASF process, the cobalt present in the crude product mixture is oxidized by oxygen and formic or acetic acid to give an aqueous solution containing Co^{2+} mainly as acetate or formate. The crude product can then be separated from the catalyst by simple phase separation. The cobalt is then reduced to Co^- and sent back to the reactor. In the Kuhlman-Exxon process the cobalt is recycled without change of the metal oxidation level. The cobalt catalyst present in the crude product is transformed in water-soluble cobaltate by contact with an aqueous alkali solution. After phase separation the catalyst is regenerated by treatment with sulfuric acid in the presence of syngas. For modified cobalt complexes, the increased thermal stability gained by stabilization with phosphine ligands allows the high boiling products to be directly distilled from the reaction crude (Shell process). The major drawback of these cobalt based processes are the high pressures (200-300 bar) and temperatures (150-200°C) required to achieve acceptable space-time yield, making the process very energy demanding.

Rhodium-phosphine systems developed for hydroformylation in the 1960s, are much more active and can convert alkenes to aldehydes under relatively low pressure and temperature (typical industrial conditions: 20 bar; 100°C)[6]. This led to the commercial development of the Low Pressure Oxo process (LPO process) that produces butanal using a rhodium-PPh_3 catalyst. In this process, the low boiling products are separated from the catalyst either continuously by stripping (gas recycle, UCC) or semi-continuously by distillation in a separated unit (liquid recycle, UCC). Unfortunately, this low energy demanding process is limited to the hydroformylation of propene. Due the low isomerisation activity of the rhodium-phosphine catalyst, only expensive terminal alkenes can be used as feedstock. More importantly, the low thermal stability of the rhodium complex greatly limits the working temperature of the distillation operation, making the separation of product heavier than butanal impracticable. Stripping of the product is also not applicable for products heavier than butanal.

The search for alternative catalyst-product separation methodologies has led to the next generation of rhodium-catalyzed hydroformylation processes. Instead of carrying out the reaction homogeneously, the rhodium catalyst is immobilized in an aqueous phase via the water-soluble ligand, triphenylphosphine trisulfonated trisodium salt (TPPTS), **1**, while the alkene and the produced aldehydes form a separated phase. The catalyst, dissolved in the water phase, can thus be separated from the product by simple decantation and fed back to the reactor avoiding any thermal stress (Figure 1. 3). This constitutes the basis of the Ruhrchemie/Rhône-Poulenc process (RCH/RP process), which was first commercialized in 1984 for the production of butanal[7]. Nowadays, 5 plants are operating and produce annually 800 000 tons of C_4 and C_5 aldehydes[4]. The process is operated semi-continuously, a small portion of the crude reaction mixture is continuously taken out of the reactor via a simple overflow to a gravity separator. There, the mixture quickly splits into two phases, the bottom aqueous phase containing the catalyst is recirculated to the reactor while the products and unreacted starting material are sent to downstream separation units. The process produces virtually only aldehydes (99% selectivity to aldehydes) with very high linear selectivity (l/b = 96:4) under moderate conditions (125°C, 50 bar). More importantly, during the production of the first 2 000 000 tons of butanal, only 2 kg of rhodium have been taken out with the product, in other words the leaching lies in the ppb range, clearly demonstrating the efficiency of the aqueous-biphasic methodology to immobilize the catalyst[8].

This alternative catalyst-product separation technique could offer a solution to the problem encountered when trying to separate high boiling products from the rhodium catalyst in homogeneous hydroformylation. Unfortunately, middle to long chain alkenes



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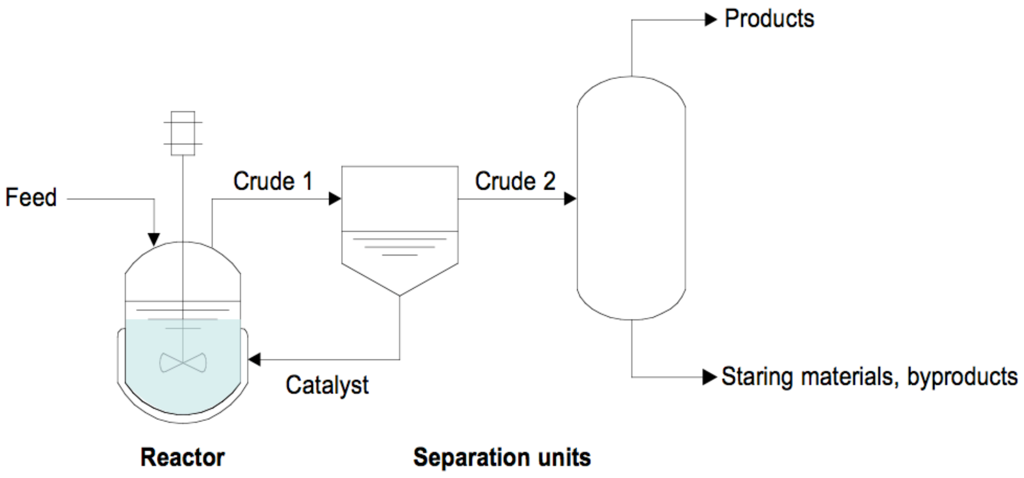


Figure 1. 3 *Simplified flow chart for aqueous-biphasic process.*

and aldehydes are poorly soluble in water and mass transfer brings the reaction rate below any that would be economically viable (Figure 1. 4). However, due to the important commercial interest in long chain aldehydes, many efforts are devoted to extend the aqueous-biphasic concept for the rhodium hydroformylation of alkenes > C_5. Several other methodologies for catalyst–product separation have also been investigated for this transformation.

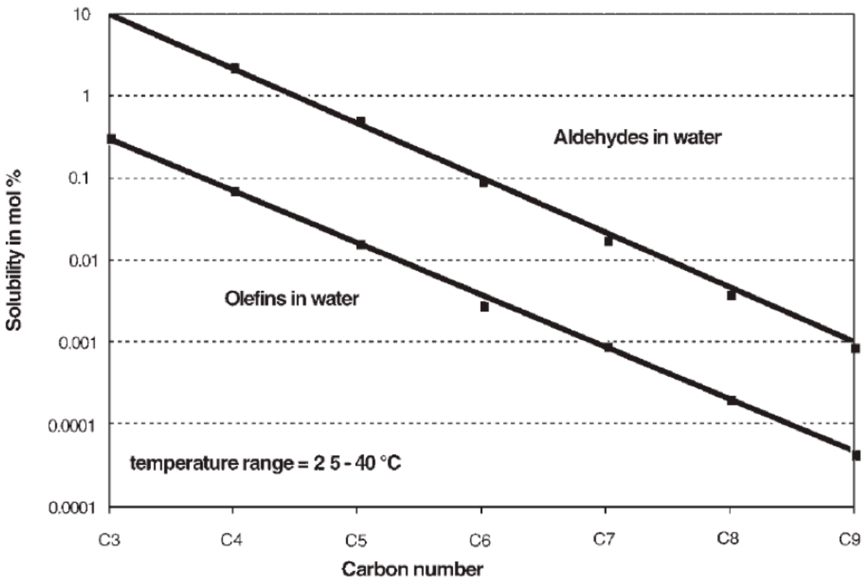


Figure 1. 4 *Solubility of alkenes and aldehydes in water*[9].

1.3 Extension of the aqueous-biphasic methodology

The different methodologies developed so far to extend the substrate scope of the aqueous-biphasic can be roughly classified as depicted in Figure 1. 5.

1.3.1. Additives.

The use of additives such as co-solvents, surfactants or inverse phase transfer catalyst is aimed at increasing the concentration of substrate in the aqueous catalytic phase. Each types of additive differ by their mode of action and present different advantages and drawbacks. A complete discussion of their use in aqueous-biphasic catalysis appears in the second chapter of the present thesis.

1.3.2. Surface active catalysts.

Designing ligands that enhance the contact between the catalyst and the substrate in aqueous-biphasic catalysis has been an area of intense research over the years. One of the first approaches was to use mixture of water soluble ligands (TPPTS) and non polar ligands (triphenylphosphine, TPP) in order to generate complexes of mixed coordination

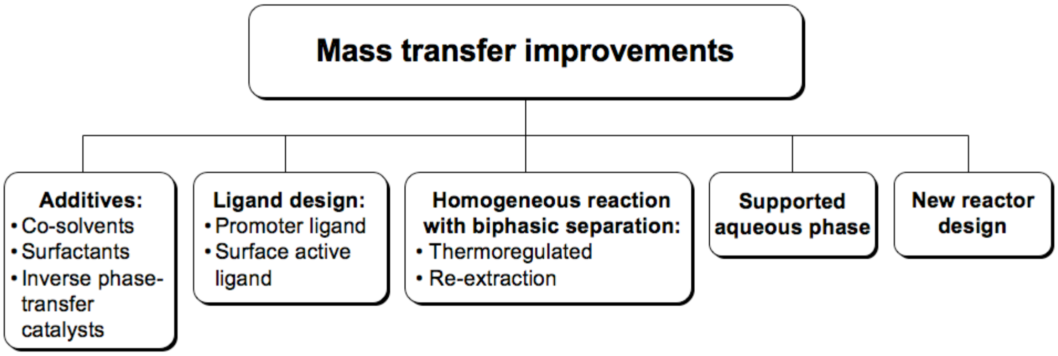
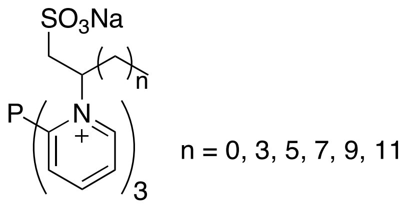


Figure 1. 5 *Schematic representation of the different approaches developed for mass transfer improvements in aqueous-biphasic catalysis.*

$[HRh(CO)(TPPTS)_{3-n}(TPP)_n]$which would preferentially be soluble at the water-organic interface[10]. Such an approach resulted in an impressive increase of the reaction rate. However, it was later shown that the reason for the rate improvement was the in-situ formation of $[HRh(CO)(PPh_3)_3]$ complexes catalysing the reaction in the organic phase and leading to high leaching of the catalyst from the aqueous phase[11].

Another approach was to design ligands displaying surface-active behaviour. The idea of using such ligands relies on the fact that they could enhance the solubility of alkenes by enclosing them in the hydrophobic core of a micelle formed by the aggregation of catalyst molecules. This would bring the substrate and the catalyst in close proximity and hence increase the reaction rate.

The first water-soluble system specifically designed to combine the functions of ligand and surfactant is the zwitterionic trisulfoalkylated tris(2-pyridyl)phosphine **2**[12]**.** Turnover frequencies up to 340 h^{-1} where achieved in the biphasic hydroformylation of 1-tetradecene using rhodium/**2** as catalyst. The conversion was found to be very sensitive to the chain length of the hydrocarbon tail of the ligand. A maximum in pentadecanal yield was found by using rhodium/**2** with n = 5. Further increases of the chain length resulted in lower yields and ultimately when n = 9, 11 very stable emulsions were formed. With short to medium hydrocarbon chains (n = 0 - 7) the Rh/**2** catalyst was quantitatively recovered by simple phase separation. According to the authors, the rate enhancement was caused by solubilization of the alkene in the core of micelles formed by the catalyst.



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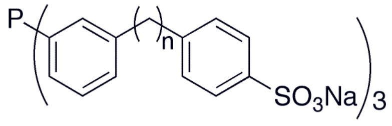
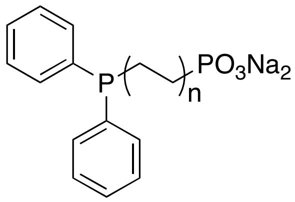


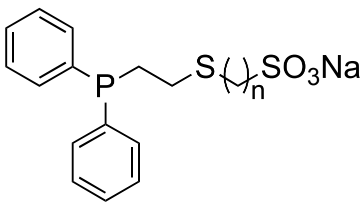
3 n = 3
4 n = 6
5 n = 10

Phosphines **3**-**5** have been used as ligands to give surfactant properties to rhodium catalysts in the hydroformylation of long-chain alkenes in aqueous media. Hydroformylation of 1-octene in aqueous methanol with rhodium/**3** or **4** as catalysts led to turnover frequencies of 335 h^{-1} and 360 h^{-1} respectively[13]. The linear selectivities observed (l/b = 8 and 9.5 respectively) were high for reactions carried out in the presence of a co-solvent. Phase separation at the end of the reaction was excellent and no emulsion was observed. Increase of the spacer chain length of the ligand (**5**) up to 10 methylenes increased further the activity of the catalyst while retaining the high linear selectivity[14]. When the biphasic reaction was performed in pure water, the reaction rates clearly diminished[15, 16, 17]. The linear selectivity was still high but inferior to the ones observed when TPPTS was used as ligand under the same reaction conditions.

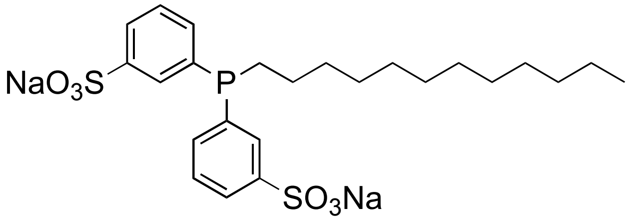
Phosphonated phosphine ligands **6** and **7** have been successfully used in the biphasic hydroformylation of 1-octene and 1-dodecene[18]. The rhodium catalysts generated from $[Rh(acac)(CO)_2]$ and **6** or **7** showed activities higher than the classical rhodium/TPPTS system. However, the linear selectivity seemed to be slightly lower. The surface activity of the ligands **6** and **7** led to emulsions instead of the biphasic system usually obtained



6 n = 5
7 n = 6



8 n = 2`
9 n = 3



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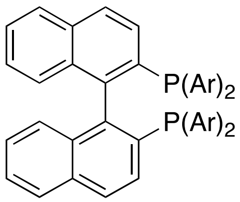
after the reaction. Addition of methanol to the reaction medium or at the end of the reaction can overcome this problem by breaking the micelles. However this led to a decrease in linear selectivity and more complicated separation of the products. Thioether-containing ligands **8** and **9** have been used in the biphasic rhodium catalysed hydroformylation of 1-dodecene[19]. These ligands displayed higher activity than TPPTS, especially at low catalyst concentration. The combination of a rhodium/**8** or **9** catalyst and non-ionic surfactants, led to even higher activity and allowed the system to be recycled 5 times without significant lost of activity. Catalysts formed from rhodium and the amphiphilic ligand **10** have been shown to be much more active than rhodium/TPPTS catalyst for the biphasic hydroformylation of long-chain alkenes[20]. Surprisingly, the conversion increased when the chain length of the alkene increase from 1-hexene to 1-dodecene.

Surface-active ligands based on diphosphine backbones such as bisbi, binap and xantphos have been developed. Catalysts based on the ligands **11** and **12** have been compared with the rhodium/TPPTS catalyst for the hydroformylation of 1-octene in aqueous methanol[21, 14]. Ligand **12** led to more active and more selective catalyst than TPPTS whereas a catalyst containing the diphosphine, **11,** was less active and selective than one containing TPPTS. Ligand **13** led to an even more active catalyst than **12** but the linear selectivity decreased slightly. For all these ligands, no emulsion was observed at



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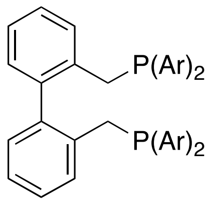

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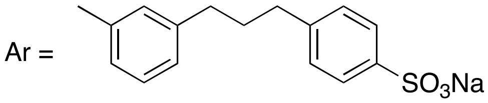
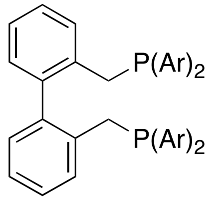
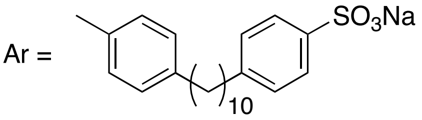


the end of the reaction. Moreover, rhodium leaching was determined by ICP to be < 1 ppm.

Surface-active bidentate phosphines based on the xantphos backbone were also designed[22]. The ligands **14** and **15** have been shown to form spontaneously large and thermally stable vesicles in aqueous solution. Moreover, incorporation of 1-octene inside the vesicle bilayer has been observed. Rhodium catalysts formed with the ligands **14** and **15** were compared with the water-soluble parent sulphoxantphos ligand **16** in the aqueous biphasic hydroformylation of 1-octene. The activity was found to follow the order **16** < **14** < **15**.

Surface-active ligands show promising rate-enhancement effects in the hydroformylation of higher alkenes yet sometimes with a slightly decreased linear selectivity. However, none of these systems have been so far used for commercial





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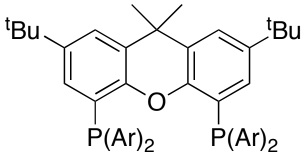
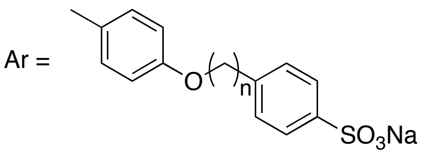
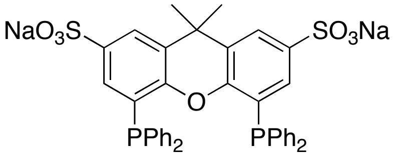




14 n = 3
15 n = 6



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application. The high cost of those rather complex ligands might be one of the main reasons. The tendency to form emulsions under certain conditions may also impede their extended use. More investigation and development of new ligand structures would be highly desirable to further assess their potential.

1.3.3. Homogeneous reaction with biphasic separation.

A more general solution to avoid mass transfer limitation is to carry the reaction in a homogeneous fashion and to separate the catalyst from the product using aqueous extraction after reaction in a separate unit. This greatly simplifies the reaction engineering, since the "know-how" developed for homogeneous reactions can simply be applied for the reaction section.

To apply this methodology, either the catalyst can be designed so its solubility can be switched upon an external trigger or the reaction medium can be designed to switch from a biphasic system to a single phase and reversed to the biphasic system upon an external stimulus (Figure 1. 6).

Fluorous biphasic systems were the first to be developed for such a reversible phase switching[23]. Fluorous solvents form biphasic systems with many organic solvents, but turn into monophasic systems upon heating and switch back to biphasic mixtures upon cooling. This property has been elegantly used to recycle homogeneous catalysts, even enabling continuous-flow operation[24].

For aqueous biphasic systems, non-ionic surfactants were used to generate temperature reversible micro-emulsions. Catalysts, for which the solubility can be reversibly switched upon temperature or pH swings, have also been designed for catalyst recycling.

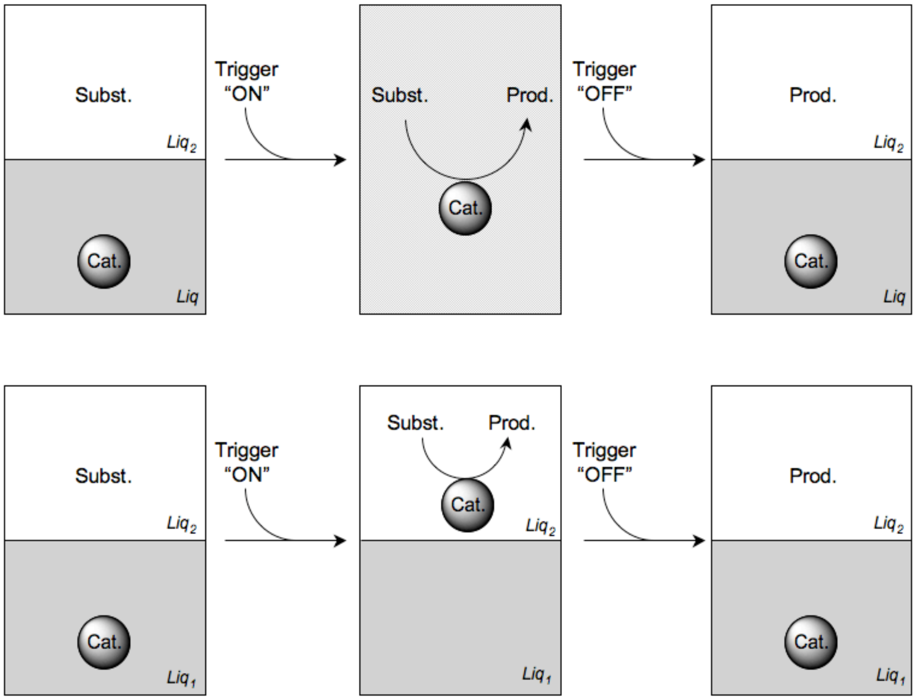


Figure 1. 6 *Schematic representation of a switchable solvent system (top) and a phase-switchable catalyst (bottom).*

A complete discussion of those concepts is contained in the third chapter of the present thesis.

1.3.4. Supported aqueous-phase catalysis – SAPC

A long lasting question in aqueous-biphasic catalysis is the location of the chemical reaction. The reaction can take place in the bulk of the aqueous phase in which case hydrophobic substrates will have to cross the water-organic interface and then diffuse in the aqueous phase to react with the catalyst. The decrease of the reaction rate observed with the increase of the substrate hydrophobicity was the main argument in favour of this model. On the other hand, the reaction can take place at the aqueous-organic interface were part of the catalyst resides and quickly transforms the slowly diffusing substrate.

The pressure uptake observed during the aqueous-biphasic hydroformylation of propene has been modelled using both bulk phase and interface reaction derived equations[25]. The correlation between experimental and calculated pressure uptakes was only satisfactory with the interface model, making it most likely to be the place of the reaction.Therefore, measures that increase the interfacial area should in principle increase the reaction rate, although this may also be the case if mass transport across the interface is rate limiting because the interfacial area will be increased. Improved reaction rates observed with surfactants can to some extent be attributed to the increase of the interfacial area (see Chapter 2).

A very elegant approach to maximise the water-organic interface was developed in the early nineties by Davis and co-workers. They supported a thin film of water containing [HRh(CO)(TPPTS)$_3$] on the surface of a high surface-area hydrophilic solid which was then used for the hydroformylation of alkenes[26]. These supported aqueous-phase catalysts (SAPC) were shown not to leach rhodium into the product phase and to be stable at optimized water content. More importantly, comparison between SAPC, aqueous-biphasic and homogeneous hydroformylation showed that the activity of the SAPC lies between the homogenous and the biphasic system[27]. Moreover, when an equimolar mixture of substrates, namely hexene, octene and decene, was hydroformylated, an equimolar mixture of the products was obtained for the SAPC and the homogeneous systems while the aqueous-biphasic system yielded mainly heptanals, *i.e.* the products arising from the most water-soluble olefin. These observations supported the idea of a purely interfacial reaction for the SAPC. Long stability tests were carried out in a tubular trickle-bed reactor for 38 h[27]. The activity was shown to increase after 4 h while the linear selectivity decreased. Neither rhodium, nor phosphorus was found to leach from the catalyst. However, significant water leaching was evident. The water content was found to have a dramatic influence on the activity of the catalyst. Typically, curves of the activity as a function of the catalyst water content display a bell shape (Figure 1. 7)[28]. At low water content, the low mobility of the rhodium complex on the surface, as demonstrated by solid-sate NMR studies, accounts for the lower activity. After reaching an optimum, the activity decreases with the increasing amount of water. As the thickness of the water phase is increased the system becomes more like an aqueous-biphasic system where the rhodium is dissolved in the bulk of the aqueous phase.

To further assess the stability of the system, self assembly tests were carried out[29]. The separate components of the SAPC, *i.e.* the rhodium complex, TPPTS, the support and water, were introduced into an autoclave together with solvent and substrate. The autoclave was heated, pressurized and stirred for the desired reaction time. The same test was carried out but without the support. The conversion profile of the reactions showed

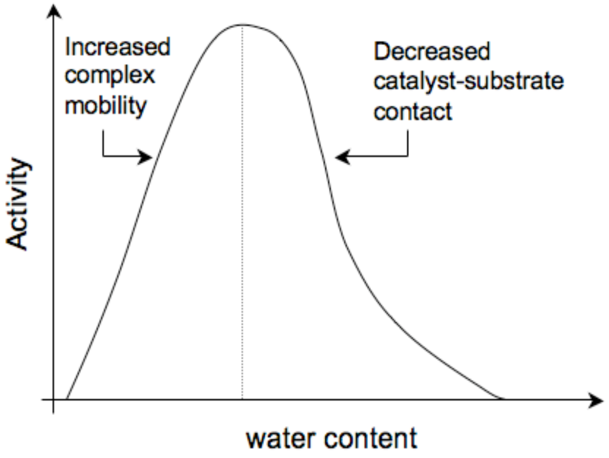
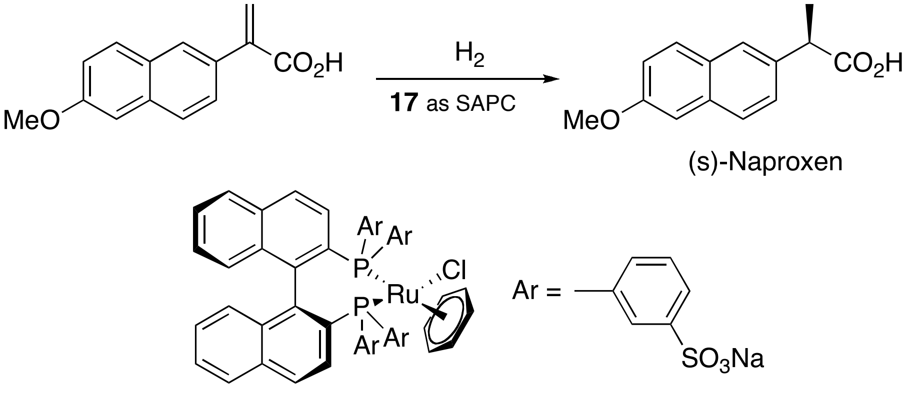


Figure 1. 7 *Schematic representation of the activity of an SAPC catalyst as a function of its water content. Adapted from ref*[28]

that when the support was present, catalyst activity similar to that of a preformed SAPC was observed while in absence of support very low activity was found. This indicates that, under the reaction conditions, the individual components of the SAPC self-assemble rather than remaining separated. Therefore, the reverse, *i.e.* separation of the components under reaction conditions, is unlikely to occur.

The success of SAPC has prompted their use for immobilization of asymmetric catalysts. A ruthenium-sulfonated binap complex, **17**, was immobilized following the SAPC concept and tested for the asymmetric hydrogenation of dehydro-naproxen (Scheme 1. 1)[30a]. While the analogous homogeneous system yielded the product with 95 % *ee*, 70 % *ee* was observed when the SAPC was used. This decrease in enantioselectivity was attributed to the hydrolysis of the Ru-Cl bond. Replacing water by ethylene glycol as the supporting film gave a heterogenised catalyst, which displayed high *ee* together with high retention of the catalyst (Ru leaching < 32 ppb) and an activity of one third that of the analogous homogeneous catalyst[30b].

Hydroformylation of acrylates has been studied under homogeneous, aqueous-biphasic and SAPC conditions[31]. Interestingly, SAPC systems showed the highest activity



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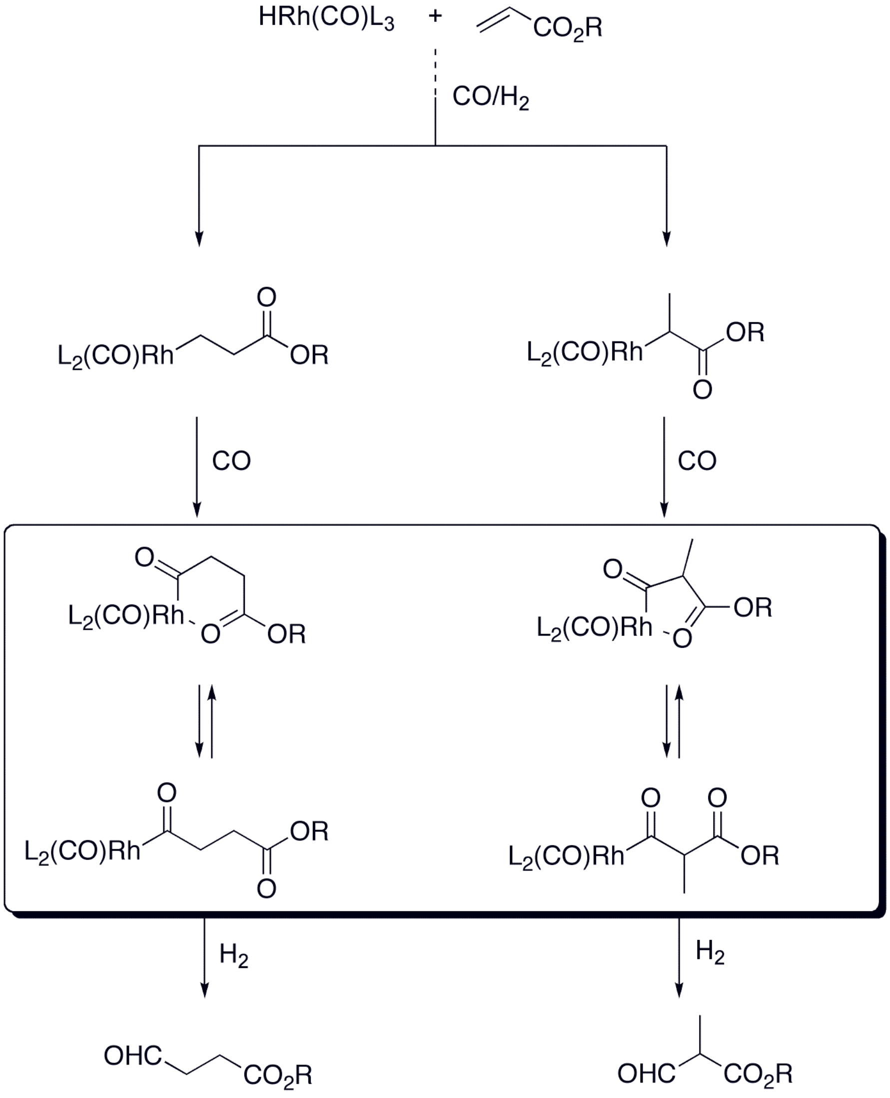
Scheme 1. 1 *Asymmetric hydrogenation of dehydro-naproxen using a ruthenium complex immobilized as an SAPC. Adapted from ref*[30a] followed by the aqueous-biphasic system and finally the homogeneous system. These rather unusual results were attributed to the beneficial effect of water on the reaction mechanism. The acyl intermediates in the hydroformylation cycle form 6- and 5-membered chelate rings with the rhodium (Scheme 1. 2). These are believed to be the catalyst resting states. By hydrogen bonding with the ester moieties, water destabilizes these chelate complexes and hence speeds up the catalytic reaction.



Scheme 1. 2 *Part of the catalytic cycle during the hydroformylation of acrylates esters (framed: the equilibrium between chelate and linear acyl complex).*

This emphasizes the fact that water, either in biphasic system or on a support, cannot be solely viewed as an inert supporting phase but can in some situations have a dramatic influence on the reaction outcome. Similarly to what was observed for the hydroformylation of higher alkenes, the water content had an important impact on the catalyst activity. Similar bell-shaped curves were obtained, at different reaction times and for different support materials. Interestingly, it was shown that, for water soluble substrates, the optimal water content corresponds to materials for which the pores are fully filled with water, regardless of the pore size or the surface area of the support. On the other hand, for more hydrophobic substrates, maximum catalyst activity was found for material with a low degree of pore filling. When recycling the SAPC catalyst for the hydroformylation of methylacrylate, the activity was found to decrease after each run. Rhodium leaching in the 5-10 ppm range was observed but, according to the authors, the leaching of water from the support was the dominant factor in this deactivation process.

Davis and Hanson further extended the hydroformylation under SAPC conditions by using a wide variety of complexes (Figure 1. 8)[32].

Bimetallic rhodium complex, **18,** has been intensively studied for hydroformylation reactions under SAPC conditions[33]. The complex could be efficiently immobilized as no rhodium could be detected in the organic phase. A SAPC formed from **18** and apatitic tricalcium phosphate support was used for the hydroformylation of 1-octene[34]. With this support, the catalyst displayed constant catalyst activity over a wider range of hydration levels than with silica-based material. However, beyond 35 wt % H_2O partial decomposition of the support occurred under the reaction conditions. More recently, kinetic models have been developed for the octene and linalool hydroformylation under

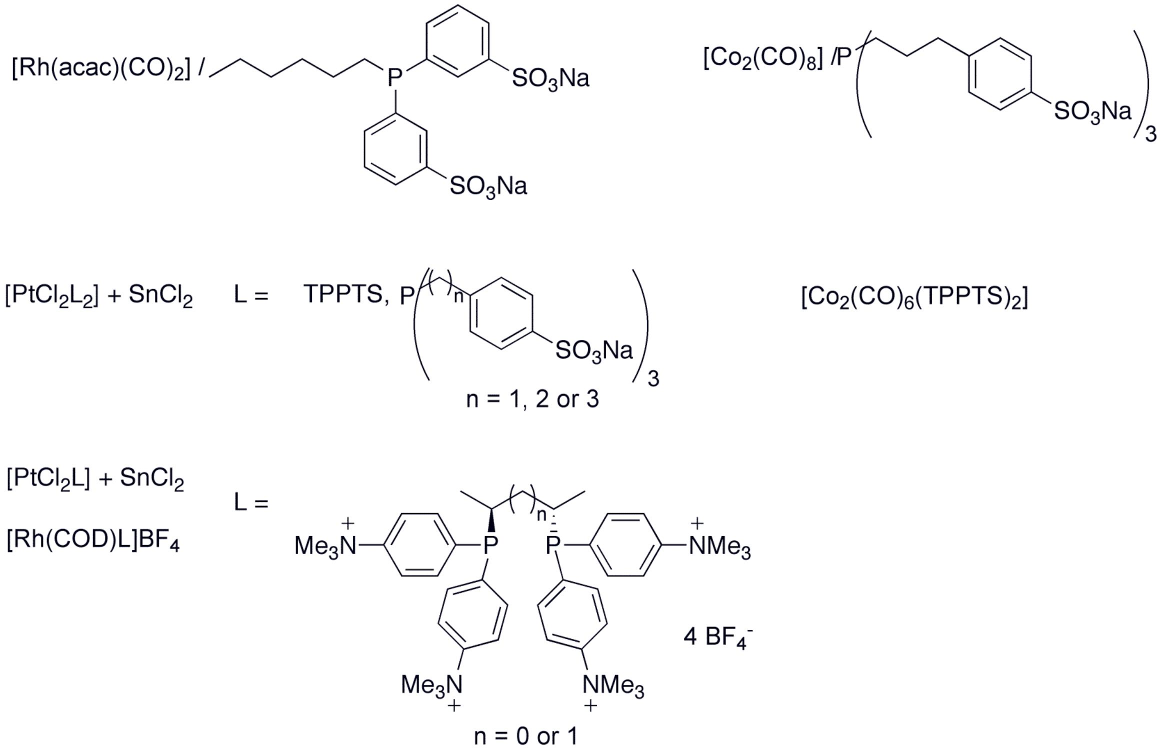
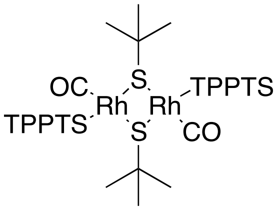


Figure 1. 8 *Structure of the different complexes used for hydroformylation as SAPC*[32].

SAPC conditions with **18**[35].

Rh/sulfoxantphos, **16**, catalyst led to a very stable and selective system for the hydroformylation of 1-octene under SAPC conditions[36]. The catalytic system could be recycled 10 times with rhodium leaching being below the detection limit (1 ppm). Under identical conditions, Rh/TPPTS catalyst was shown to deteriorate over time. Moreover, The catalyst could be stored for weeks under a CO atmosphere and yet retain its activity. However, Rh/**16** displayed rather low activity under the investigated conditions (highest reported TOF = 55 h^{-1}).



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Phosphine ligands bound to water-soluble poly-acrylic acid (PAAP) or poly-ethyleneimine (PEIP) were also used for the rhodium SAP catalyzed hydroformylation of propene and octene[37]. For the gas phase hydroformylation of propene, Rh/PAAP catalyst typically displayed high initial activity but it quickly decreased to a lower constant value. When Rh/PEIP was used, the activity decreased more rapidly and after 3h no activity could be detected. For the liquid phase hydroformylation of octene, Rh/PAAP was found to be active and could be recycled. The activity remained constant although the selectivity to linear product dropped.

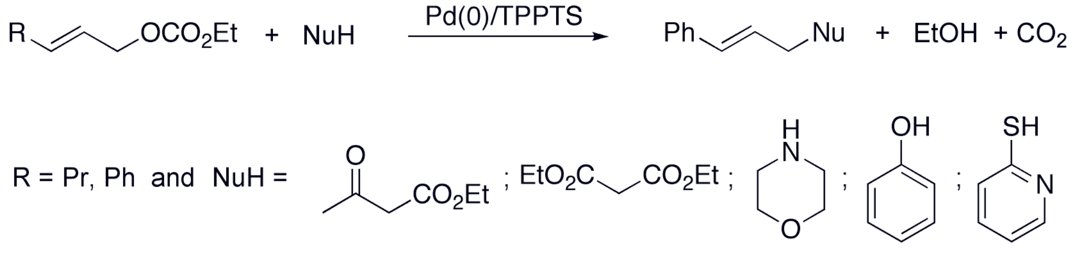
Recently studies have been mainly focused on varying the nature of the support while using the highly efficient Rh/TPPTS complex. Fumed silica nanoparticles have been compared to classical granular porous silica for the hydroformylation of 1-hexene[38]. The SAPC on nanoparticles displayed higher activity than the classical silica support especially with smaller particles displaying large surface area. However, the rhodium leaching was found to be one order of magnitude higher for nanoparticles than for granular support, 6 and 0.6 ppm respectively. Interestingly, nanoparticle supported catalysts showed optimum activity over a much wider range of hydration level than their granular analogs. Activated carbon has also been used as a support for the hydroformylation of alkenes using Rh/TPPTS SAP catalyst[39]. Using this support, the rhodium leaching was found to be very low (ppb range). However the activity of this system proved to be highly dependent on the water content. Surprisingly, a decrease in reaction rate was observed when increasing the chain length of the substrate.

SAPC catalysts, composed of rhodium particles dispersed on a silica support coated with a water film containing TPPTS ligand, TPPTS-Rh/SiO_2, have been described[40].

These systems displayed lower activity than systems containing a defined metal complex immobilized as SAPC for the hydroformylation of 1-hexene. However, they showed very little rhodium leaching into the organic phase (< 0.1 ppm) and could be recycled 4 times with almost complete retention of activity albeit with a small continuous decrease in selectivity.

In addition to hydroformylation and hydrogenation, SAPC has also been developed for palladium catalyzed allylic substitution. The substitution of *(E)*-allyl carbonate derivatives by various nucleophiles has been intensively studied by Sinou and co-workers (Scheme 1. 3) [41]. In this reaction it was found that the SAPC approach offers several advantages compared to the aqueous-biphasic methodology[41a-b]. The obtained catalyst showed increased stability, no palladium black was detected at the end of the reaction, although it had been in the biphasic system. Moreover, in the biphasic system, hydrolysis of the carbonate can be a serious side reaction. This is suppressed when using a SAP version of the catalyst. Immobilizing the catalyst also allowed reaction of phenol, dimethyl malonate and 2-mercaptopyridine with allyl carbonate[41d]. These alternative nucleophiles proved to be unreactive under biphasic conditions.

The activity of the SAPC showed, as in the previous examples, a strong dependence on the hydration level. Nevertheless, palladium leaching was low (< 0.5 mol %). The solvent system also showed a strong influence on the system. Higher catalytic activities



Scheme 1. 3 *Palladium (0) catalyzed allylic substitution of (E)-allyl ethyl carbonate.*

were observed when benzonitrile was used as the organic phase instead of acetonitrile. Ultimately, the alkylation of morpholine with cinnamyl carbonate was carried out under continuous flow conditions[41d]. Since one of the main causes of catalyst deactivation is water leaching, water-saturated benzonitrile was used to ensure a constant hydration level for the catalyst. Alkylation was performed continuously for 11 h showing constant activity over time and reaching a turnover number of 2200.

1.3.5. New reactor design.

It has been shown that in stirred vessels, agitation speed and stirrer/gas contactor/propeller design can greatly affect the reaction rate in aqueous-biphasic systems[42]. Beside modification of classic continuously stirred tank reactors (CSTR) other systems have been developed in order to improve the contact between the two phases.

A shock-wave reactor or Cavitron was tested as a mean of improving mass transfer in aqueous-biphasic hydroformylation[43]. In this system, high shear forces are induced by an optimized rotor/stator system with passage gaps at the rotor and stator. The gaps are filled with material, which is centrifugally accelerated by the rotor to the next row of gaps. Similarly to ultrasound, an alternating pressure field is generated. However, this system led to only minor rate improvement for the hydroformylation of 1-hexene compare to a CSTR

Hydroformylation of 1-hexene in aqueous-biphasic systems has been studied under ultrasonic irradiation at low frequency. A dipping probe fitted to an autoclave was used as an ultrasound source. Under sonication, the yield was increased by a factor of 2 compared to conventional stirring.[44].

A new process has been designed by Wiese and co-workers aimed at solving the problem of mass transfer limitation in multiphasic reactions[45]. The idea consists of using a tubular reactor equipped with static mixers (Sulzer SMV), which provide a large surface area, in place of a stirred vessel. The catalyst phase is kept in large excess relative to the substrates (syngas and alkene) and high flow rates are applied. When entering the reactor, alkene and syngas are finely divided by shear into droplets and bubbles, respectively. By this means, a large surface for mass transfer is generated. After the reaction the phases were separated and the catalyst fed back to the reactor.

Biphasic hydroformylation of propene has been used as the model reaction to demonstrate the efficiency of the process. The key factor has been shown to be the catalytic phase mass flow. By increasing the circulation speed of the catalytic phase relative to the substrates, the space-time yield could be increase by a factor of 5 compared to stirred vessels. At high propene hold-up and high catalyst flow, a 10-fold improvement in reaction rate was achievable. Moreover, the high velocities applied led to an extremely short residence time in the reactor, *c.a.* 2 s m^{-1} that diminished the formation of secondary products like heavy ends. Selectivity of 99% was achievable by this process. According to the authors economically viable space-time yields for the biphasic hydroformylation of 1-octene can be obtained with this new process design[46, 47].

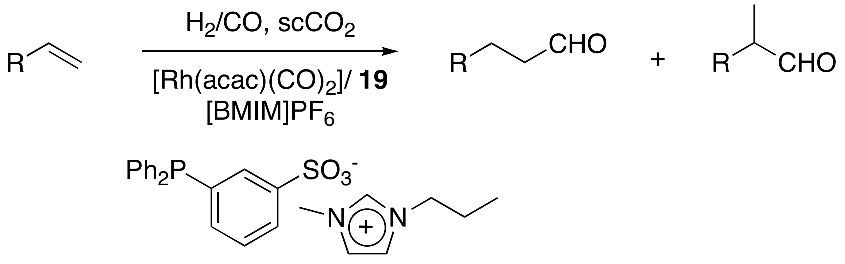
1.4 Other biphasic systems

Since the successful commercial exploitation of the aqueous-biphasic methodology, several other biphasic systems have been developed to overcome the long lasting problem of catalyst separation and recycling in homogeneous catalysis. A complete review of these new systems is out of the scope of the present thesis. We just give here some of the more relevant examples and the current state of the art for these new technologies. For further reading several excellent recent books and reviews are available[48].

As mentioned earlier, switchable biphasic solvent systems using fluorous solvents have given promising results. However, concerns regarding the toxicity and the persistent nature of the fluorous solvents have so far impede their commercial use. Moreover, the high price of such solvent further limit their use on large-scale applications such as hydroformylation.

Ionic liquids (IL's) are salts made up of a bulky organic cations with organic or inorganic anions melting below 100 °C or ideally at room temperature. There has been and still is a tremendous interest in using ionic liquids as a catalyst immobilizing phases[49]. The main driving force is their excellent and tunable solvent properties together with their lack of a measurable vapor pressure, making them very interesting candidates for the replacement of classical organic solvents. The tunable nature of those new solvents allow them to be designed to some extend to form biphasic systems for specific substrates and products. For example, in the nickel-catalyzed dimerization of propene it has been shown that ionic liquids could solubilize the propene but form a biphasic system with the product[50]. This avoids mass transfer limitation while allowing the product to be separated from the catalyst by simple phase separation. Moreover this avoids further reaction of the product with the catalyst improving the selectivity of the reaction. This has led to a new process for the dimerization of butadiene, Difasol, developed on pilot scale by the IFP[51].

Ionic liquids have also been advantageously used in conjunction with supercritical carbon dioxide. Ionic liquids are highly polar and non-volatile while $scCO_2$ is essentially non-polar and has gas-like properties. These diametrically opposite properties make them almost ideal for combined use in a biphasic system. Important work by Brennecke, Beckmann and co-workers showed that, in contrast with permanent gases such as carbon monoxide and hydrogen, $scCO_2$, is highly soluble in ionic liquids such as $[BMIM]PF_6$ (up to 60 mol %).[52]Ionic liquids, on the other hand, are essentially insoluble in $scCO_2$. In addition, it was shown that organic compounds could be quantitatively extracted from ionic liquids by using $scCO_2$[53]. Those very interesting physico-chemical properties together with the increasing number of examples of efficient use of organometallic catalysts in IL's prompted researchers to investigate catalytic reactions in biphasic IL-$scCO_2$ systems. The major advantage of this methodology is the possibility to operate the system under continuous flow condition where the catalyst, immobilized into the ionic liquid phase, never leaves the reactor while the substrate and product are transported by CO_2. Continuous flow operation has been demonstrated for the hydroformylation of medium chain alkenes (C_8-C_{12}) catalyzed by rhodium complexes containing triphenylphosphine analogue ligands **19** (Scheme 1. 4) and the asymmetric hydrovinylation of styrene catalyzed by Wilke's complex **20** (Scheme 1. 5)[54], [55].



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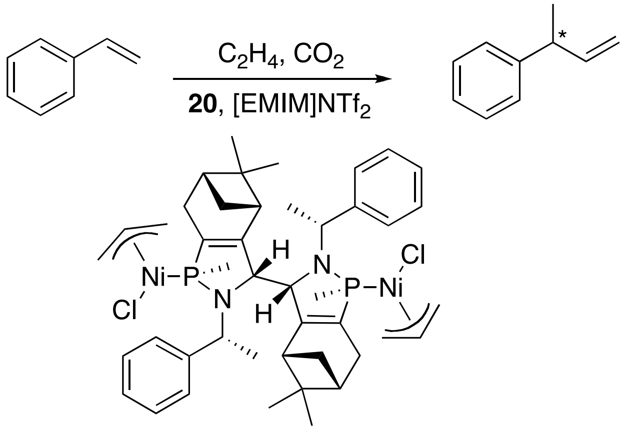
Scheme 1. 4 *Continuous flow hydroformylation of alkenes in an IL–$scCO_2$ biphasic system.*



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Scheme 1. 5 *Continuous flow hydrovinylation of styrene in an IL–CO_2 biphasic system.*

Despite the very high efficiency of ionic liquid biphasic systems (with organic solvent or CO_2), very few applications have made it to the commercial stage. The relatively high price of ionic liquids together with concern regarding their toxicity has so far impeded their use in industry. A new concept where the ionic liquid is supported onto a solid matrix (analogous to the SAPC) has recently received increased attention and could circumvent this limitation by lowering the amount of ionic liquid required[56]. Use of such supported ionic liquid phase (SILP) in conjunction with $scCO_2$ has been demonstrated for the continuous hydroformylation of octene[57].

Regarding CO_2, the important compression energy requirement has been the major impediment to its commercial use. Further investigation aimed at decreasing the operating pressure will be highly desirable. Cascade reactions where the same stream of CO_2 transports the substrates over several successive catalysts could also offer a solution to this limitation.

1.5 Aim and scope of the present thesis

The aim of this thesis is to develop new strategies for the rhodium catalyzed aqueous-biphasic hydroformylation of medium to long chain alkenes (>C_5). As discussed in the introduction, rhodium based systems would be highly desirable for this process compared to cobalt based system owing their milder operating conditions leading to a decrease in the overall energy consumption of the process.

Several methods have already been developed to overcome mass transfer limitation encountered in aqueous-biphasic hydroformylation. So far none of them has led to new commercial application of this elegant technology.

The new methodology developed should fulfil several key points that make the strength of the existing RCH-RP process:

- Efficient immobilization of the rhodium catalyst in the aqueous phase, *i.e.* rhodium leaching in the ppb range.
- Fast and complete phase separation.
- Acceptable reaction rate, *i.e.* turnover frequency $\geq 500\ h^{-1}$.

Ideally, this should be done without major modifications of the existing process so existing know-how and installations could be used. Moreover, hydroformylation being in the bulk chemical business range, costs (sophisticated ligands, special equipment, etc) should be kept to a minimum. Finally, the new methodology should be applicable to a wide range of alkenes (C_6 to C_{20} for example) and not limited to only one type of feed to ensure maximum flexibility.

We chose to focus on three different methodologies; the use of new additives, the development of new phase switchable catalysts and the use of a new reactor system.

Additives have the advantage that they can readily be used in existing processes requiring only minor changes. However, the additives developed so far suffer from several disadvantages, mainly increased rhodium leaching and complicated phase separation. Special attention will be devoted to these issues.

Phase switchable catalysts have the virtue of combining homogeneous reaction, limited only by intrinsic kinetics, with biphasic separation. Already developed switchable systems use heat and pH swings as reversible triggers. The main problem with such approaches is the energy consumption associated with heating and cooling cycles and the formation of salt by products. We therefore will focus on “benign” reversible triggers, which neither require extensive energy input nor chemical transformations leading to formation of waste by-products.

Only few new reactor systems have been studied for aqueous-biphasic catalysis. However as discussed in this chapter, some improvements are possible by changing the contact mode between the two phases. We therefore propose to investigate a new reactor design, the oscillatory baffled reactor, for the aqueous-biphasic hydroformylation of alkenes.

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Chapter
TWO

Aqueous-biphasic hydroformylation of medium alkenes promoted by "weak" surfactants

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2.1 Introduction

There is an important commercial interest in replacing existing cobalt based process for the hydroformylation of medium to long chain alkenes (> C_5). Switching from cobalt to more active and selective rhodium based catalysts could decrease the overall energy consumption of the process and increase the yield of the desired linear aldehydes. However, homogeneous rhodium catalyzed hydroformylation of high boiling alkenes is greatly limited by the thermal stability of the expensive rhodium complex, which renders direct distillation of the products from the crude reaction product impractical. Aqueous-biphasic technology, the Ruhrchemie/Rhône-Poulenc process, could be perfectly suited to overcome this limitation since the catalyst is not subject to any thermal stress during the separation process. However, this efficient and reliable technology is greatly limited by the solubility of the substrate in the catalyst aqueous phase and is only applied for propene and butene. For medium to long chain alkenes (> C_5), mass transfer limitations bring the reaction rate below any that could be economically viable. Improvements of the substrate transfer into the aqueous catalytic phase are highly desirable since it could allow replacement of the cobalt catalyzed hydroformylation by more efficient rhodium systems.

Several approaches have been developed to tackle this problem. Among them, it has been proposed to use additives to improve the solubility or the transport of the substrate into the aqueous catalytic phase. The main advantage of using additives is that they do not require drastic change of the existing technology. The know-how developed during the 20 years of industrial application of aqueous-biphasic hydroformylation could advantageously be used and possibly, the existing installation could be used to process different feeds with minor modifications.

In order to preserve the inherent strength of the process, several parameters have to be carefully examined when considering additives for aqueous-biphasic hydroformylation.

- The additive has to be inert toward the catalyst, substrate and starting material. Care must be taken that it does not act as a substrate for the catalytic cycle or react with the starting material or product through catalysed and/or uncatalysed processes.
- While increasing the solubility of the substrate in the aqueous phase, care must be taken not reciprocally to increase the solubility of the catalyst in the organic phase, since this could result in significant leaching of the catalyst.
- The influence of the additive on the efficiency of the phase separation should be kept to a minimum.

- Interactions between the additive and the different catalytic species involved in the cycle should not result in a dramatic decrease in chemo- and/or regio-selectivity.
- Care must be taken regarding leaching of the additive into the product phase. This could complicate the separation of the different products and starting material. Moreover, if the additive is carried away together with the product, replenishment might be necessary to conserve the promoting effect.

Three main types of additives have so far been used in aqueous–biphasic catalysis: co-solvents, surfactants and inverse-phase transfer catalysts.

2.1.1. Co-solvents

The addition of co-solvents such as lower alcohols, acetone and acetonitrile to the water phase was one of the first strategies used to improve the solubility of the substrate in the aqueous phase[1]. In this way, the lipophilicity of the catalytic phase is increased, enhancing the solubility of the substrate and hence the reaction rate. Octene for example is estimated to be 10^4 times more soluble in 50 % aqueous ethanol than in pure water[2]. When this solvent mixture was used to carry out hydroformylation of 1-octene, it led to an effective increase of the reaction rate. However, acetal formation due to condensation of the aldehydes with the ethanol was observed together with a transfer of the co-solvent into the product phase[2]. A different study, using methanol as a co-solvent also led to a rate increase but a decrease of the linear selectivity was observed[3]. According to the authors, this lower linear selectivity is due to the presence of low coordinated phosphine species, *i.e.* $[HRh(CO)_3P]$, the formation of which is facilitated by the decrease of the ionic strength of water induced by the presence of the co-solvent[4]. A more recent study comparing methanol, ethanol and *n*-butanol as co-solvent also showed an increase in activity together with a decrease in linear selectivity[5].

In spite of their ability to increase the reaction rate through better solubilization of the substrate in the catalyst phase, the use of co-solvents is still subject to many drawbacks. The decrease of linear selectivity, the partitioning of the co-solvent into the product phase and, in the case of hydroformylation, their reaction with the product hinders their use for commercial applications. Moreover, no data regarding the leaching of the catalyst in the presence of co-solvent has been reported. Leaching is likely to become important since co-solvents decrease the polarity gap between the two phases.

2.1.2. Surfactants

Surfactants are another type of additive that has been widely studied to improve substrate transfer in aqueous-biphasic catalysis. By forming micelles above the critical micelle concentration (CMC), surfactants can solubilize organic compounds within the core of micelles and increase the interfacial area in biphasic systems hence promoting the transfer of the substrate between the phases. Interestingly, in some cases it has been demonstrated that, while anionic surfactants do not provide any promoting effects, cationic surfactants greatly increase the reaction rate [5, 6]. When conducting the hydroformylation of 1-dodecene in the presence of cetyltrimethylammoniumbromide (CTAB), 61 % conversion to aldehydes was observed. On the other hand, when sodium dodecyl sulfate (SDS), an anionic surfactant, was used, no aldehyde was detected. According to the authors, both surfactants form micelles and solubilize the substrate.

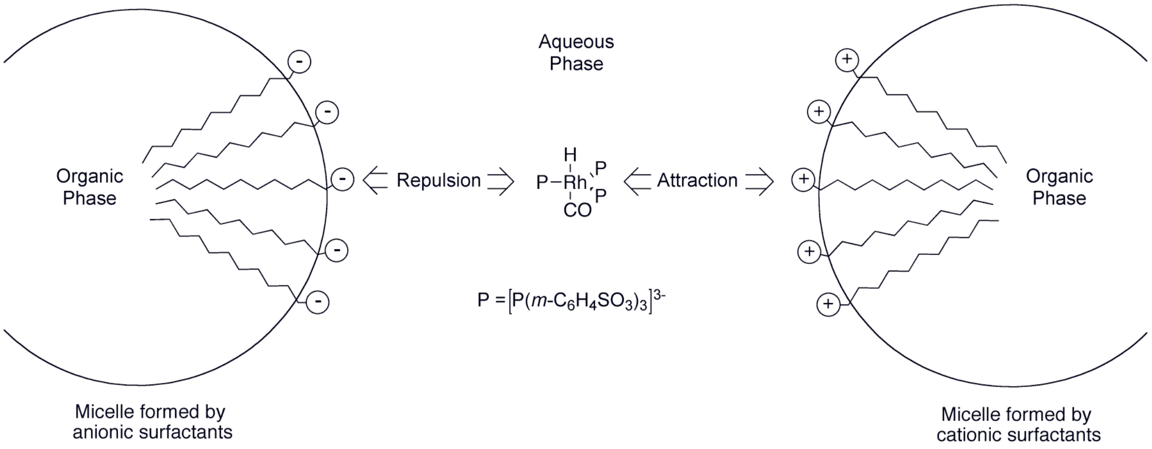


Figure 2. 1 *Schematic representation of the interaction between [HRh(CO)(TPPTS)$_3$] and micelles formed by cationic and anionic surfactants.*

In the case of anionic surfactants, the external surface of the micelle is negatively charged repelling the negatively charged catalyst (Figure 2. 1). However, when cationic surfactants are used, there is an electrostatic attraction between the positively charged micelle surface and the ionic catalyst, creating a high micro-concentration of catalyst in the vicinity of the micelle, which contains a high concentration of substrate, and hence increases the reaction rate. Supporting this hypothesis, interactions between TPPTS and CTAB were demonstrated by ^{31}P-NMR spectroscopy[7]. Static light scattering experiments were also consistent with the binding of [HRh(CO)(TPPTS)$_3$] and free TPPTS onto the positively charged micelle surface[8]. After reaction, rhodium levels in the interfacial layer were found to be *ca.* 90 times higher than in the bulk of the water phase, also supporting the idea of an interaction between the complex and the micelles[8]. Regarding the linear selectivity, the influence of surfactant addition is less marked and somehow less consistent. Some authors reported an increase in the linear selectivity[6, 9] while others noticed a decrease[5].

Since the addition of CTAB enables high reaction rates, TOF up to 900 h^{-1} have been reported[10], several other cationic surfactants have been studied (Figure 2. 2) [11, 12, 13]. The use of gemini surfactants with alkyl bridges led to slightly higher rates and linear selectivity than CTAB[11]. Interestingly, the shorter the alkyl bridge, the more the linear selectivity increased. According to the authors, these surfactants tend to form more compact micelles in which the formation of the less crowded linear aldehyde is enhanced. Among the different gemini surfactants based on piperazine, **1-3**, the iodide salt, **1**, performed the best[12]. On the contrary, among the trimeric surfactants based on triazine, **4-6**, the oxalate **5** and chloride **6** salts gave higher rates and selectivity. Double long-chain surfactants (DLCS) allow huge rate improvements. Turnover frequencies as high as 7500 h^{-1} can be obtained under certain conditions[13]. It has been demonstrate that the key parameter to obtain high reaction rates is the length of both chains. The activity jumps

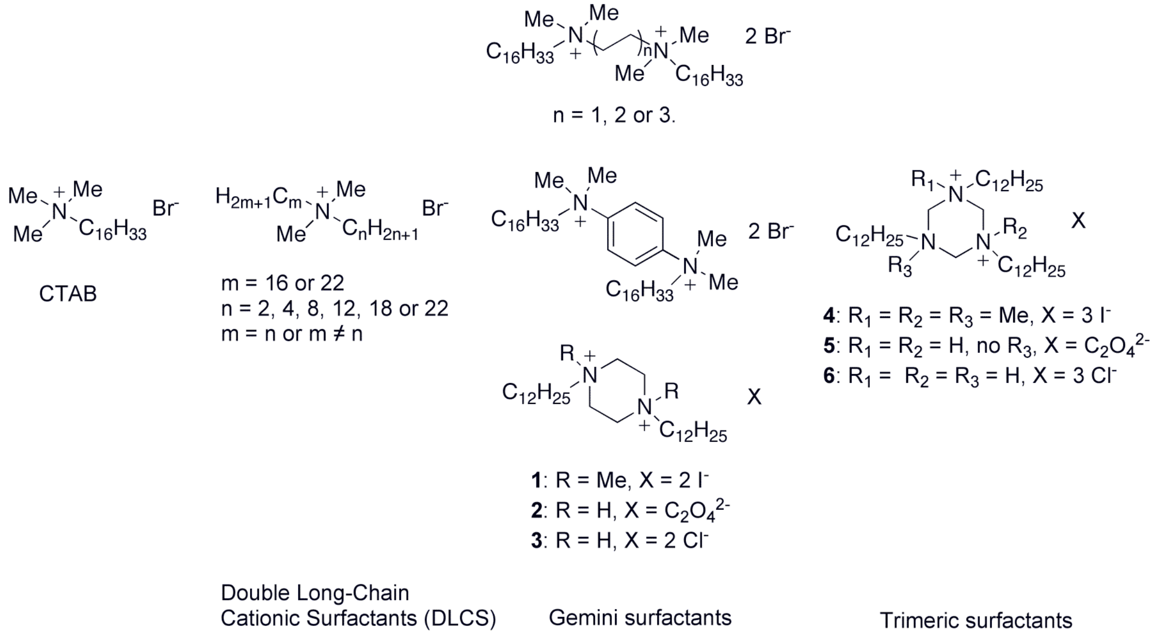


Figure 2. 2 *Structure of the different cationic surfactants used in aqueous-biphasic hydroformylation of higher alkenes.*[11, 12, 13]

once a threshold chain length is reached (when n = 8 if m = 22 and when n=12 if m = 16, see structure in Figure 2. 2). This is suspected to be due to the formation of vesicles instead of micelles once both chains are long enough[13].

Regarding the leaching of the catalyst into the product phase and the efficiency of the phase separation after reaction, only rather few data were available until recently.

For the hydroformylation of 1-dodecene in presence of CTAB, a rhodium concentration of 0.04 ppm in the product phase has been reported[8]. Worryingly the authors described the product phase as "saturated with water". Regarding the phase separation, the extent of emulsification during hydroformylation promoted by CTAB has been studied as a function of different parameters[14]. Emulsification tends to be promoted by high stirring rates and high concentrations of surfactant and typically increases with the conversion. In the worst case, the mixture after reaction is severely emulsified and no separation could be observed at ambient temperature over 4 hours. When using $[CoCl_2(TPPTS)_2]$ instead of the rhodium based catalyst in the presence of CTAB for the hydroformylation of C_8 and C_{10} olefins, the phases have been reported to take up to 1 h to separate fully [15]. Interestingly, in the presence of excess ligand, this time can be reduced to 5 min. When using a gemini surfactant with ethyl bridge, at least 10 min were required for the phases to separate[11]. At a P/Rh ratio of 18, the rhodium level in the product phase was found to be 9.8 ppm. Rhodium was no longer detected in the product phase at P/Rh ratio of 54. The aqueous phase containing the catalyst with the surfactant was recycled 4 times with little decrease in activity and selectivity. In the presence of the trimeric surfactant **5**, the phases separated quickly[12]. Leaching of the metal in the product phase was found to be 2.27 ppm and the catalyst-containing phase could be reused 5 times without obvious decrease in activity. When DLCS are used, the phases separate forming 3 distinct layers, a colorless organic phase, a yellow aqueous phase and a brown interfacial emulsion layer[13]. When both aqueous phase and interfacial layer were taken for recycling, the system could be recycled 7 times with slight decrease in activity. However if only the aqueous phase was used for recycling, the conversion dropped after one recycle from 90 % to 60 %. This is consistent with the rhodium levels found in the different phases, 0.52 ppm in the product phase, 18.1 ppm in the bottom aqueous phase and 70.3 ppm in the interfacial emulsion layer.

Under certain conditions, the addition of surfactants allows very fast reaction with good phase separation and low leaching. Nevertheless, those additives are prone to form stable emulsions, which completely remove the possibility of simple catalyst separation.

2.1.3. Inverse phase-transfer catalysts

Inverse phase-transfer catalysts, compounds able to transfer lipophilic molecules from an organic phase to an aqueous phase, have been used to overcome mass transfer limitations in aqueous-biphasic catalysis. The two main classes of such compounds that have been investigated are cyclodextrins and calixarenes. By formation of host-guest complexes, they transfer the substrate into the aqueous phase or into the interfacial layer where it can react with the water-soluble catalyst[16]. The product is then released into the organic phase where the supramolecular carrier can trap another molecule of substrate (Figure 2. 3).

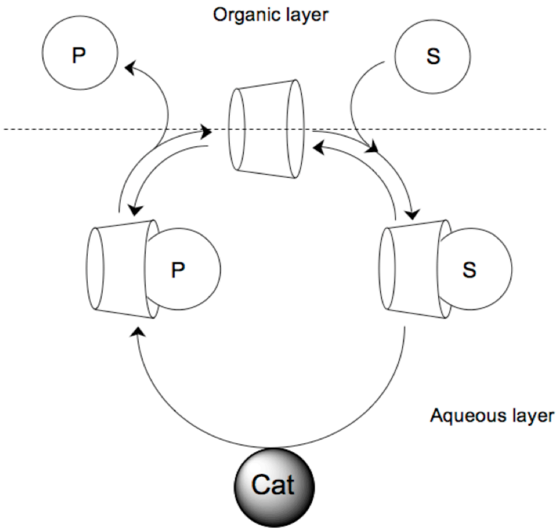


Figure 2. 3 *Schematic representation of the inverse-phase catalysis concept (S = Substrate; P= product; Cat = water-soluble catalyst). Adapted from* [25e].

This methodology has received considerable attention and has been use in several aqueous-biphasic transition metal-catalysed reactions such as the oxidation of alkenes (Wacker Process)[17, 18], hydrogenation of α,β-unsaturated acids and dienes [19], deoxygenation of allylic alcohols[20], Suzuki-Miyaura cross-coupling[21], Tsuji-Trost reaction of alkylallylcarbamate and carbonate[22, 16b], ruthenium-catalysed hydrogenation of aldehydes[23], hydrocarbonylation[24] of alkenes and hydroformylation of long-chain alkenes[22e, 25].

Cyclodextrins (CD) are cyclic oligosaccharides composed of 6 (α-), 7 (β-) or 8 (γ-) glucopyranose units. Those compounds are characterized by the shape of a truncated cone were the primary and secondary hydroxyl groups occupy the narrower and the wider rim of the cone respectively (Figure 2. 4).

It has been proposed that several conditions must be satisfied for CDs to promote catalyzed reactions in aqueous-biphasic systems[17b].

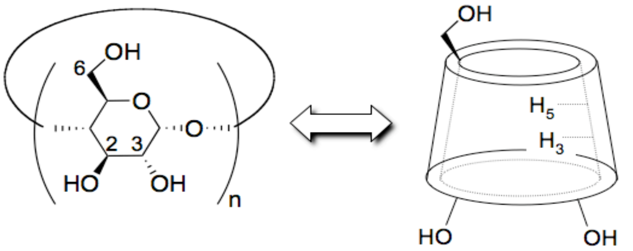


Figure 2. 4 *Schematic representation of the shape of α- (n =6), β- (n = 7) and γ- (n = 8) cyclodextrins. The protons* H_3 *and* H_5 *are situated inside the cavity whereas the protons* H_1, H_2 *and* H_4 *point outwards.*

CDs have to form readily an inclusion complex with the substrate, this inclusion complex has to be soluble in water, the reactive function of the substrate must still be accessible to the catalyst once enclosed in the CD and the reaction product must dissociate easily from the CD. To fulfil these requirements the nature of the CD (α, β or γ) together with the nature and the extent of its chemical modification play decisive roles. β-CDs have been shown to be more efficient than their narrower (α-CD) and wider (γ-CD) analogs in enhancing Wacker oxidation[17b] and the hydroformylation[25b] of higher alkenes. This has been attributed to a better recognition between the substrate and the CD in the case of the β-CD. Partial or complete substitution of the primary and secondary hydroxyl groups by various substituents (OMe, OAc, O-*i*-PrOH, OSO_3) led to significant variations in yield and selectivity of CD-mediated biphasic reactions[17b-d, 25b-c]. Among the different chemically modified CDs investigated, partially methylated β-CD (12.6 OH group on average replaced by OMe at positions 2,3 and 6) has been found to be the most efficient in enhancing the rate of the aqueous-biphasic hydroformylation of decene (Table 2. 1)[25c]. This enhancement has been mainly attributed to the high solubility in both aqueous and organic phase of the methylated-β-CD. Supporting this, it is remarkable that while β-CD and sulfonated-β-CD display high solubility in water they are almost insoluble in the

Table 2. 1 *Hydroformylation of 1-decene in an aqueous biphasic system in the presence of chemically modified cyclodextrins* [a]. *Reproduced from* [25c].

Entry	β-CD			t (h)	Conversion (%)	Aldehyde selectivity (%)	l/b
	R[b]	Nb[c]	S (g dm^{-3})[d]				
1	-	-	-	6	10	60	2.7
2	H	0	18.5	8	19	78	2.1
3	OMe	12.6	570 (20)	8	76	91	1.8
4	OMe	14	570 (20)	8	75	91	1.9
5	OMe	21	570 (<10)	8	30	57	2.5
6	OAc	14	>100	8	46	57	2.6
7	OAc	21	<1	8	6	66	2.6
8	*i*PrOH	6.3	>330	8	32	84	2.0
9	OSO_3	9	>400	8	7	69	2.8

[a] Conditions: [Rh(acac)$(CO)_2$]: 0.16 mmol; TPPTS: 0.8 mmol; CD: 1.12 mmol; H_2O : 45 cm^{-3}; decene: 80 mmol; P (CO/H_2): 50 bar; T: 80°C.

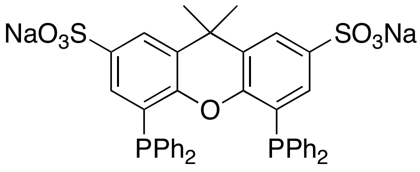
[b] Cyclodextrin modification.

[c] Average number of substituted hydroxy group.

[d] Solubility of the CD in water at 25°C. Numbers in brackets correspond to the solubility at 80°C.

organic phase and have little effect on the reaction rate (Table 2. 1, Entry 1 and 9). In contrast, permethylated and peracetylated β-CDs are highly soluble in the organic phase but sparingly soluble in the aqueous phase at 80°C. Consequently they display little or no enhancement effect on the reaction rate (Table 2. 1, Entry 5 and 7). Interestingly, whereas partially methylated-β-CDs improve the reaction rate, they tend to decrease the linear selectivity (Table 2. 1, Entry 1 and 3). Formation of an inclusion complex between TPPTS and β-CD has been observed but its influence on the reaction was not fully understood[26]. Further studies showed that this inclusion complex was responsible for the lower linear selectivity obtained[27]. In the presence of β-CDs (native or randomly methylated), dissociation of TPPTS from the complex is facilitated, leading to the formation of low coordinated phosphine species such as [HRh$(CO)_2$TPPTS], which are known to give low l/b ratios. To avoid this, different CD/catalyst combinations have been studied in order to maintain high linear selectivity. When using TPPTS ligand with rhodium or palladium for hydroformylation or Tsuji-Trost reactions of higher alkenes, methylated-α-CD, sulfobutyl ether-β-CD and 2,3-dimethyl-di-*O*-methyl-6-*O*-sulfopropyl-β-CD have all been shown to enhance the reaction rate while having little or no interaction with the catalytic system[25g, 22d-e]. This avoids a decrease in the linear selectivity in hydroformylation reactions and avoids poisoning of the CDs by the ligand. When using sulfonated xantphos **7,** instead of TPPTS, in conjunction with methylated α or β CD, interactions between the ligand and the CD have been shown to have positive effects on the reaction[25e]. Formation of an inclusion complex between the phenyl rings of **7** and the CDs was observed by NMR spectroscopy, but those interactions did not promote the dissociation of the ligand from the metal. Therefore, improved reaction rate together with improved chemo-and regioselectivity were observed in the hydroformylation of 1-octene and 1-decene. Methylation on the ortho position of the phenyl ring of TPPTS also proved to be a fruitful methodology to avoid interaction between the ligand and the methylated-β-CDs[22f].

α-CDs bearing ammonium groups have been shown to have a positive effect on the rate and selectivity of the hydroformylation of 1-decene[25f]. In this case, TPPTS and the CDs interact through ion pairing but do not form inclusion complexes. It has been postulated that the improved linear selectivity was due to the in situ formation of new



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catalytic supramolecular species by ion-exchange between the anionic ligand and the cationic CD.

Regarding the phase separation and leaching of the catalyst, CDs were shown early on not to be detrimental to the process. In the hydroformylation of 1-decene with Rh/TPPTS catalyst in the presence of a large excess of methylated-β-CD, the phase separation was found to be excellent and the rhodium and phosphorus leaching into the product phase were found to be <0.5 ppm and 1.2 ppm respectively[25b]. Similar results were reported later and the catalyst was recycled 4 times without noticeable loss in activity[24]. Other authors reported an increase of activity upon recycling during the hydroformylation of 1-octene. They attributed this unexpected result to a gradual organisation of the interface[25d]. Even when surface-active CDs such as 2,3-dimethyl-di-*O*-methyl-6-*O*-sulfopropyl-β-CD were used, the system was described as strictly biphasic[22e]. The phases readily separated and the catalyst could be recycled three times without loss in activity. In the hydrogenation of aldehydes, the ruthenium content in the organic phase was found to be < 1 ppm. It was described later that the phases quickly separated and that the catalytic system could be recycled five times without loss of activity[23a-b].

CDs appear to provide a very elegant solution to mass transfer limitation in aqueous-biphasic catalysis. Numerous systems have been developed and in addition to improved reaction rates, CDs have been shown to enhance chemo- and regioselectivity. More importantly, the addition of CDs to aqueous-organic biphasic systems seems to have little effect on the ease of phase separation. Moreover they seem not to promote transfer of the rhodium into the organic phase. However, their rather complicated synthesis and the associated cost might impede their application in large scale application such as hydroformylation. Nevertheless, they could be used in fine chemical applications where the important added value of the product could make their use economically viable.

Calixarenes, cyclic oligomers of benzene units, have also received attention as inverse phase transfer catalysts (Figure 2. 5). Calix[4,6]arenes substituted on the upper ring by sulfonated or amino groups have been used as promoters in aqueous-biphasic Suzuki coupling reactions[28]. They appeared to be superior mass transfer promoters than native β-CDs. The amino substituted derivatives were shown to be more efficient than the sulfonated derivatives. Water-soluble calixarenes have also been shown to be efficient promoters for the biphasic Wacker oxidation of long-chain alkenes[29]. Sulfonated and *O*-alkylated calixarenes showed the highest activity. Calix[4]arenes were more efficient in promoting the oxidation of 1-hexene, while calix[6]arenes were more efficient for 1-octene oxidation, which, according to the authors, was due to molecular recognition between the substrate and the calixarene. Recycling of the aqueous catalyst phase was carried out. It appeared that O-alkylation of the lower ring of the calixarene was a critical factor in maintaining the activity for several runs. These inverse-phase transfer catalysts were recycled three times without loss of activity while the non O-alkylated compounds lost all their activity after the first run.

More recently, calixarenes and substituted CDs were compared as promoters for Suzuki coupling in aqueous-biphasic systems[21b]. It appeared that, while sulfonated

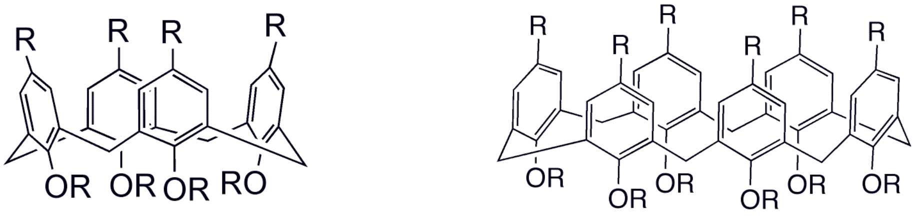
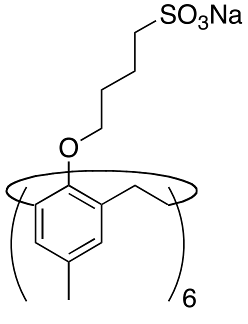


Figure 2. 5 *General structure of calix[4]arenes (left) and calix[6]arenes (right).*

calixarene **8** was 3 times more efficient in promoting the reaction than methylated-β-CD, it led to troublesome phase separation.



8

The use of calixarenes as inverse phase transfer catalysts in aqueous-biphasic systems is still in its infancy. Although considering their wide possibility of modification, further developments are highly desirable and could lead to interesting new systems.

2.2 Aim and scope of this chapter

A wide variety of additives have been used to improve mass transfer in aqueous-biphasic catalysis. Each of them goes with their own advantages and disadvantages, but none has so far been used for industrial application. For hydroformylation, cationic surfactants are very attractive; they allow very fast reaction, they are cheap and readily available. However, their detrimental (and unpredictable) tendency to form stable emulsions completely remove the possibility of catalyst separation.

In this chapter we describe the use of "surfactant-like" additives based on imidazolium, pyridinium and ammonium cations bearing one apolar chain of medium length for the aqueous–biphasic hydroformylation of medium alkenes (C_6-C_{10}). Due to their "weak" surfactant ability, such additives could offer a good balance between rate improvement and ease of phase separation.

2.3 Results and discussion

2.3.1. Additives preparation

The structures of the different additives studied for the aqueous-biphasic hydroformylation of alkene are depicted in Figure 2. 6. All the additives were obtained by alkylation at the nitrogen atom by alkyl halides using standard procedures followed, if necessary, by anion exchange with silver salts (Figure 2. 7).

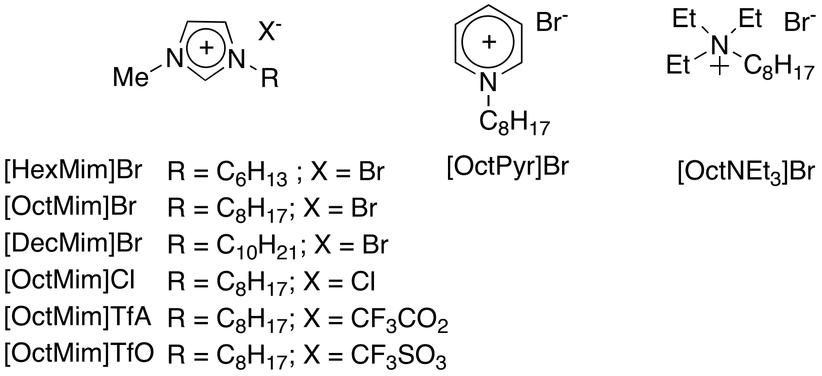


Figure 2. 6 *Structure of the different additives used in this study.*

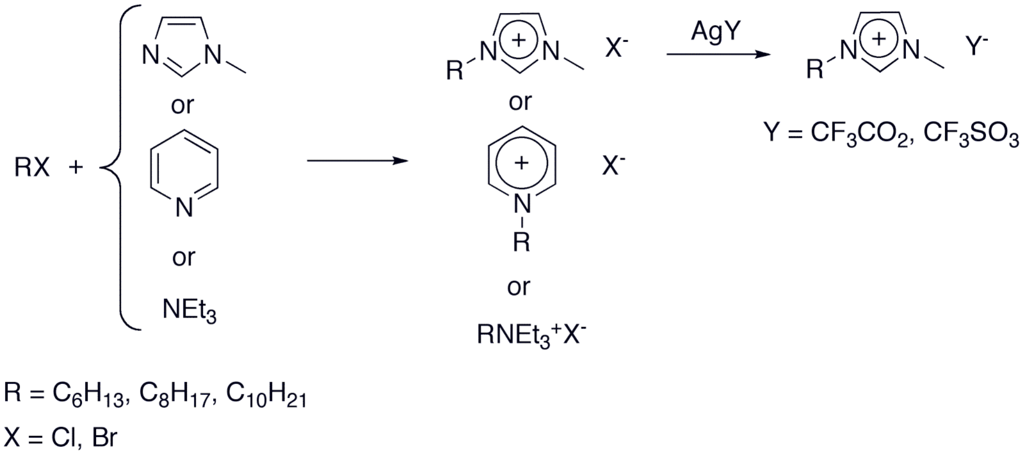


Figure 2. 7 *Synthesis of the different additives used in this study.*

2.3.2. Screening investigation

In preliminary screening investigations, 1-octene was hydroformylated under aqueous-biphasic conditions in the absence and in the presence of various amounts of 1-octyl-3-methylimidazolium bromide, [OctMim]Br, in a closed reactor. The active rhodium phosphine complex, having the general formula $[HRh(CO)_n(TPPTS)_m]$,was formed *in situ* by bubbling syngas through an aqueous solution containing $[Rh(acac)(CO)_2]$ (acac: acetylacetonate), a 10 fold excess of TPPTS and the desired amount of [OctMim]Br.

A plot of the obtained average turnover frequencies (<TOF>) and linear to branched ratio (l/b) as a function of the [OctMim]Br concentration is presented in Figure 2. 8. In the absence of additive the aqueous biphasic hydroformylation of 1-octene proceed very slowly (<TOF> = 30 h^{-1}) under the investigated conditions with a linear to branched ratio of 3.9. In the presence of 0.1 mol dm^{-3} of [OctMim]Br, the average turnover frequency increased to 213h^{-1} while the linear selectivity remained almost identical.

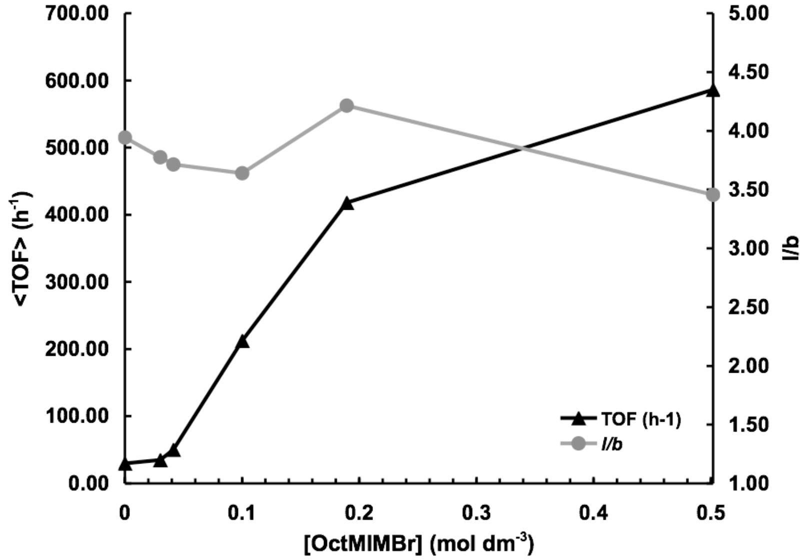


Figure 2. 8 *Effect of the concentration of [OctMim]Br on the average TOF and the l/b ratio for the hydroformylation of 1-octene (100 °C; 20 bar; CO : H_2 = 1 : 1; 2h; $[Rh]_{H2O}$ = 1.25 mmol dm^{-3}; P/Rh = 10; H_2O: 8 cm^3; 1-octene: 2 cm^3).*

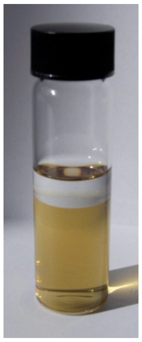


Figure 2. 9 *Typical photograph of the separated phases obtained after hydroformylation of 1-octene in the presence of [OctMim]Br (This picture: [OctMimBr] = 0.5 mol dm^{-3}).*

Importantly, by the time the autoclave was opened, *ca.* 10 minutes after the reaction was stopped, the phases were perfectly separated and the organic layer did not show any coloration (Figure 2. 9).

Further increases in the amount of [OctMim]Br present in the water phase further accelerated the reaction while having little effect on the linear selectivity. Again the phase separation was found to be excellent. No [OctMim]Br was detected in the organic phase using ^{1}H-NMR spectroscopy.

2.3.3. Hydroformylation of alkenes in the presence of several structurally related additives

Since addition of [OctMim]Br to the aqueous-biphasic system allowed the reaction to proceed at high rate while maintaining very efficient phase separation, we extended the use of this additive to other alkenes, 1-hexene and 1-decene. Moreover, we investigated the effect of structure variation of the additive on the performance of the aqueous-biphasic hydroformylation of alkenes. To get a better insight into the reaction rate, the experiments were carried out in a constant pressure reactor. In this system, the syngas pressure inside the autoclave is maintained constant via a pressure regulator attached to a ballast vessel, in which the pressure can be recorded over time allowing gas uptake curves to be obtained. Initial turnover frequencies (TOF_0) were calculated by linear regression at the origin of the gas uptake curve obtained (corresponding to 20 % conversion). The rhodium content of the product phase was determined by inductively coupled plasma mass spectroscopy (ICP-MS) in order to evaluate the effect of the additive on the retention of the catalyst in the aqueous phase. All the experiments were carried out using 0.5 mol dm^{-3} of additive in the aqueous phase.

In accordance with our preliminary finding, the hydroformylation of medium chain alkenes is very slow in the absence of additive (see Figure 2. 10 and Table 2. 2). For example, 1-octene gives only 1.9 % conversion to aldehydes in 3 h ($TOF_0 = 10\ h^{-1}$, under the conditions of Table 2. 2) but reached a TOF_0 of 1105 h^{-1} in the presence of 5 10^{-3} mol dm^{-3} of [OctMim]Br with a decrease of linear selectivity (l/b = 2.9 *vs.*. 4.9 in the absence of additive) (Table 2. 2). Again, the two phases were fully separated by the time the autoclave was opened. Analysis of the organic phase by inductively coupled plasma mass spectroscopy (ICP-MS) showed that, despite the lack of color, the organic phase contained 126 ppm of rhodium, *i.e.* an unacceptable level of leaching. These reactions were carried out with a P/Rh ratio of 10, whilst commercial processes operate with very much higher ligand excess (P/Rh > 100). Reasoning that a higher ratio might improve the l/b ratio, but might also enhance the catalyst retention, we carried out a reaction with P/Rh = 50. The reaction rate was not much affected, but the l/b ratio increased to 3.2. Crucially, the rhodium content of the organic phase dropped dramatically to 0.49 ppm. The gas uptake curves obtained are depicted in Figure 2. 11.

Table 2. 2 *Aqueous-biphasic hydroformylation of alkenes in the presence of different 1-alkyl-3-methyl-imidazolium salts*

Entry	Alkene	Additive	P/Rh	Aldehydes (%)	Isomerized Alkenes (%)	*l/b*[b]	TOF$_0$ (h^{-1})[c]	[Rh]$_{org}$ (ppm)[d]	Phase separation
1	1-octene	-	10	1.9	1.4	4.9	10	n.d.[f]	<10 min[e]
2	1-octene	[HexMim]Br	50	8.2	1.9	8.7	47	0.13	<10 min[e]
3	1-octene	[OctMim]Br	10	91.5	5.7	2.9	1105	126.20	<10 min[e]
4	1-octene	[OctMim]Br	50	91.9	2.9	3.2[g]	912	0.49	<10 min[e]
5	1-octene	[DecMim]Br	50	94.0	1.4	3.0[g]	1239	0.31	Stable emulsion
6	1-hexene	-	10	37.8	3.8	4.5	317	n.d.[f]	<10 min[e]
7	1-hexene	[HexMim]Br	10	19.8	0	7.8	147	0.30	<10 min[e]
8	1-hexene	[HexMim]Br	50	36.5	0	13.7	222	0.21	<10 min[e]
9	1-hexene	[OctMim]Br	10	90.2	8.9	2.8[h]	1561	27.6	<10 min[e]
10	1-octene	[OctMim]Cl	50	81.0	3.0	3.2	668	n.d.	<10 min[e]
11	1-octene	[OctMim]TfA	50	82.8	3.7	3.1	645	0.13	<10 min[e]
12	1-decene	-	10	1.3	30.3[i]	3.1	n.d.[j]	n.d.[f]	<10 min[e]
13	1-decene	[OctMim]Br	10	62.8	18.1[i]	2.5	340	23.38	<10 min[e]

[a] Reaction conditions : T = 100 °C; P = 20 bar (CO:H_2 = 1:1); stirring rate = 1000 rpm; 3 h; [additive]$_{aq}$ = 0.5 mol dm^{-3}; [Rh]$_{aq}$ = 1.25 10^{-3} mol dm^{-3}; alkene: 2 cm^3; H_2O : 8 cm^3. [b] mole of linear aldehyde/mole of all the branched aldehydes. [c] Initial turnover frequency (mole of alkene converted per mole of rhodium per hour); calculated from linear regression at the origin of the gas uptake curve obtained corresponding to 20 %conversion. [d] Concentration of rhodium detected in the organic phase by ICP-MS. [e] The phases were fully separated by the time the autoclave was vented and opened, *ca.* 10 min after the reaction was stopped. [f] Non determined. [g] 2-ethylheptanal detected. [h] 2-Ethylpentanal detected. [i] including 12% of isomers present in the starting material. [j] the reaction is too slow for the gas uptake to be measured.

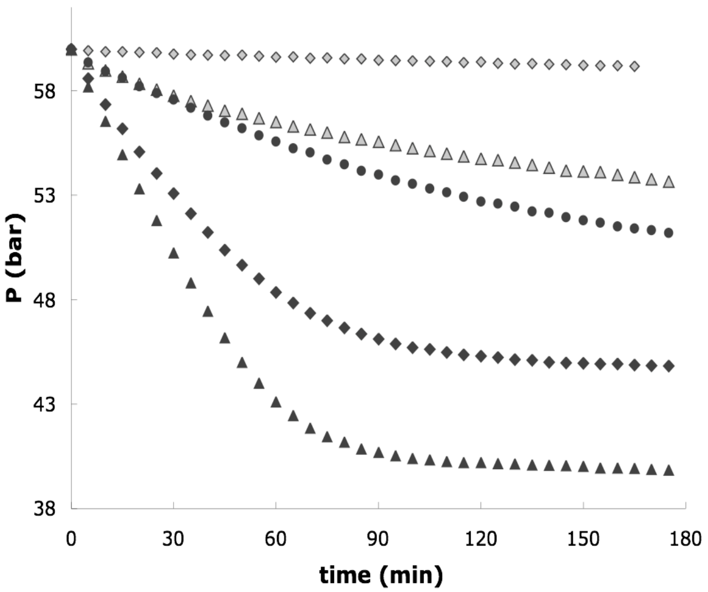


Figure 2. 10 *Gas uptake plots from a ballast vessel for the hydroformylation of various alkenes.in the absence (grey) and presence (black) of [OctMim]Br (0.5 mol dm^{-3}).▲1-hexene, ♦ 1-octene, ● 1-decene (for conditions see Table 2. 2 footnote^{a}, P/Rh = 10)***.***

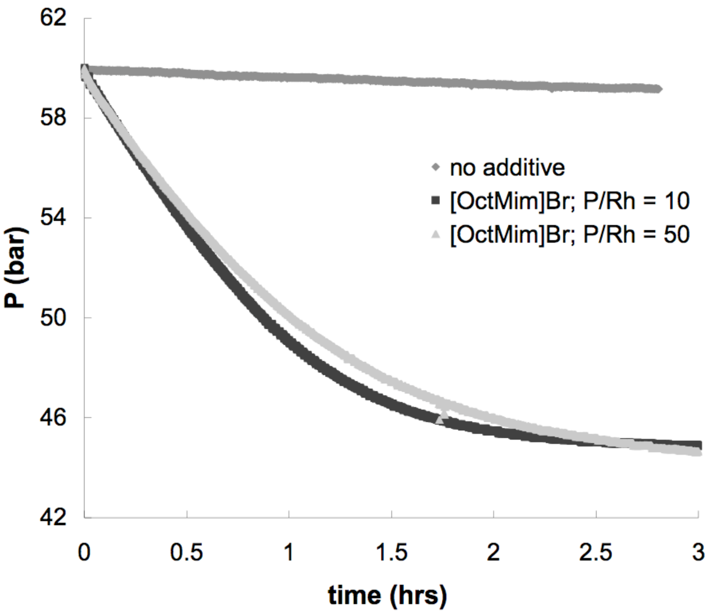


Figure 2. 11 *Effect of the presence of [OctMim]Br and different P/Rh ratio on the gas uptake from a ballast vessel during the aqueous-biphasic hydroformylation of 1-octene (for conditions see Table 2. 2 footnote a).*

Similar improvements were obtained using 1-hexene and 1-decene (Table 2. 2 and Figure 2. 10). For the former, the reaction was complete in < 1.5 h (38 % conversion, after 3 h in the absence of additive), whilst for 1-decene there was no observable gas uptake in the absence of catalyst, but the reaction to aldehydes had proceeded to 71.4 % in 3 h, allowing for the isomerised alkenes in the starting 1-decene, in the presence of [OctMim]Br (0.5 mol dm^{-3}).

In all cases, the observed amount of isomerised alkene was enhanced by the presence of the additive, but not relative to the amount of aldehyde formed. For 1-octene and 1-decene, isomerisation was suppressed relative to hydroformylation. For 1- hexene and for 1-octene with P/Rh = 10, the gas uptake plots from a ballast vessel (Figure 2. 10 and Figure 2. 11) were linear over substantial parts of the reaction. This is probably because gas transfer became rate determining. This would also explain why the initial rate of hydroformylation of 1-octene is only slightly different when using P/Rh = 10 or 50. Normally, hydroformylation reactions are inhibited by the presence of excess phosphine (negative order in [P]), but, if the reaction is gas transport limited, this order will not be observed). The gas uptake curve for 1-octene with P/Rh = 50 fits to first order kinetics so that the reaction is probably limited by the intrinsic kinetics at the higher loading of phosphine.

2.3.4. Variation of the apolar chain on the additive

In order to try to understand the origin of the dramatic rate increase for 1-octene hydroformylation when using [OctMim]Br as additive, as well as to see whether further improvements are possible, we have studied the effect of varying the chain length of the alkyl substituent on the methyl imidazolium salt. [DecMim]Br, having a C_{10} side chain, enhances the reaction rate even further but leads to the formation a stable emulsion (Figure 2. 12 and Table 2. 2, entry 5).

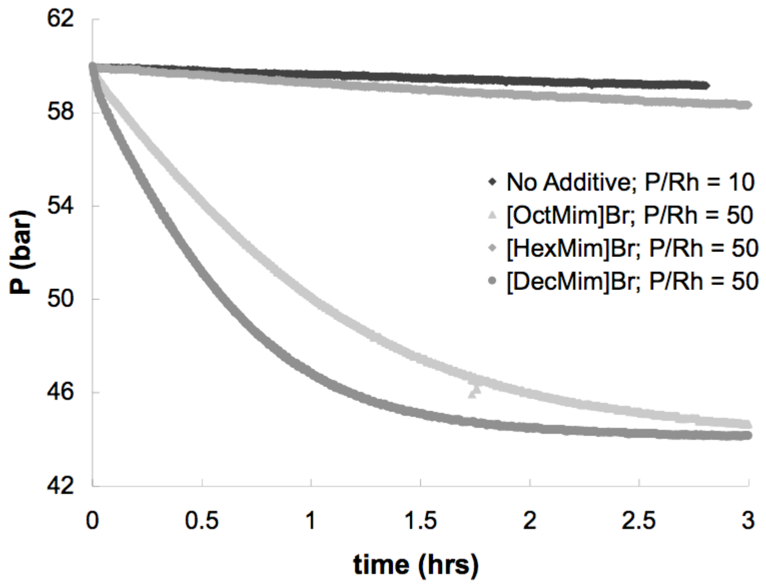
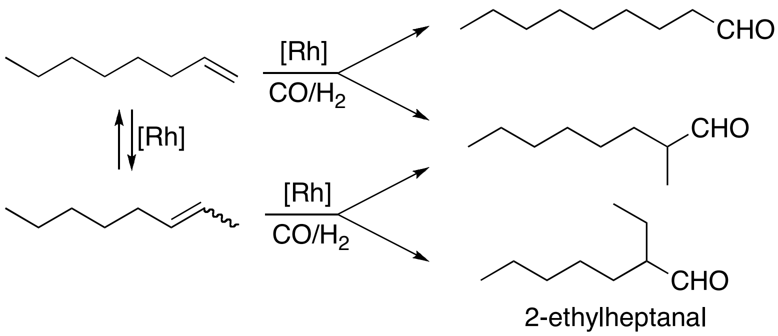


Figure 2. 12 *Gas uptake from a ballast vessel during the aqueous-biphasic hydroformylation of 1-octene in the presence of 1-alkyl-3-methylimidazolium bromide bearing alkyl chain of different lengths (for conditions see Table 2. 2 footnote a).*

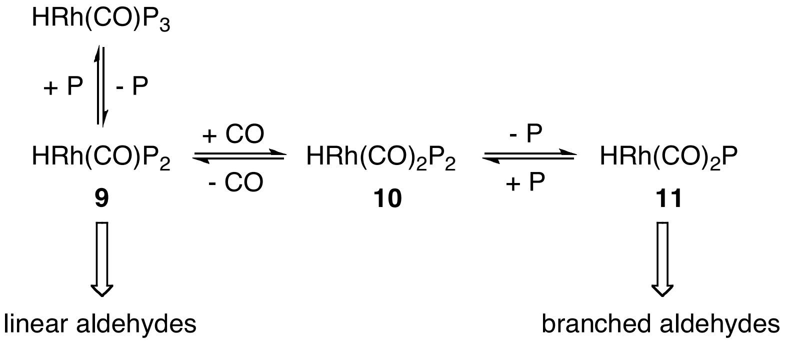
The effect of [HexMim]Br, bearing a slightly shorter chain, C_6, is intriguing. It shows little influence on the reaction rate (Figure 2. 12 and Table 2. 2). However, it has a dramatic effect on the linear selectivity (Table 2. 2, entry 1 - 2). The linear to branched ratio for the C_9 aldehyde reaches 8.7 in the presence of [HexMim]Br albeit with a 50 fold excess of ligand. This marked difference in linear selectivity can be attributed to different parameters. When comparing [HexMim]Br with [OctMim]Br it should be kept in mind that the linear selectivities are observed at very different conversions. At low conversion, the linear alkenes are mainly transformed, yielding linear aldehydes if the catalyst is selective. On the other hand, internal alkenes, which build up in the reaction mixture due to competitive isomerisation (Scheme 2. 1), are hydroformylated to yield branched products when high conversion is reached and only small amounts of terminal alkenes remain in the reaction mixture. This may explain the low linear selectivity observed in presence of [OctMim]Br and [DecMim]Br (Table 2. 2, entry 4 - 5).



Scheme 2. 1 *Hydroformylation-isomerisation of 1-octene.*

Supporting this, 2-ethylheptanal, arising from the hydroformylation of 2-octene (Scheme 2. 1), was detected in reactions carried out to high conversion. However, when the reaction with 1-octene in the presence of [OctMim]Br was run for a shorter time (1. 2 h) *i.e.* to lower conversion (58.7 % aldehydes), the l/b ratio was 3.3. This suggests that the low linear selectivity is rather due to a poorer selectivity of the catalytic system in the presence of [OctMim]Br than to the hydroformylation of isomerised alkenes. The difference in linear selectivity observed between [OctMim]Br and [HexMim]Br thus seems genuine and not due to a conversion artifact.

In order to assess the influence of [HexMim]Br on the reaction selectivity at higher conversion, we investigated the hydroformylation 1-hexene, which shows some activity even in the absence of additive. For this substrate, [HexMim]Br showed an inhibition effect on the reaction rate but again led to higher linear selectivity compared with the neat biphasic system at similar conversion rate (Table 2. 2, entry 6 - 7). Moreover, no isomerised alkenes were detected in the reaction mixture. When using a larger ligand excess, the l/b ratio increased to 13.7. Surprisingly, the reaction rate also increased whereas excess ligand usually has an inhibiting effect on the reaction rate. When using [OctMim]Br, high reaction rate could be achieved but with poor linear selectivity and significant isomerisation of the substrate. The high linear selectivity observed for the



Scheme 2. 2 *Equilibria involved in the formation of the different active catalytic species*

hydroformylation of 1-hexene seems very likely to be due to the presence of [HexMim]Br. One explanation for this could be the increase of the ionic strength of the aqueous phase in the presence of [HexMim]Br. Hanson and coworkers reported that the linear selectivity of the aqueous-biphasic hydroformylation of 1-octene catalyzed by Rh/TPPTS can be improved upon addition of Na_2HPO_4 (0.5 mol dm^{-3})[4]. They showed, by variable temperature ^{31}P-NMR studies, that the dissociation energy of TPPTS from [HRh(CO)$(TPPTS)_3$] increases with the ionic strength of the solution. Dissociation of TPPTS is required to form the low phosphine coordinated complex, **11,** responsible for the formation of branched aldehydes (Scheme 2. 2).

Therefore, in aqueous media with high ionic strength, the equilibria lie in favor of **9** leading to a higher proportion of linear products. In our system [HexMim]Br, presumably dissociated in the water phase, may increase the ionic strength which would explain its effect on the reaction selectivity, although we note that [HexMim]Br is not expected to be as structure directing towards the water as is Na_2HPO_4. The low linear selectivity observed with [OctMim]Br and [DecMim]Br may be due to the formation of micelles. Conductivity measurements show that [OctMim]Br has a critical micelle concentration of 2.16 10^{-2} mol dm^{-3} at 25 °C, *i.e.* well below the concentration used in the catalytic experiments. These longer chain additives, forming aggregates under reaction condition, do not significantly increase the ionic strength of the water and hence have no promoting effect on the linear selectivity.

2.3.5. Variation of the “ionic head”

Having established that, in our system, the optimum balance between high reaction rate and good phase separation is obtained with an additive bearing a C_8 alkyl chain, we investigated the effect of structural variation of the additive “ionic head” while keeping the length of the “tail” to 8 carbon atoms. We investigated the use of water soluble *N*-octylpyridinium bromide, [OctPyr]Br, and *N*-octyl-*N,N,N*-triethylammonium bromide, [OctNEt$_3$]Br as additives for the aqueous biphasic hydroformylation of 1-octene with a 50-fold excess of TPPTS over rhodium (Figure 2. 13). From the gas uptake curves obtained, it appears that changing the structure of the “ionic” head of the additive dramatically changes its influence on the reaction rate. Surprisingly, [OctPyr]Br showed very little effect on the reaction rate. Moreover, opposite to what was observed with [HexMim]Br, it also had almost no influence on the regio selectivity, the l/b values observed being typically 4.1. On the other hand, the addition of [OctNEt$_3$]Br to the system allowed octene to be transformed with a TOF$_0$ of 350 h^{-1} and l/b value of *ca.* 3.0. None of those additives showed detrimental effects on the phase separation. The phases were fully separated by the time the autoclave was opened, *ca.* 10 min after the reaction was stopped. The smaller effect on the reaction rate observed for [OctNEt$_3$]Br compared with [OctMim]Br may arise from steric interactions. We propose (see below) that the accelerating effect observed with [OctMim]Br arises from the formation of an emulsion.

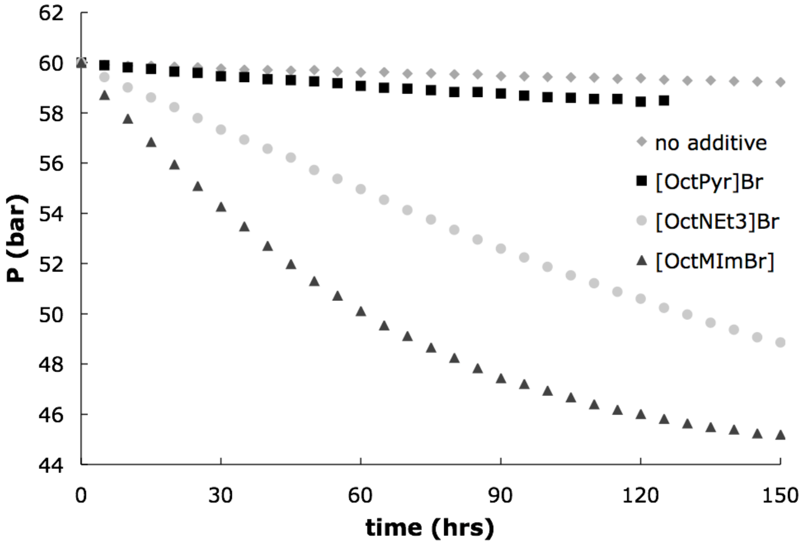


Figure 2. 13 *Effect of the variation of the additive ionic "head" on the gas uptake from a ballast vessel during the aqueous-biphasic hydroformylation of 1-octene. (For conditions see Table 2. 2 footnote a)*

Li has attributed the increased rate of hydroformylation reactions in the presence of cationic surfactants to the high concentration of Rh/TPPTS at the positively charge surface of the micelle[6, 8, 13]. This brings the catalyst and the substrate, solubilized in the core of the micelles, in close proximity and hence accelerates the reaction through a local concentrating effect. When using [OctNEt$_3$]Br, the ethyl groups may lead to a more sterically crowded micelle surface than the planar imidazolium cation and thus hinder the contact between the substrate and the catalyst.

2.3.6. Variation of the anion

Having investigated some of the possible structural variation of the cationic part of the additive we tested the effect of changing the nature of the anion. It is well established that the nature of the anion has a dramatic impact on the water solubility of 1-alkyl-3-methylimidazolium salts. We synthesized 1-octyl-3-methylimidazolium salts with bromide, chloride, trifluoroacetate and triflate anions, since they are likely to yield water-soluble salts. Unfortunately, the triflate salt, [OctMim]TfO, proved to be insoluble in water and so unsuitable for our purpose. All the other salts were fully miscible with water at the investigated concentrations. [OctMim]Cl and [OctMim]TfA both led to higher reaction rates compared to the reactions carried out without additive. However, they were less efficient than their bromide analogues in speeding up the reaction (Table 2. 2, entries 4, 10 and 11). The reaction selectivities were similar to those observed in the presence of [OctMim]Br. The rhodium leaching was found to be very low when using [OctMimTfA]. However, the crude reaction solution obtained in the presence of this additive had a strong "vinegary" smell presumably arising from the protonation of the CF_3CO_2 anion.

2.3.7. Origin of the promoting effect

Two different mechanisms could explain the rate enhancement effect observed when conducting the reaction in presence of our additives. The additive could form micelles under reaction condition. In this case, the cationic head of the additive would attract the negatively charged catalyst at the positively charged surface of the micelle, creating a high concentration of catalyst around the substrate solubilized within the core of the micelles. Alternatively the additive could act as a phase transfer agent, exchanging the sodium cation of the TPPTS by an additive cation making the catalyst soluble in the organic phase. The reverse exchange would bring the catalyst back into the aqueous phase (Figure 2. 14). The fact that we started to observe rate enhancement effects in the presence of [OctMim]Br at concentration close to the CMC is in favor of the additive behaving as a surfactant. When considering the

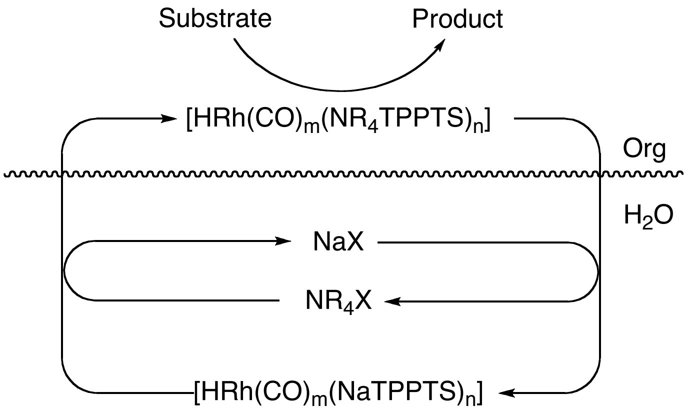


Figure 2. 14 *Graphic representation of the additive (NR_4X) acting as a phase transfer agent.*

results obtained with additives having different apolar tails, [HexMim]Br, [OctMim]Br and [DecMim]Br (Table 2. 2 entry 2, 4 and 5) it appear that the shorter chain alkylimidazolium bromide, [HexMim]Br, has only limited effect on the reaction rate. On the other hand, in the presence of the longest chain additive, [DecMim]Br, high reaction rate is observed together with the formation of stable emulsions. The rate improvement observed with [OctMim]Br is more likely to be due to its surfactant properties. If a genuine phase transfer mechanism were operating, significative rate improvement would have been expected when [HexMim]Br was used as the additive. Moreover, this would significaly promote rhodium leaching. With both additives the rhodium leaching in the organic phase was less than 0.5 ppm.

To test further the hypothesis of [OctMim]Br acting as a surfactant, we visualised the mixing behaviour of aqueous-octene biphasic systems with and without added [OctMim]Br at room temperature and atmosheric pressure, using a yellow dye to colour the organic phase (Figure 2. 15). From the photographs, it can be seen that, while the system is poorly mixed without additive, a much more homogeneous system is obtained in the presence of [OctMim]Br after only 6 sec of stirring.

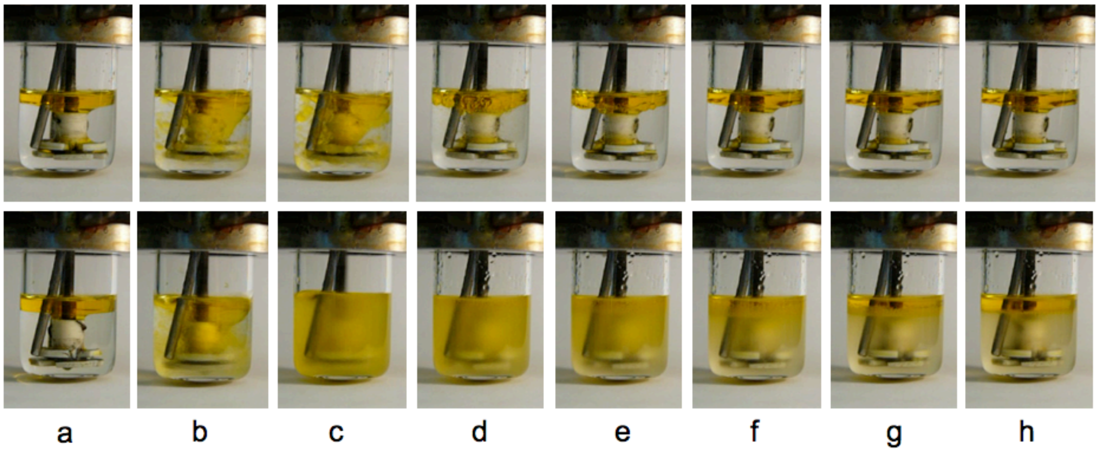


Figure 2. 15 *Photographs of an octene – water biphasic system (octene: 2 cm^3, dyed; water: 8 cm^3) without additive (top line) and with [OctMim]Br (0.5 mol dm^{-3}, bottom line). (a) at t = 0 sec; (b) after 2 sec stirring ;(c) after 6 sec stirring; (d) after 12 sec stirring (stirring is stopped); (e) after 2 sec settling; (f) after 6 sec settling; (g) after 12 sec settling and (h) after 20 sec settling (stirring rate = 1000 rpm)*

When the stirring is stopped, the phases instantly separate when no additive is present. In the presence of [OctMim]Br, the two phases take longer to separate, but after 20 sec a biphasic system is obtained with a clear interface. The persisting yellow coloration of the aqueous phase indicates that some of the octene dyed phase remains trapped in the water.

These results together with those obtained using different alkyl chains on the imidazolium salt, support our proposal that [OctMim]Br acts as a weak surfactant. It promotes the formation of an emulsion whilst being stirred but the emulsion is too unstable and breaks quickly after the stirring is stopped. Consistent with this hypothesis, the effect of the additive is only noticeable above the CMC (Figure 2. 8)

2.4 Conclusions

We have studied the use of several structurally related additives in the aqueous-biphasic hydroformylation of medium alkenes. By careful choice of the cationic head group and its alkyl side chain, high reaction rates can be obtained without impairing the phase separation or the metal retention. These additives could greatly improve the scope of the aqueous-biphasic methodology. The structural features of the additive play an important role. The length of the side chain appears to be the most critical feature. The nature of the cationic head group also has an important influence on the reaction rate but for reasons that remain rather unclear. Regarding the anion, its effect is less marked, although care should be taken with regard to its stability under the reaction conditions. The most promising additive is based on the 1-octyl-3-methylimidazolium cation. We propose that it affects the reaction by forming emulsions with poor stability that improve the contact between the catalyst and the substrate but break after settling for a short time. These unstable emulsions seem to be very promising media for aqueous-biphasic systems since switching between a pseudo monophasic system (good for high reaction rates) and a biphasic system (good for catalyst product separation) is just a matter of switching the stirrer on and off.

2.5 **Experimental**

2.5.1. General

All experiments were carried out under dry argon on a vacuum line using standard Schlenk techniques.

Gases; argon and syngas, were purshased from BOC gases. Water was distilled, degassed by vacuum and stored under argon. Triphenylphosphine trisulfonate sodium salt, TPPTS, (Aldrich, 96 % or prepared according to [30]), rhodium acetoacetonate dicarbonyl, $[Rh(acac)(CO)_2]$ (Strem chemical, 99 %). deuterium oxide (Aldrich, 99.9

atom % D) and silver trifluroacetate (Aldrich, 98 %) were used as received. Alkenes; 1-hexene (Aldrich, 99 %), 1-octene (Aldrich, 98 %) and 1-decene (Aldrich, 95 %) were purified from peroxides by extraction with aqueous $(NH_4)_2Fe(SO_4)_2.6H_2O$ followed by filtration trough basic alumina and stored in the dark under Ar.

Ethylacetate (Fischer, technical grade) was dried over magnesium sulfate and distilled over P_2O_5. Acetonitrile (Fischer, technical grade) was distilled over CaH_2. N-methylimidazole (Acros Organics, 99 %) was distilled over sodium. Pyridine (Aldrich, 99 %) was distilled over KOH. Triethylamine (Aldrich 98 %) was refluxed overnight with KOH and then distilled. 1-Bromohexane (Aldrich, 98 %) was dried over CaH_2 and distilled over P_2O_5. 1-Bromooctane(Aldrich, 99 %) was distilled over K_2CO_3. 1-Chlorooctane (Aldrich, 99 %) was distilled over CaH_2 under vacuum. 1-Bromodecane (Aldrich, 98 %) was dried over CaH_2 and distilled over P_2O_5 under vacuum.

Gas chromatography analyses were carried out using a Hewlett-Packard 5890 series gas chromatograph equiped with a flame ionisation detector (FID) fitted with a Supelco MDN-35 (35 % phenyl/65 % methyl-polysiloxane) capillary column for quantitative analysis. The temperature programme used was: 50 ^{o}C (4 min), Δ 20 °C/min to 130°C (2 min), Δ 20°C/min to 260 (13.5 min). The temperature of the injector and the detector were both 250 °C. The split ratio used was 100/1. Helium was used as the carrier gas with a flow of 1 ml min^{-1}.

^{13}C, ^{1}H and ^{31}P NMR spectra were recorded on Bruker AM 300/400 NMR spectrometers or a Varian 300 NMR spectrometer. Broadband decoupling was used for ^{13}C and ^{31}P NMR spectra. ^{1}H and ^{13}C NMR spectra were referenced internally to deuterated solvents, which were referenced relative to TMS at δ = 0: $CDCl_3$: ^1H, δ = 7.27 ppm, ^{13}C, δ = 77.23 ppm; D_2O: ^1H = 4.53 ppm. ^{31}P NMR spectra were referenced externally to 85 % H_3PO_4. Coupling constants are given in Hz.

2.5.2. Catalyst preparation

Catalyst solutions were prepared as follows: weighed amounts of $[Rh(acac)(CO)_2]$ and TPPTS were dissolved in a known volume of water containing the additive at the desired concentration. Syngas was then gently bubbled through the resulting yellow solution at 60°C for 1 h. δ_P (300MHz; D_2O;) -4.55 (s, broad).

To check that the procedure was efficient to form the catalytically active complex *in situ*, the same procedure was followed but with higher concentration to allow detection by $3^1P\{^1H\}$-NMR spectroscopy. δ_P (300 MHz; D_2O;) -4.55 (s, broad) and 44.78 (d, $^1J_{P\text{-}Rh}$ 155). Litterature values: δ_P (D_2O) 42.8 (d, $^1J_{P\text{-}Rh}$ 156)[31] and δ_P (D_2O 300 MHz) -5.7 (s) 44.7 (d, $^1J_{P\text{-}Rh}$ 156)[27]

2.5.3. Hydroformylation of alkenes

Typical procedure for the hydroformylation of alkenes at consant pressure: an autoclave fitted with a mechanical stirrer, thermocouple pocket, pressure transducer and attached to a ballast vessel *via* a catalyst injector and mass flow controller was degassed by pressurizing three times with CO/H_2 and releasing the pressure. 8 cm^3 of catalyst solution was transferred into the autoclave and degassed by pressurizing three times with CO/H_2 and releasing the pressure. The autoclave was pressurized with CO/H_2 (1:1, 16 bar) and heated to 100 ^oC (Stirrer speed = 1000 rpm). Meanwhile, the substrate injector was charged with the substrate (2 cm^3). Once the reactor had reached 100 °C, the substrate was injected using an overpressure of CO/H_2 and the pressure brought to 20 bar. CO/H_2 was then fed from the ballast vessel so as to maintain the pressure in the autoclave at 20 bar and the pressure in the ballast vessel was monitored electronically. At the end of the reaction, the autoclave was quickly cooled and depressurized. The content of the autoclave was transferred to a vial for visual inspection of the phase separation. The organic phase was analysed by GC for organics and by ICP-MS for rhodium. The results presented (Table 2. 2) are the average of at least 3 runs under each set of conditions.

Typical procedure for hydroformylation of 1-octene in a closed reactor: an autoclave, fitted with a mechanical stirrer, thermocouple pocket, pressure transducer, gas inlet and injection port, was degassed by 3 alternate vacuum -. N_2 cycles. The stock catalyst solution (8 cm^3) and 1-octene (2 cm^3) were transferred into the autoclave. The autoclave was purged three times with pressurised $CO-H_2$. The autoclave was pressurized with $CO-H_2$ (1:1, 20 bar) and heated with stirring to 100 °C. After 2 h, the autoclave was quickly cooled, depressurised and the contents analysed using GC for the organic products. The results presented (Figure 2. 8) are the average of at least 3 runs under each set of conditions.

2.5.4. Synthesis of the additives

1-hexyl-3-methylimidazolium bromide, [HexMim]Br

N-methylimidazole (10 cm^3, 10.30 g, 0.125 mol), 1-bromohexane (21 cm^3, 24.70 g, 0.150 mol) and ethyl acetate (30 cm^3) were heated under reflux for 24 h in an atmosphere of argon. The biphasic system obtained was separated and the upper organic phase discharged. The bottom product phase was washed with ethylacetate (3 x 30 cm^3) and dried under vacuum (0.01 mbar) at 50°C to give 1-octyl-3-methylimidazolium bromide (23.47 g, 75 %) as a colorless liquid. δ_H(300MHz, CDCl$_3$) 0.21 (3H, t, ^3J 6.7, NC$_7$H$_{14}$CH_3), 0.55-0.78 (6H, m, CH_2), 1.30 (2H, quintet, ^3J 6.9 NCH$_2$CH_2), 3.52 (3H, s, NCH$_3$), 3.74 (2H, t, ^3J 7.4, NCH_2), 7.14 (1H, t, ^4J 1.7, NCHC*H*N), 7.25 (1H, t, ^4J 1.7, NC*H*CHN) and 9.59 (1H, s, NC*H*N). In agreement with litterature data[32]

1-octyl-3-methylimidazolium bromide, [OctMim]Br

N-methylimidazole (29 cm^3, 29.87 g, 0.364 mol), 1-bromooctane (69 cm^3, 77.14 g, 0.399 mol) and ethyl acetate (100 cm^3) were heated under reflux for 16 h in an atmosphere of argon. The biphasic system obtained was separated and the upper organic phase discharged. The bottom product phase was washed with ethylacetate (3 x 100 cm^3) and dried under vacuum (0.01 mbar) at 50°C to give 1-octyl-3-methylimidazolium bromide (87.16 g, 87 %) as a colorless liquid. δ_H(400MHz, CDCl$_3$) 0.65 (3H, t, ^3J 6.9, NC$_7$H$_{14}$CH_3), 0.99 - 1.16 (10H, m, CH_2), 1.71 (2H, quintet, ^3J 7.2 NCH$_2$CH_2), 3.93 (3H, s, NCH$_3$), 4.13 (2H, t, ^3J 7.4, NCH_2), 7.37 (1H, t, ^4J 1.8, NCHC*H*N), 7.56 (1H, t, ^4J 1.8, NC*H*CHN) and 9.97 (1H, s, NC*H*N). In agreement with litterature data[32]

1-decyl-3-methylimidazolium bromide, [DecMim]Br

N-methylimidazole (10 cm^3, 10.30 g, 0.125 mol), 1-bromodecane (29 cm^3, 77.14 g, 0.140 mol) and ethyl acetate (40 cm^3) were heated under reflux for 28 h in an atmosphere of argon. The biphasic system obtained was separated and the upper organic phase discharged. The bottom product phase was washed with ethylacetate (3 x 40 cm^3). And dried under vacuum (0.01 mbar) at 50°C to give 1-decyl-3-methylimidazolium bromide (33.74 g, 89 %) as a colorless viscous liquid. δ_H(300MHz, $CDCl_3$) 0.69 (3H, t, ^3J 6.7, $NC_7H_{14}CH_3$), 0.99 - 1.22 (14H, m, CH_2), 1.75 (2H, quintet, ^3J 7.2 NCH_2CH_2), 3.97 (3H, s, NCH_3), 4.16 (2H, t, ^3J 7.4, NCH_2), 7.40 (1H, t, ^4J 1.8, NCHC*H*N), 7.59 (1H, t, ^4J 1.8, NC*H*CHN) and 10.08 (1H, s, NC*H*N). In agreement with litterature data[32]

1-octyl-3-methylimidazolium chloride, [OctMim]Cl

N-methylimidazole (40 cm^3, 41.2 g, 0.502 mol), 1-chlorooctane (103 cm^3, 89.52 g, 0.602 mol) and ethyl acetate (100 cm^3) were heated under reflux for 5 days in an atmosphere of argon. The biphasic system obtained was separated and the upper organic phase discharged. The bottom product phase was washed with ethylacetate (3 x 50 cm^3). And dried under vacuum (0.01 mbar) at 50°C to give 1-octyl-3-methylimidazolium chloride (63.0 g, 54 %) as a pale yellow liquid. δ_H(300MHz, $CDCl_3$) 0.69 (3H, t, ^3J 6.8, $NC_7H_{14}CH_3$), 1.12 (10H, m, CH_2), 1.75 (2H, quintet, ^3J 7.3 NCH_2CH_2), 3.97 (3H, s, NCH_3), 4.18 (2H, t, ^3J 7.7, NCH_2), 7.39 (1H, t, ^3J 1.7, NCHC*H*N), 7.63 (1H, t, ^3J 1.7, NC*H*CHN) and 10.42 (1H, s, NC*H*N). In agreement with litterature data[33]

1-octyl-3-methylimidazolium trifluoroacetate, [OctMim]TfA

1-octyl-3-methylimidazolium chloride (7.48 g, 0.032 mol) in solution in water (25 cm^3) was added to a suspension of silver trifluoroacetate (7.42 g, 0.034 mol) in water (25 cm^3) and the mixture was stirred overnight. The silver chloride precipitate was removed by filtration and the aqueous phase was extracted with dichloromethane (4 x 25 cm^3). The organic phases were combined and washed with small portions of water (10 cm^3) until silver nitrate tests on the washings gave no precipitate. The solvent was evaporated and further drying under vacuum (0.01 mbar) gave 1-octyl-3-methylimidazolium trifluoroacetate (3.2 g, 31%) as a colourless liquid. δ_H(400MHz, $CDCl_3$) 0.81 (3H, t, ^3J 6.9, $NC_7H_{14}CH_3$), 1.27 (10H, m, CH_2), 1.88 (2H, quintet, ^3J 7.2 NCH_2CH_2), 4.04 (3H, s, NCH_3), 4.24 (2H, t, ^3J 7.4, NCH_2), 7.27 (1H, t, ^4J 1.7, NCHC*H*N), 7.33 (1H, t, ^4J 1.7, NC*H*CHN) and 10.36 (1H, s, NC*H*N). In agreement with litterature data[34]

N-octylpyridinium bromide, [OctPyr]Br

Pyridine (10 cm^3, 9.78 g, 0.124 mol), 1-bromooctane (24 cm^3, 26.83 g, 0.139 mol) and ethyl acetate (30 cm^3) were stirred under reflux for 14 h in an atmosphere of argon. The biphasic system obtained was separated and the upper organic phase discharged. The bottom product phase was washed with ethylacetate (3 x 30 cm3). And dried under vacuum (0.01 mbar) at 50°C to give *N*-octylpyridinium bromide (26.1 g, 77 %) as a colorless liquid. δ_H(300MHz, $CDCl_3$) 0.66 (3H, t, ^3J 6.8, $NC_7H_{14}CH_3$), 0.96 – 1.26 (10H, m, CH_2), 1.89 (2H, quintet, ^3J 7.3 NCH_2CH_2), 4.83 (2H, t, ^3J 7.5, NCH_2), 8.04 (2H, t, ^3J 7.2, C*H*CHC*H*), 8.42 (1H, tt, ^3J 7.8, ^4J 1.2, CHC*H*CH) and 9.46 (2H, dd, ^3J 6.7, ^4J 1.2, C*H*NC*H*). In agreement with litterature data[35]

N-octyl-N,N,N-triethylammonium bromide,[OctNEt$_3$]Br

Triethylamine (12 cm^3, 8.71 g, 0.086 mol), 1-bromooctane (12 cm^3, 13.41 g, 0.069 mol) and acetonitrile (25 cm^3) were heated under reflux for 18 h in an atmosphere of argon. The mixture obtained was cooled to 0 °C and ethylacetate was added in portions until precipitation of a white solid. The cold suspension was filtered, the solid collected, washed with ethyl acetate (3 x 30 cm^3) and dried under vacuum (0.01 mbar) to give *N*-octyl-*N*,*N*,*N*-triethylammonium bromide (15.12 g, 74 %) as a white solid. δ_H(300MHz; CDCl$_3$) 0.87 (3H, t, ^3J 6.8, NC$_7$H$_{14}$C*H*$_3$), 1.21 – 1.44 (19H, m, C*H*$_2$ and NCH$_2$C*H*$_3$) , 1.70 (2H, quintet, ^3J 7.1, NCH2C*H2*), 3.24 – 32.27 (2H, m, NC*H*$_2$C$_7$H$_{15}$) and 3.52 (6H, q, ^3J 7.3, NC*H*$_2$CH$_3$); *m/z* (ESI) 214 (M+, 100 %).

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Chapter
THREE

Carbon dioxide induced phase switching for homogeneous catalyst recycling

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3.1 Introduction

The use of rhodium catalysts to replace cobalt catalysts for the hydroformylation of higher alkenes is still impeded by the difficulty of separating the catalyst from the high boiling product. However, this transition to a more active and selective catalyst is highly desirable from an economical and environmental point of view.

Several methods have been developed, aimed at efficient ways of recycling homogeneous catalysts[1]. An aqueous biphasic system is currently used in industry for the hydroformylation of propene and butene[2]. In this process, the catalyst is dissolved in an aqueous phase by the use of sulfonated ligands, whilst the starting material and products form a separate phase. This methodology allows fast and efficient separation of the product from the catalyst by simple decantation. The aqueous phase containing the catalyst can then be reused for further operation.

While the introduction of a second phase ensures efficient catalyst separation and recycling, it induces mass transfer limitations that reduce the reaction rate. For higher alkenes ($>C_5$), which display poor solubility in water, mass transport limitations render the reaction rate to be lower than any that could be economically viable, greatly limiting the scope of this elegant technology.

Numerous methods aimed at extending the scope of the aqueous-biphasic methodology to more hydrophobic substrates have been developed. As we described in the previous chapters, this can be done using additives, surface-active ligands or new reactor design. However for most of the investigated new approaches, there is still a discrepancy in rate when alkenes of different hydrophobicity are used. This means that, practically, the new processes developed could only efficiently be used for a narrow range of substrates.

A more general solution, *i.e.* independent of the substrate solubility in water, is to carry out the reaction in a homogeneous fashion and to separate the catalyst from the product using aqueous extraction after reaction.

3.1.1. Homogeneous reaction with biphasic separation

To apply this methodology, either the catalyst can be designed so its solubility can be switched upon an external trigger or the reaction medium can be designed to switch from a biphasic to a single phase and reversed to the biphasic system upon an external stimulus (Figure 3. 1). Switchable solvent systems have been mainly achieved with fluorous systems[3]. Fluorous solvents form biphasic systems with many organic solvents, but turn into monophasic systems upon heating. This property has been elegantly used to recycle

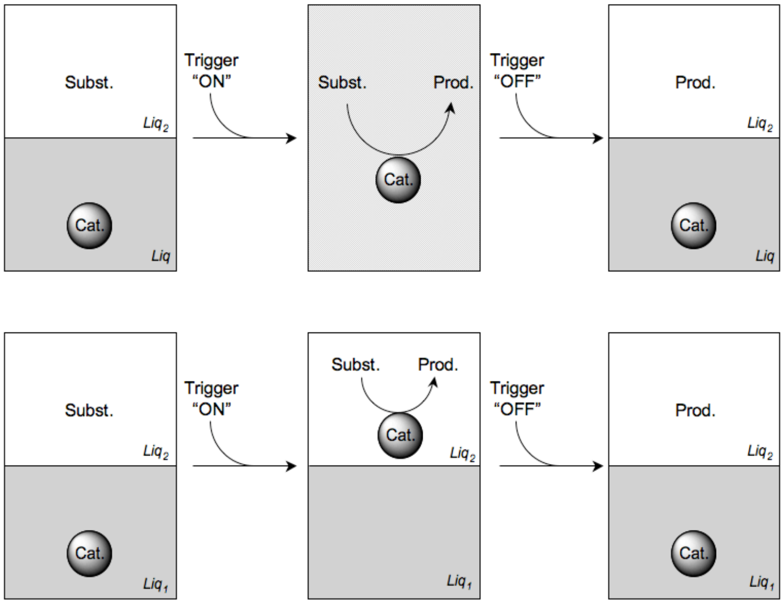


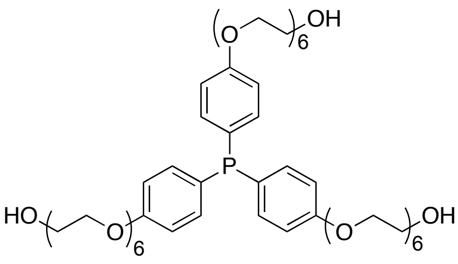
Figure 3. 1 *Schematic representation of a switchable solvent system (top) and a phase-switchable catalyst (bottom).*

homogeneous catalysts, even enabling continuous-flow operation[4].

When considering aqueous systems, water-oil microemulsions stabilized by non-ionic surfactants have been shown to form either a pseudo-monophasic system (microemulsion) or biphasic systems (aqueous-organic) depending on the temperature[5]. Such media have been used for the hydroformylation of long chain alkenes catalyzed by water-soluble rhodium or cobalt complexes[6]. At the reaction temperature, a water in oil microemulsion was formed allowing 1-dodecene to be hydroformylated at high rate, while, upon cooling, the system splits into a biphasic system with the aqueous phase retaining the catalyst and most of the surfactant[6a]. However, the phase separation is not as complete as in the neat aqueous-organic system, so the authors recommended a subsequent ultrafiltration step to ensure complete separation. Nevertheless, the rhodium content in the product phase after phase separation was found to be 1 ppm without ultrafiltration. The methodology was further extended to more demanding substrates such as internal alkenes using rhodium- or cobalt - TPPTS complexes. Under the reaction conditions, unmodified [$HRh(CO)_3$] and [$HCo(CO)_4$] complexes are believed to be the active species. According to the authors, by changing the conditions upon phase separation, the unmodified metal species can recoordinate TPPTS and thus be retained in the aqueous phase. In another study, the hydroformylation of 1-octene in a microemulsion was reported to proceed at a high rate (TOF_0 = 10000-14000)[6d]. Moreover, by careful choice of the surfactant and its concentration, rhodium leaching below 1 ppm could be obtained.

Some non-ionic surfactants, such as polyethylene glycol (PEG), show reversible solubility in water upon temperature swings. Advantage has been taken of this property to develop ligands bearing polyethylene glycol moieties, for which the solubility in water can be switched by temperature changes[7]. Catalysts based on such ligands have been demonstrated to display anti-Arrhenius behaviour during the hydrogenation of allylic alcohol in water. This unusual behaviour was attributed to their insolubility in the reaction medium at higher temperature, resulting in a lower reaction rate. One possible use of this effect would be to moderate variations in catalyst activity due to (undesired) temperature changes[7].

Jin and co-workers elegantly took advantage of this property to carry out rhodium-catalyzed hydroformylation under thermoregulated phase transfer catalysis conditions (TRPTC)[8]. They used polyether substituted triphenylphosphine ligands in an aqueous-biphasic system, which allowed the catalyst to be soluble in the organic phase at reaction temperature but to transfer back into the aqueous phase upon cooling. By careful adjustment of the amount of polyethoxy group on the ligand, the cloud point of the



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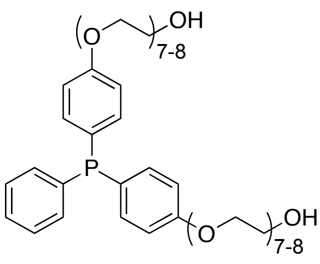

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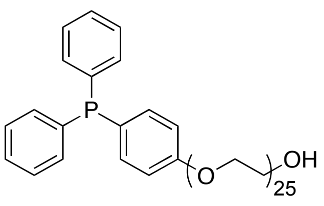

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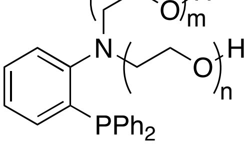
ligand, *i.e.* the temperature at which it precipitates from water, could be tuned. Ligand **1**, has a cloud point of 95°C and could be recycled 5 times with only a slight decrease in activity during the hydroformylation of dodecene. The similar ligand, **2,** showed anti-Arrhenius behaviour during the hydrogenation of allylic alcohol, supporting the idea of a temperature dependent solubility[9]. Competitive hydroformylation of 1-hexene and 1-dodecene using Rh/**3** as catalyst in an aqueous-biphasic system yielded an equimolar mixture of the C_7 and C_{13} aldehydes. By comparison, Rh/TPPTS yielded mainly the C_7 aldehyde while Rh/PPh_3 yielded an equimolar mixture of the C_7 and C_{13} products under identical conditions suggesting that, under reaction condition, the catalysis takes place in the organic phase. Moreover, the catalyst, Rh/**3,** was recycled 4 times during the hydroformylation of 1-hexene with an almost constant TOF of 180 h^{-1}. Phosphine ligand **4** with n+m = 45 has been used for the rhodium catalyzed hydroformylation of 1-decene under TRPTC conditions[10]. Impressively, the catalytic system could be recycled 20 times with almost constant activity (TOF = 190 h^{-1}) and constant selectivity to aldehyde (95%). Rhodium catalyzed hydroformylation under TRPTC conditions has been extended to



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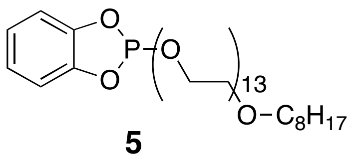
more demanding substrate such as diisobutylene[11a] and cyclohexene[11b] with the catalyst being recycled 3 times without noticeable loss in activity. Moreover, for cyclohexene hydroformylation, the rhodium leaching was found to be < 1 wt % and no residual activity was found in the organic phase after phase separation. Hydroformylation of higher alkenes has also been carried out under TRPTC conditions without aqueous phase, the organic phase being decanted from the pure catalyst upon cooling[12]. Such methodology allowed the catalyst to be recycled 8 times without noticeable loss in activity. Phosphite ligand **5** was tested under TRPTC but the activity dropped quickly after 3 recycles, presumably because of ligand hydrolysis[13]. Hydrogenation of styrene using a ruthenium catalyst was also carried out under TRPTC mode allowing the system to be recycled up to 10 times[14]. Recently, formation of colloid rhodium particles was observed during the hydroformylation of 1-octene using ligand **6**[15]. The particles, which were presumably initially stabilised by the PEG tails, were identified by TEM. They aggregated upon consecutive recycling and finally precipitated from the reaction medium. They were shown to be active for hydroformylation and to display thermoregulated phase transfer behaviour raising questions about the nature of the active species in this and other thermoregulated systems. The precipitation of the larger aggregates led to a decrease of the active catalyst concentration, which enhanced isomerisation and hence decreased the aldehyde yield.

Very recently, dipyridyl ligand **7** bearing a polyethoxy substituent has been used for



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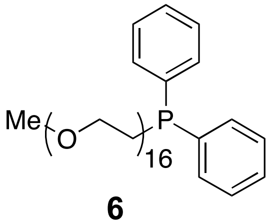

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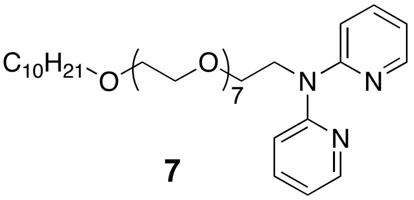

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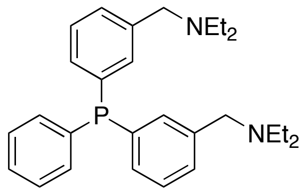
the palladium catalyzed Heck coupling of iodobenzene with styrene and ethyl acrylate under TRPTC conditions[16]. Such methodology allowed the catalyst to be recycled but a significant decrease in activity was observed. The authors attributed the decrease of activity to the increase of the ionic strength caused by the accumulation of the salt by-product (NaI in the present case) in the aqueous phase. This affects the cloud point and the phase behaviour of the system and hence the recycling of the catalyst.

Beside heat, pH swings have also been used to trigger the transfer of the catalyst back and forth from an organic to an aqueous phase[17]. Phosphine ligands bearing amino substituents have mainly been used for this purpose. Typically, catalysts comprising such ligands are soluble in common organic solvents but can be extracted into acidic water by protonation at the nitrogen. After separation of the product, neutralisation of the aqueous phase and reextraction into an organic phase, the catalyst can be reused for further operation. Among the different catalytic systems developed, complexes bearing triphenylphosphine type ligands **8-9** and xantphos type ligands **10** were shown to be the most successful of their kind for the rhodium catalyzed hydroformylation of higher alkenes. Rh/**8** catalyst system could be recycled by several extractions at pH 2.2 followed by neutralization with $NaHCO_3$ conserving 87 % of its initial activity (TOF = 1800 h^{-1}) with 97 % of the rhodium being recovered[18]. Ligand **10** also allowed good catalyst recycling (recovered activity = 86 %) with low rhodium leaching (98% of the rhodium recovered), the initial activity was much lower (TOF = 137 h^{-1}) but the linear selectivity



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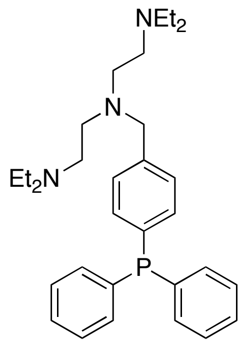

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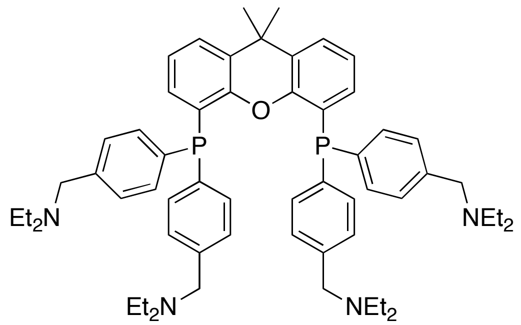

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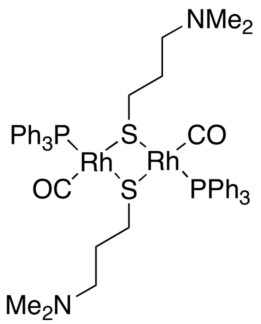
was greatly improved (l/b = 49 against 2.8 for ligand **8**)[19]. Rh/**9** catalyst was used in the hydroformylation of 1-hexene and could be separated from the reaction products using aqueous extraction with methane sulfonic acid[20]. Neutralisation with KOH and reextraction into toluene allowed the recovery of 86% of the catalyst's initial activity (TOF = 736 h^{-1}). With an improved extraction procedure, *i.e.* extraction with HCl, neutralization followed by anion metathesis with $NaBPh_4$, the catalyst could be recycled 3 times without loss in activity[21]. Interestingly, ligand **9** has also been used in a reverse system for the hydrocarbonylation of pentenoic acid in water[22]. In this system, the reaction takes place in a homogeneous acidic aqueous phase that is neutralized at the end of the reaction and the catalyst is then extracted into toluene leaving the diacid product in the aqueous phase. The catalyst could be reused by reextraction into acidic water, showing only slight decrease in activity. Dinuclear rhodium complexes with bridging thiol ligands have also been developed as recoverable catalysts. Complex **11** was used for the hydroformylation of 1-hexene and could be recovered and reused without loss in activity by precipitation with aqueous H_2SO_4 followed by dissolution in a basic aqueous phase and reextraction with an organic solvent[23]. Complex **12** or its sodium salt was used



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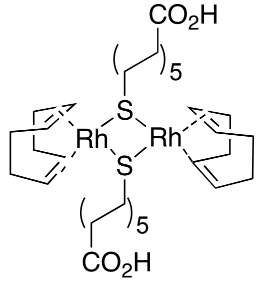

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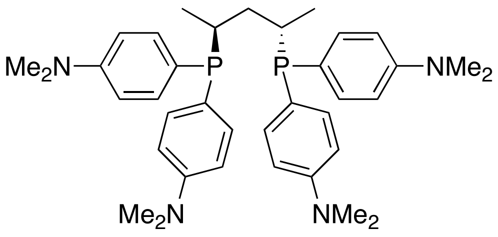
for the hydroformylation of substituted styrenes and terminal alkenes in an aqueous biphasic system and in THF[24]. When the reaction was carried out in THF, the catalyst could be precipitated by treatment with NaOH, recovered, dissolved in water and then precipitated by addition of HCl. According to the authors, the recovered solid could be reused in hydroformylation showing similar activity. Interestingly, the concept of acid/base transfer of the catalyst was used for recycling enantioselective catalysts. A SkewPhos ligand bearing dimethylamino groups, **13,** has been shown to protonate reversibly at the nitrogen when coordinated to rhodium[25]. Rh/**13** catalyst was used for the homogeneous asymmetric hydrogenation of dehydro-amino acid derivatives in methanol with enantioselectivities up to 93%. The catalyst was separated by acidification with aqueous HBF_4 at the end of the reaction. The obtained aqueous solution containing the catalyst was further used for the hydrogenation of the same substrate as a slurry yielding the product with 97% ee. Rhodium leaching in the separated product was found to be 3.7



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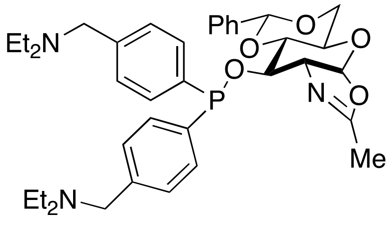

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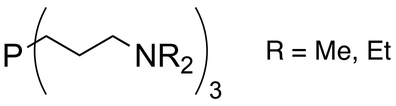
and 1.1 ppm for the first and second reaction, respectively. More recently, a phosphinite oxazoline chiral ligand, **14,** has been used as a ligand for palladium catalyzed asymmetric allylic substitution[26]. The reaction between dimethyl malonate and 1,3-diphenyl-3-acetoxyprop-1-ene was conducted in toluene yielding the product with 93% ee. The catalyst was recycled by protonation with aqueous HBF_4 followed by neutralization with $NaHCO_3$ and finally reextraction in toluene. Unfortunately, the recovered catalyst was much less active (5 % yield after 36 h against 85 % after 1 h with the fresh catalyst) but conserved an appreciable level of enantioselectivity (86 % ee). By replacing the toluene by THF, and slight modification of the extraction procedure, the recovered activity could be increased while keeping the same level of enantioselectivity.

Instead of acidic extraction, neutralisation and reextraction, *in-situ* formation of carbonic acid by addition of gaseous CO_2 to an aqueous phase and subsequent removal of the gas can be used to recycle catalysts bearing ligands with basic substituents. Alkyl phosphine **15**, bearing dialkylamine end groups has been used for the homogeneous rhodium catalysed hydroformylation of 1-octene[27]. After reaction, the crude reaction phase was contacted with gaseous CO_2 (3 bar) and then extracted 2 to 3 times with water saturated with CO_2. The aqueous phase was then contacted with fresh substrate and brought to boil in order to remove the CO_2. The fresh substrate phase, now containing the catalyst could be reintroduced into the reactor and hydroformylated under syngas. This allowed continuous operation for 100 to 200 hours but required constant addition of fresh catalyst to compensate for catalyst losses.



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Pressurized CO_2 can also be used to induce phase splitting of a homogeneous mixture of water and co-solvent into a gas-expanded liquid phase (GXL) and an aqueous phase[28]. This strategy has been used for the rhodium catalyzed hydroformylation 1-octene in a THF/H_2O mixture[29]. Pressurisation of the reactor with carbon dioxide after the reaction causes the separation of the phases, the catalyst remaining in the aqueous phase while the product is preferentially soluble in the GXL and thus can be separated from the catalyst. The catalyst was recycling 3 times using such an approach without noticeable decrease in activity. The rhodium leaching was found to be below the detection limit (< 1 ppm).

3.2 Aim and scope of this chapter

The two main triggers that have so far been used to promote phase or catalyst switching are temperature and pH swings. Promising results regarding activities and recycling of the catalyst have been obtained using those methodologies. However, for thermoregulated system, the heating and cooling cycles required an important energy input, especially in large-scale applications such as hydroformylation, which may impede their use for commercial application. For extraction and re-extraction techniques, several extractions are sometimes required with excess bases and acids generating substantial amounts of salt by-products.

In order to enable practical application of the attractive homogeneous reaction - biphasic separation methodology, benign triggers, having low energy requirement and generating no by-products, need to be developed. For this purpose, the early example developed by Andreetta *et al.* where aqueous carbonic acid generated from CO_2 and water was used as the extraction phase is particularly attractive[27]. However, only unselective and sensitive alkyl phosphine ligands bearing alkyl amine groups were suitable for this purpose. Moreover, a gradual decrease of activity was observed during continuous operation requiring addition of fresh catalyst to compensate for the losses.

Recently, Jessop and co-workers have described CO_2 phase-switchable surfactants[30]. They demonstrated that hydrophobic long chain alkyl amidines could be protonated and become water soluble surfactants upon addition of CO_2. The amidinium ion could then be deprotonated and returned to the organic phase by removing the CO_2 using N_2 (Figure 3. 2). This allowed the reversible formation and breaking of water-oil emulsions stabilized by the amidine-based surfactants. We reasoned that, by introducing amidine moieties onto phosphorus ligands, we could make catalysts for which the solubility could be switched using CO_2 as a trigger.

In this chapter we describe the synthesis of triphenylphosphine ligands bearing amidine groups and their use for the rhodium-catalyzed hydroformylation of 1-octene. We evaluate the recycling and reuse of such catalytic systems by aqueous extraction in the presence of CO_2 and re-extraction with fresh organic solvent with a nitrogen stream. We also explore the possibility of using such ligands for reactions in the aqueous phase in the presence of CO_2 followed by recycling using organic extraction with nitrogen and re-extraction in an aqueous phase with a CO_2 stream.

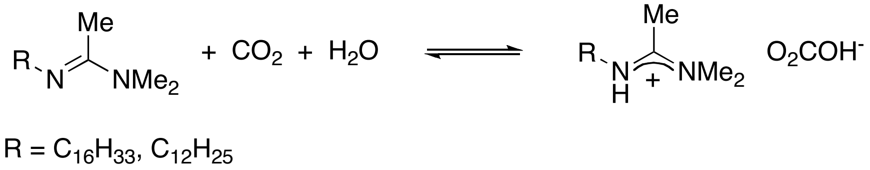


Figure 3. 2 *Reversible reaction of amidine-based surfactant with CO_2 and water.*

3.3 Results and discussion

3.3.1. Ligand synthesis

We prepared ligand based on triphenylphosphine bearing 1, 2 and 3 dimethylacetamidine groups on the meta position of the phenyl rings, respectively named mono-, bis- and tris-SwitchPhos (Figure 3. 3).

Mono-SwitchPhos was prepared by palladium catalyzed P-C coupling between diphenylphosphine and *m*-iodoaniline followed by condensation with dimethylacetamide dimethylacetal (Scheme 3. 1). The crystal structure of the obtained mono-SwitchPhos is presented in Figure 3. 4.

Bis- and tris-SwitchPhos were prepared by reaction of protected *meta*-amino phenymagnesium chloride with dichlorophenylphosphine and phosphorus trichloride, respectively. Methanolysis afforded the deprotected bis- and tris-*m*-amino triphenylphosphine. The corresponding dimethylacetamidines were obtained by condensation with dimethylacetamide dimethylacetal under microwave irradiation (Scheme 3. 2).

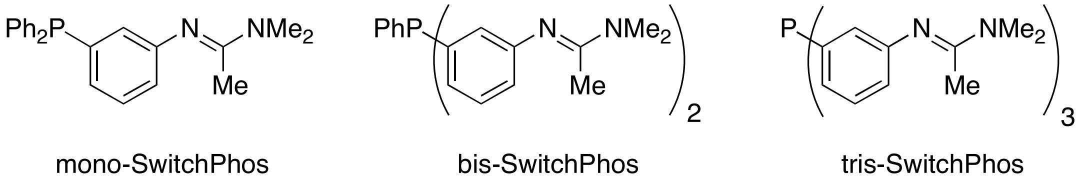
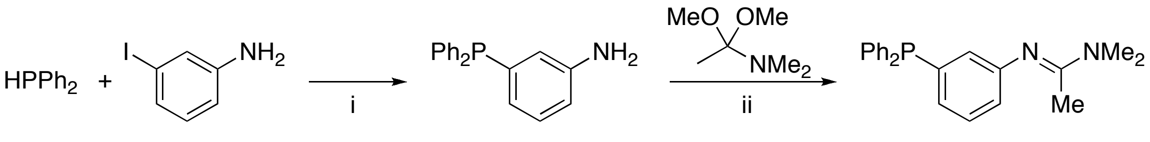


Figure 3. 3 *Structure of the new switchable ligands.*



Scheme 3. 1 *Synthesis of mono-SwitchPhos. (i: $Pd(OAc)_2$, DMA, KOAc, Δ, 4.5 h; ii: Toluene, Δ, 14h)*

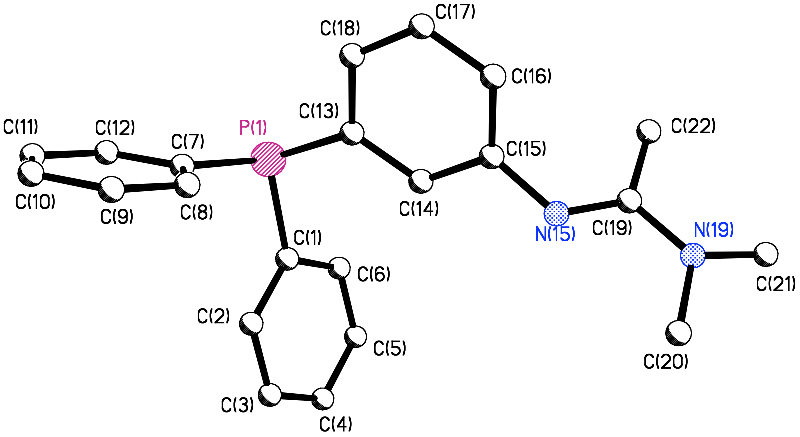
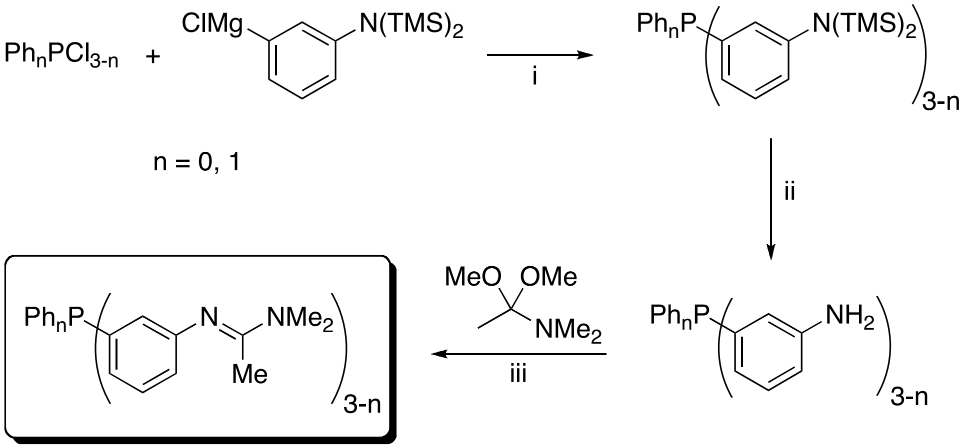


Figure 3. 4 *Molecular structure (ORTEP plot) of mono-SwitchPhos (hydrogen atoms are omitted for clarity).*

The crystal structure of the obtained tris-SwitchPhos is presented in (Figure 3. 5)

3.3.2. Catalysis using mono-SwitchPhos

Mono-SwitchPhos was tested for the homogeneous rhodium-catalyzed hydroformylation of 1-octene followed by recycling using aqueous extraction in the presence of CO_2 followed by re-extraction with a nitrogen stream. The catalyst was



Scheme 3. 2 *Synthesis of bis- and tris-SwitchPhos (i: THF, RT, 1 h; ii: MeOH, Δ, 14 h; iii: MW, 160 °C, 1 h).*

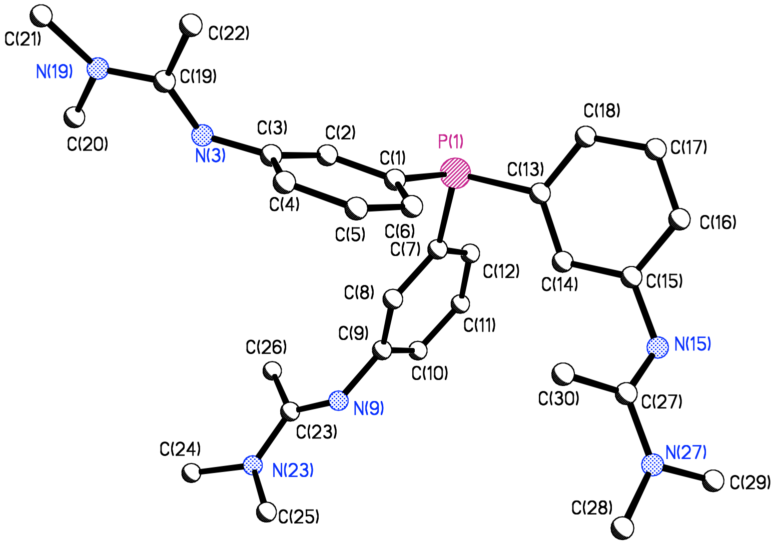


Figure 3. 5 *Molecular structure (ORTEP plot) of tris-SwitchPhos (hydrogen atoms are omitted for clarity).*

prepared *in-situ* by bubbling syngas into toluene containing [Rh(acac)$(CO)_2$] (acacH: 2,4-pentanedione) and mono-SwitchPhos at 60°C yielding a yellow solution.

The hydroformylation of 1-octene was carried in a constant pressure reactor. In this system, the syngas pressure inside the autoclave is maintained constant via a pressure regulator attached to a ballast vessel which pressure can be recorded over time allowing gas uptake curves to be obtained. Initial turnover frequencies (TOF_0) were calculated by linear regression at the origin of the gas uptake curve obtained (corresponding to 20 % conversion).

The catalytic system was found to be very active with almost complete conversion after 15 min (Table 3. 1). The linear selectivity was found to be in the expected range for monodentate triaryl phosphines. The gas uptake curve recorded is typical of a reaction being first order in 1-octene (Figure 3. 6, cycle 1). After the reaction, water was added to the yellow-orange reaction solution (Figure 3. 7.a). The biphasic system was stirred for 5 min at room temperature and left to settle. Visual observation did not show any change in

Table 3. 1 *Hydroformylation of 1-octene using mono-SwitchPhos*[a]

Cycle	Time (min)	Aldehydes (%)	Isomerised octenes (%)	l/b	TOF_0 (h^{-1})
1	15	91.7	3.5	2.6	14850
2	17	90.3	5.4	2.5	5890

a: Reaction conditions: 100 °C, 20 bar, CO:H_2 = 1:1, stirring rate = 1000 rpm, [Rh] = 1 10^{-3} mol dm^{-3}, P/Rh = 10, toluene : 8 cm^3, 1-octene : 2 cm^3

colouration of either phases (Figure 3. 7. b). This indicates that the catalyst seems not to transfer significantly to the aqueous phase in the absence of CO_2. CO_2 was then gently bubbled trough the system with stirring at room temperature. The aqueous phase quickly changed from colourless to yellow indicating some transfer of the catalyst. The bubbling was continued for 1 h leaving both phases with a yellow colouration (Figure 3. 7. c). The organic phase was separated and analyzed by gas chromatography (Table 3. 1, cycle 1). Fresh toluene was added to the aqueous phase (Figure 3. 7. d) and N_2 was bubbled with stirring for 3 h at 70°C. After the bubbling the aqueous phase was found to have

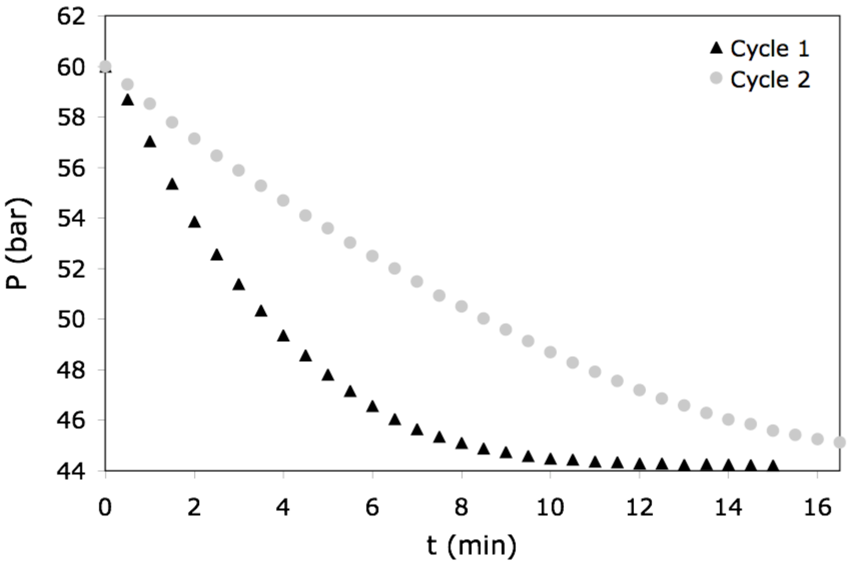


Figure 3. 6 *Gas uptake curves from a ballast vessel obtained for the hydroformylation of 1-octene using Rh/mono-SwitchPhos.*

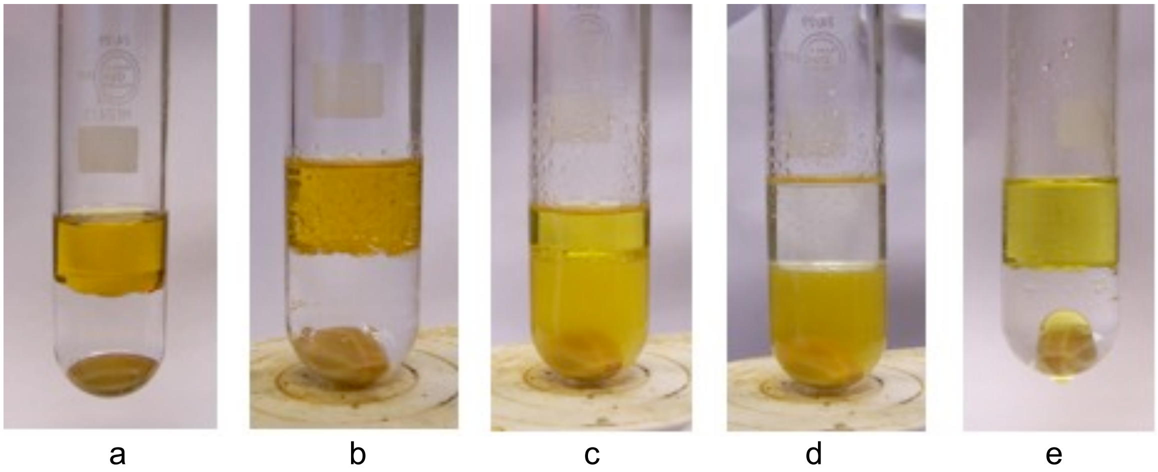


Figure 3. 7 *Photographs obtained during the catalyst recycling process (Rh/mono-SwitchPhos; P/Rh = 10). a) The reaction solution from cycle 1 with added water; b) after 5 min stirring at RT; c) after 1h stirring and* CO_2 *bubbling at RT; d) after phase separation and addition of fresh toluene; e) after bubbling* N_2 *for 3h at 70°C.*

completely discoloured while the organic phase had turned yellow indicating transfer of the catalyst to the organic phase (Figure 3. 7. e).

The organic phase, containing the recycled catalyst, was transferred to the reactor, fresh 1-octene was added and another hydroformylation reaction was carried out. The recycled catalyst was found to be active but only at 40 % of the initial activity (Figure 3. 6, cycle 2; Table 3. 1, entry 2). The selectivity toward the linear aldehyde was found to be very similar to that obtained with the fresh catalyst, albeit a slightly increased amount of isomerised octene was found.

These preliminary results indicate that the introduction of one amidine group onto the phenyl ring of triphenylphosphine allows the catalyst to be recycled by phase switching using CO_2 as a trigger. However, as indicated by the persisting yellow colouration of the organic phase after CO_2 bubbling (Figure 3. 7. c), the transfer into the aqueous phase is not complete and a substantial amount of the catalyst stays dissolved in the organic phase. One amidinium group per ligand may not impart enough water solubility to the catalyst for the partitioning to be complete. We, therefore, tested the tris-SwitchPhos ligand for the hydroformylation of 1-octene, presuming that three amidine moieties per ligand would improve the catalyst partitioning.

3.3.3. Catalysis using tris-SwitchPhos

The catalyst was prepared in-situ following the same procedure used for Rh/mono-SwitchPhos. ^{31}P-{^{1}H}-NMR analysis of the catalytic solution showed the typical signals for the free phosphine (-3.47 ppm) and a doublet corresponding to the phosphine bounded to the rhodium center (36.10 ppm, $J_{P\text{-}Rh}$ = 148 Hz).

The hydroformylation of 1-octene, under the same conditions as with Rh/mono-Switchphos (see Table 3. 1 footnote a), was carried out twice with two different freshly prepared catalytic solutions to ensure reproducibility. The recorded gas uptakes were very similar (Figure 3. 8, cycles 1a and 1b). The catalyst was found to be very active (TOF_0 of 7360 $h^{-1}$and 7280 h^{-1} were observed,) although less active than the mono substituted analog, mono-SwitchPhos (Table 3. 1, cycle 1).

The recycling procedure was carried out as follows. The crude reaction solution from cycles 1a and 1b were combined and added to water (Figure 3. 9.1.a). The system was stirred for 10 min and left to settle to allow for observation of changes in phase colouration in the absence of carbon dioxide (Figure 3. 9.1.b). Then, CO_2 was gently bubbled trough the stirred system at room temperature for a total of 1.5 h with intermediate observations of the settled system (Figure 3. 9.1.c to 3.9.1.f). The phases were separated; the organic phase was analyzed by gas chromatography for the organic content and by inductively coupled plasma mass spectroscopy (ICP-MS) for the rhodium

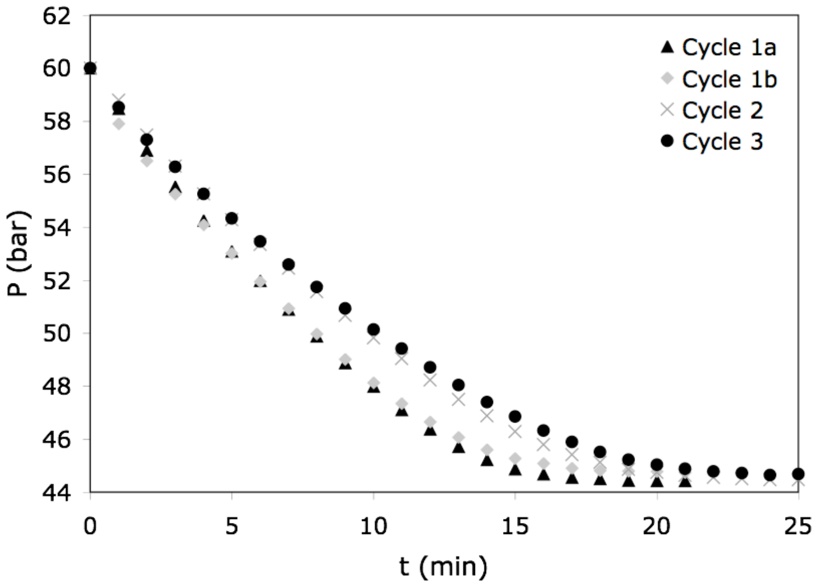


Figure 3. 8 *Gas uptake curves from a ballast vessel obtained for the hydroformylation of 1-octene using Rh/tris-SwitchPhos (P/Rh = 10).*

content (Table 3. 2, entry 1 and 2). Fresh toluene was added to the aqueous phase (Figure 3. 9.1.g) and the system was stirred for 10 min and left to settle to allow for observation of changes in phase colouration in the absence of nitrogen bubbling (Figure 3. 9.1.h). N_2 was gently bubbled through the stirred system at room temperature for 10 min. Observation of the settled system allowing for evaluation of the change in phase colouration in the presence of N_2 (Figure 3. 9.1.i). Nitrogen was then gently bubbled trough the stirred system at 60 °C for a total of 1.5 h with intermediate observations of the settled system (Figure 3. 9.1.j to 3.9.1.l). The toluene phase was separated, and after addition of fresh toluene to compensate for the losses by evaporation, a portion of the recycled catalytic solution (corresponding to the same volume used for cycle 1a and 1b) was used to carry another hydroformylation of fresh 1-octene (Figure 3. 8, cycle 2). The remaining recycled catalytic phase was kept aside (solution A). For the following recycling procedure, the crude product solution from the second cycle was combined with solution A and recycled via the same procedure (Figure 3. 9.2.a to 3.9.2.l and Table 3. 2, entry 3)[†]. A portion of the recycled catalytic phase was used for a third catalytic run (Figure 3. 8, cycle 3). The crude reaction product solution from cycle 3 together with the remaining recycled catalytic phase from cycle 2 were combined and recycled (Figure 3. 9.3.a to 3.9.3.l and Table 3. 2 entry 4). In all cases the same volume of catalytic solution was used for each reaction.

From the changes in phase colouration observed during the three catalyst recycling, several qualitative observations can be made. As for mono-SwitchPhos, the catalyst seems not to transfer significantly from the organic to the aqueous phase in the absence of CO_2 (Figure 3. 7.b and Figure 3. 9.1.b, 3.9.2.b and 3.9.3.b). When CO_2 is present, the organic phase almost completely decolourise while the aqueous phase turns yellow. This indicates that the catalysts transfer to the aqueous phase is much more efficient when

Table 3. 2 *Hydroformylation of 1-octene using Rh/tris-SwitchPhos (for reaction conditions see footnote a in Table 3. 1).*

Entry	Catalyst	Time (min)	Aldehydes (%)	Isomerised octenes (%)	l/b	TOF_0 (h^{-1})	$[Rh]_{org}$ (ppm)
1	Cycle 1a	21	94.6	2.1	2.7	7360	19.5
2	Cycle 1b	23				7280	
3	Cycle 2	25	93.3	2.2	2.7	5910	16.5
4	Cycle 3	25	93.4	2.2	2.7	5710	20.9

[†] This procedure allows carrying out the recycling with the double amount of catalytic solution required for one hydroformylation reaction ensuring that, having mechanical losses (droplets left on the wall of the glassware, liquid remaining in syringe needles, etc), the amount of catalyst and its concentration used for each run is kept constant. All the catalyst used is subjected to the recycling procedures. This ensures that there is no compensation for the eventual leaching by addition of catalyst solution that would not have been recycled.

using tris- SwitchPhos instead of mono-SwitchPhos where the organic phase kept a persistent yellow colouration (Figure 3. 9.1.c, 3.9.2.c, 3.9.3.c and Figure 3. 7.c). Supporting this, the levels of rhodium found in the organic phase after 1.5 h of CO_2 bubbling were rather low, 19 ppm on average which corresponds to 5 % of the initial rhodium charged (Table 3. 2, entry 1, 2, 3 and 4). For the re-extraction, no significant transfer of the catalyst seems to take place in the absence of nitrogen (Figure 3. 9.1.h, 3.9.2.h and 3.9.3.h). Bubbling nitrogen at room temperature seems to transfer only a small quantity of the catalyst into the organic phase (Figure 3. 9.1.i, 3.9.2.i and 3.9.3.i). However, when the system is heated (60 °C), the transfer is much more efficient as shown by the quick and complete lost of colour of the aqueous phase (Figure 3. 9.1.j, 3.9.2.j and 3.9.3.j).

The recycled catalyst was found to be very active with a TOF_0 of 5910, *i.e.* 81 % of the initial activity found for fresh catalyst. After the second recycling very similar activity was found, $TOF_0 = 5710$, corresponding to 78 % of the initial activity. The recorded gas uptakes were very similar to those obtained with fresh catalysts and typical of the reaction being first order in alkene, *i.e.* no mass transfer limitation of the substrate. The linear selectivity, typical for Rh/monodentate triaryl phosphine catalyzed hydroformylation, and the amount of isomerised octene were found to be constant over the four runs (Table 3. 2, entry 1, 2, 3 and 4). This tends to indicate that the integrity of the catalyst is conserved through the recycling.

Tris-SwitchPhos is efficient in allowing catalyst recycling via CO_2 phase switching. High reaction rates are obtained and on average 80 % of the activity can be

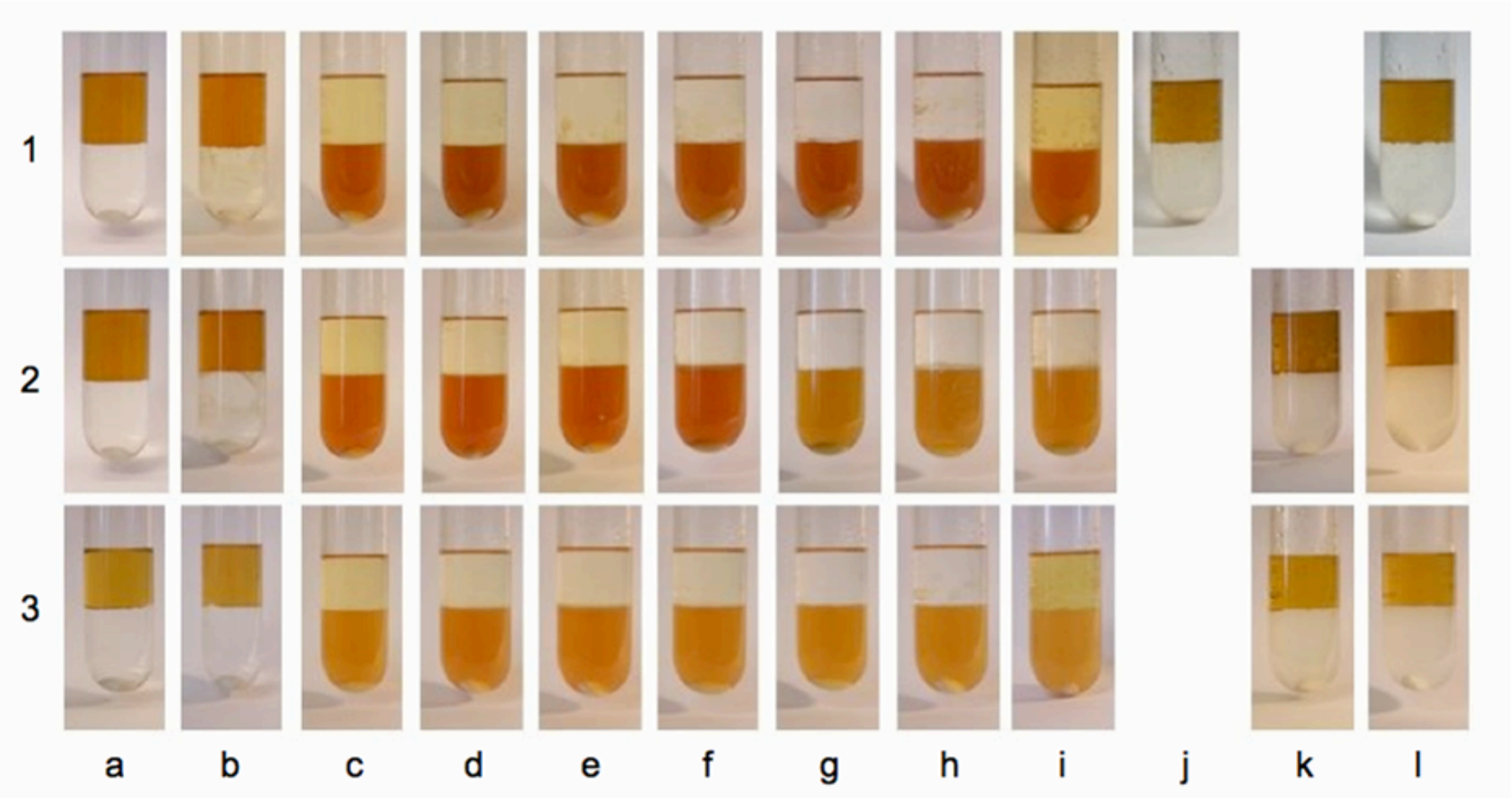


Figure 3. 9: *Photographs obtained during the catalyst recycling process (Rh/tris-SwitchPhos; P/Rh = 10). a) the crude reaction solution from cycle n with added water (number on left of row); b) after 10 min stirring; c) after 10 min stirring with* CO_2 *bubbling; d) after 30 min stirring with* CO_2 *bubbling; e) after 1 h stirring with* CO_2 *bubbling; f) after 1.5 h stirring with* CO_2 *bubbling; g) after phase separation and addition of fresh toluene; h) after 10 min stirring; i) after 10 min stirring with* N_2 *bubbling; j) after 30 min stirring at 60 °C with* N_2 *bubbling; k) after 1 h stirring at 60 °C with* N_2 *bubbling; l) after 1.5 h stirring at 60 °C with* N_2 *bubbling.*

recovered. The observed decrease in activity upon recycling is most likely due to rhodium leaching. However, only 5 % of the rhodium was found to leach from the aqueous phase. This does not account for the 20 % drop in activity observed after the first recycling. Rhodium can also leach during the re-extraction with toluene, which could explain the activity decreased observe. However, the 5 % of rhodium leaching found in the product phase is not acceptable for bulk chemical production such as hydroformylation. In order to improve the recovered activity and the metal retention, we carried the hydroformylation of 1-octene using a 50-fold excess of tris-SwitchPhos to rhodium and used the same recycling procedure.

The gas uptake curves obtained with two different fresh catalyst solutions were found to be very similar (Figure 3. 10). Surprisingly, the activity of the catalyst was found to be higher than that observed with a lower excess of ligand (TOF_0 = 11050 h^{-1} and 10000 h^{-1} for P/Rh = 50; TOF_0 = 7360h^{-1} and 7280 h^{-1} for P/Rh = 10). The changes in phase colouration during the catalyst recycling were found to be similar to those previously

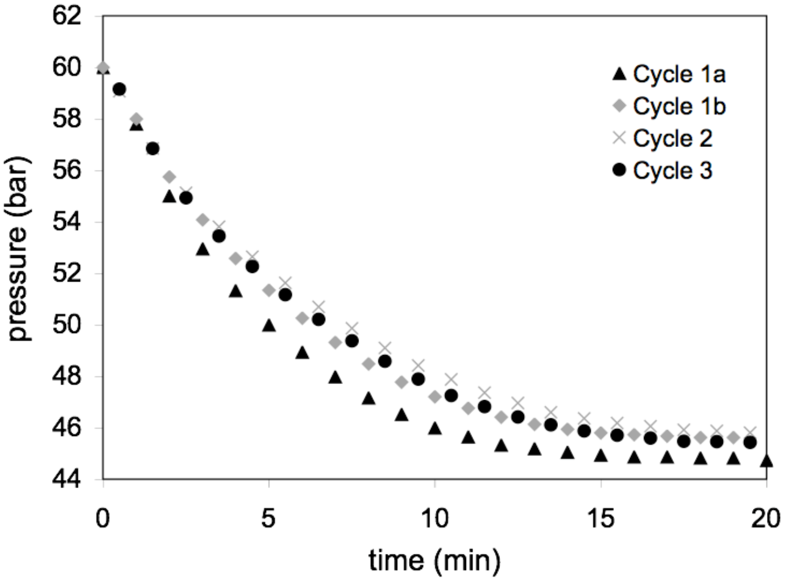


Figure 3. 10 *Gas uptake curves from a ballast vessel obtained for the hydroformylation of 1-octene using Rh/tris-SwitchPhos (P/Rh = 50).*

observed with a lower ligand excess (Figure 3. 11). However, when bubbling CO_2 for 30 min with a 50-fold excess of tris-SwitchPhos, the organic phase completely decolourise while, with a 10-fold excess ligand, a slight yellow colouration persisted even after 1.5 h of bubbling. This suggests that the transfer of the catalyst to the aqueous phase is more efficient with increased excess ligand. Supporting this, very little rhodium was found in the organic phases after CO_2 bubbling (1 ppm on average, 0.3 % of the initial rhodium charged), *ca.* 20 times lower on average than with a 10-fold excess of phosphine (Table 3. 2 and 3.3). To get a better insight into the reverse transfer, the rhodium content in the aqueous phase after nitrogen bubbling was determined by inductively coupled plasma optical emission spectroscopy (ICP-OES). Very low concentrations of the metal were detected (0.4 ppm on average, 0.1 % of the initial rhodium charged) indicating almost complete transfer of the catalyst from the aqueous to the organic phase under nitrogen bubbling. Based on the rhodium leaching measurements, both transfers of the catalyst between the phases, triggered by CO_2 or N_2, seem to proceed with more than 99 % efficiency. The separated organic and aqueous phases arising from the tree recycling

Table 3. 3 *Hydroformylation of 1-octene using a 50 –fold excess of tris-SwitchPhos (for reaction conditions see footnote a in Table 3. 1)*^{b}.

Entry	Catalyst	Aldehydes (%)	Isomerised octenes (%)	l/b	TOF_0 (%)	$[Rh]_{org}$ (ppm)	$[Rh]_{aq}$ (ppm)
1	Cycle 1a	92.8	3.2	2.9	11050	1.9	0.4
2	Cycle 1b				10000		
3	Cycle 2	94.4	1.2	2.8	9660	0.7	0.3
4	Cycle 3	90.9	4.7	2.8	9560	0.4	0.5

b : reaction time: 20 min.

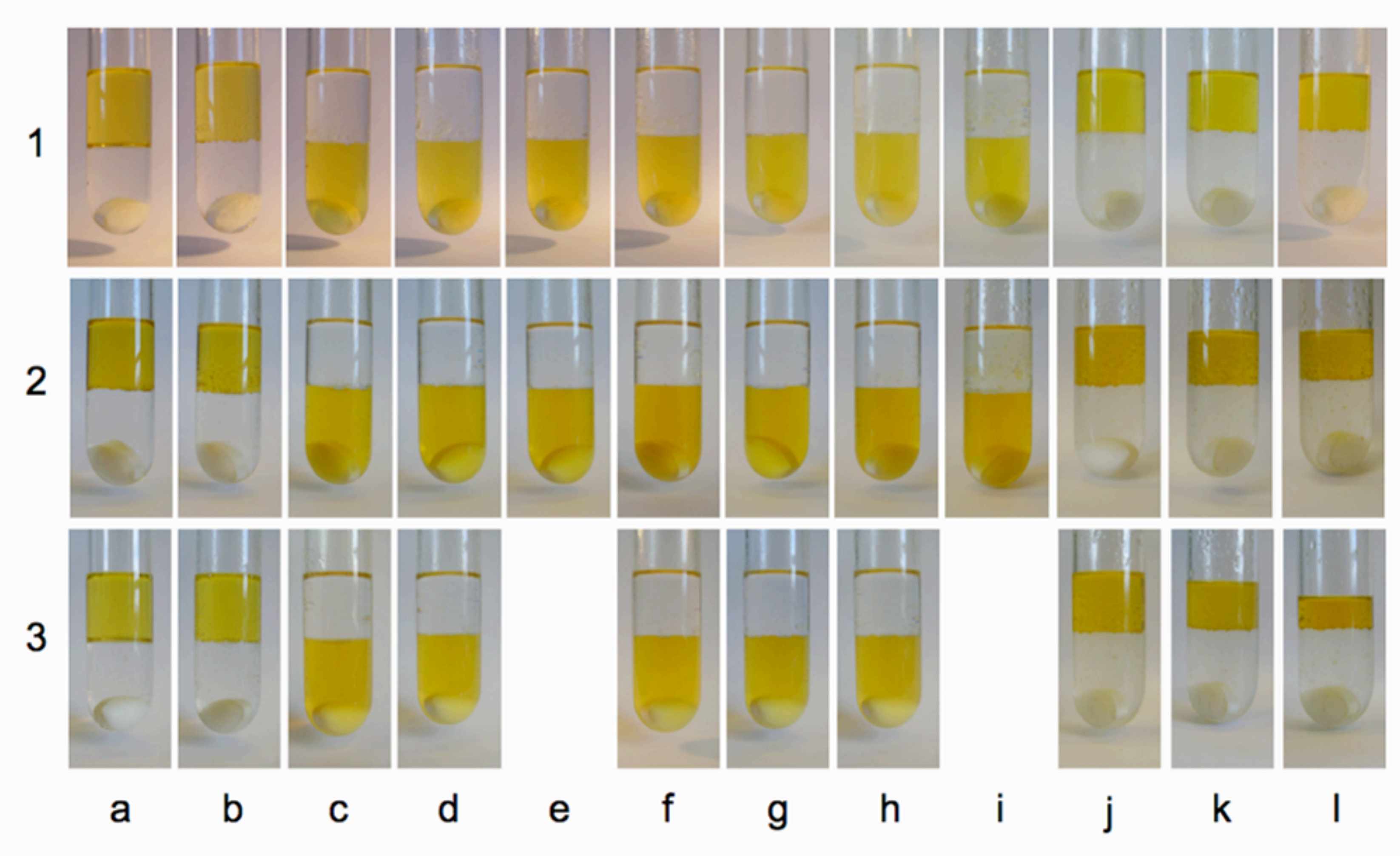


Figure 3. 11 *Photographs obtained during the catalyst recycling process (Rh/tris-SwitchPhos; P/Rh = 50). a) the crude reaction solution from cycle n with added water (number on left of row); b) after 10 min stirring; c) after 10 min stirring with CO_2 bubbling; d) after 30 min stirring with CO_2 bubbling; e) after 1 h stirring with CO_2 bubbling; f) after 1.5 h stirring with CO_2 bubbling; g) after phase separation and addition of fresh toluene; h) after 10 min stirring; i) after 10 min stirring with N_2 bubbling; j) after 30 min stirring at 60 °C with N_2 bubbling; k) after 1 h stirring at 60 °C with N_2 bubbling; l) after 1.5 h stirring at 60 °C with N_2 bubbling*

procedures were all clear and colourless (Figure 3. 12). The recycled catalysts were found to be very active with 92 % of the average initial activity being recovered after the first recycling. Taking into account the experimental error observed for the two first cycles with fresh catalyst (Cycle 1a and 1b), the recovered activity might be higher. Very little deactivation was found after the second recycling, with 99% of the previous catalyst activity being recovered. All the gas uptakes curves were very similar with an apparent first order dependence of the substrate concentration on the reaction rate. The linear selectivity of the different catalyst was found to be consistently constant. The amount of isomerised octenes showed a rather random variation.

^{31}P-{^{1}H}-NMR analysis of the catalytic solution after the third recycle showed the presence of free (-3.59 ppm) and coordinated phosphine (39.98 ppm, $J_{P\text{-}Rh}$ = 153.5 Hz) as well as a small amount of phosphine oxide (<5 %). This indicates that the integrity of the catalyst seems to be conserved thorough the recycling procedure and that oxidation of the ligand is not a serious issue.

From all these results, it appears that using tris-SwitchPhos in 50-fold excess allows

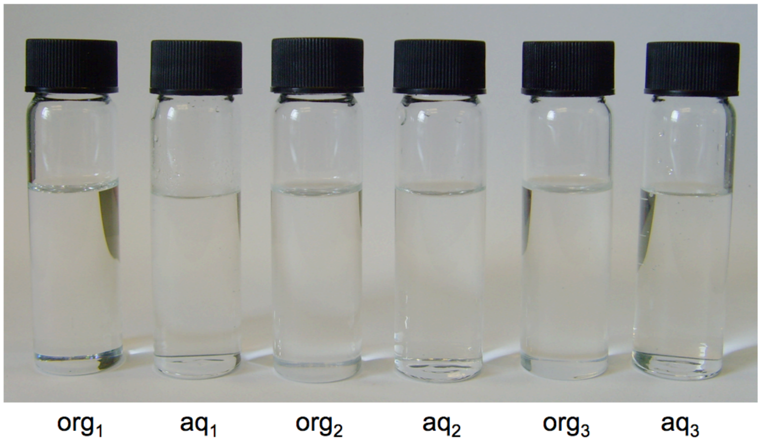


Figure 3. 12 *Photographs of the separated organic phases recovered after aqueous extraction in the presence of CO_2 from cycle n (org_n) and of the separated aqueous phases recovered after organic extraction in the presence of N_2 from cycle n (aq_n).*

efficient recycling of the catalyst. The amounts of rhodium leaching during the recycling process are 20 times lower than with a 10-fold excess ligand. Moreover, at least 92 % of the initial activity could be recovered. More importantly, the catalyst seems to go through the numerous successive extractions and re-extractions without major structural changes as observed in the NMR of the final recovered catalyst solution.

3.3.4. Reverse system – Hydroformylation of allyl alcohol.

Since the catalyst can be reversibly made organic- or water-soluble, we investigated the possibility of carrying out the reaction in the aqueous phase with subsequently recycling the catalyst by organic extraction triggered by nitrogen followed by re-extraction in water using CO_2 as a trigger. Therefore, we carried out the hydroformylation of allyl alcohol, a water-soluble substrate, using a rhodium - tris-SwitchPhos catalyst in water.

The catalyst was prepared *in-situ*. The rhodium precursor, $[Rh(acac)(CO)_2]$, and tris-SwitchPhos do not dissolve in water. However, when CO_2 was bubbled trough the slurry under ultrasonic irradiation, a clear yellow solution was obtained. Bubbling syngas through the system resulted in the formation of a precipitate, presumably the non-protonated phosphine resulting from stripping of the carbon dioxide. Bubbling CO_2 reformed a clear yellow solution. ^{31}P-$\{^1H\}$-NMR analysis of the aqueous catalytic solution obtained showed the typical signals for the free phosphine (-6.57 ppm) and a doublet corresponding to the phosphine bounded to the rhodium center (40.81 ppm, $J_{P\text{-}Rh}$ = 154 Hz).

The catalyst solution was used for the hydroformylation of allyl alcohol in water under a constant pressure of syngas (20 bar) at 75 °C. The gas uptake curves, shown in Figure 3. 13, indicate that the reactions are slower than for 1-octene and do not proceed to completion in 60 min, although it should be noted that the reactions were carried out at a lower temperature (75 °C as opposed to 100 °C for 1-octene hydroformylation). The curves also have an unusual shape, but are reproducible (Figure 3. 13, cycles 1a and 1b).

The recycling of the catalyst was carried out as for 1-octene hydroformylation, but starting by bubbling N_2 for 1.5 h at 60 °C and, after phase separation and addition of fresh water, bubbling of CO_2 for 1.5 h at room temperature (Figure 3. 14). From the observation of the change in phase colouration during the recycling of the catalyst, it seems that the transfer of the catalyst from the aqueous phase to the toluene phase in the presence of nitrogen is not complete. A pale yellow colouration persists in the aqueous phase after bubbling nitrogen for 1.5 h at 60°C (Figure 3. 14.1.g and 3.14.2.g). However,

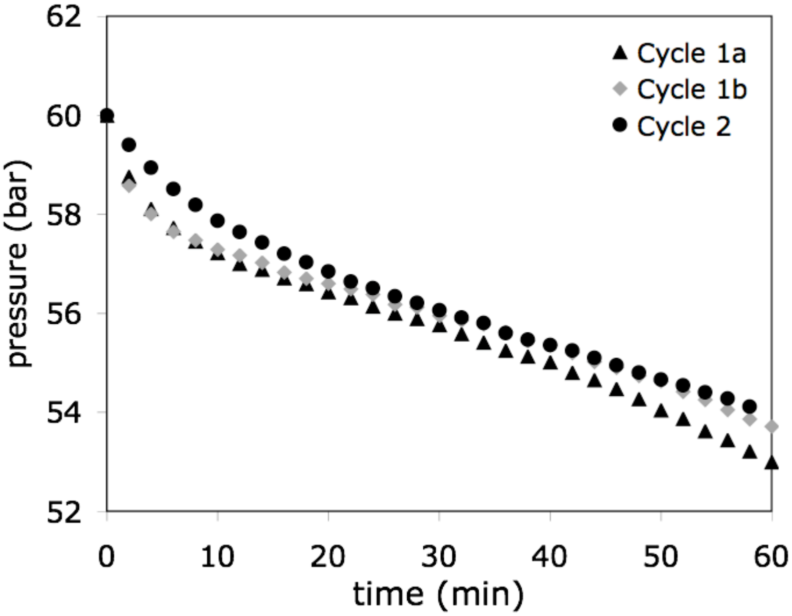


Figure 3. 13 *Gas uptake curves from a ballast vessel obtained for the hydroformylation of allyl alcohol using Rh/tris-SwitchPhos (P/Rh = 10).*

the re-extraction of the catalyst into the aqueous phase triggered by CO_2 seems more efficient owing the lack of colouration of the organic phase after 1.5 h of bubbling. The levels of rhodium found in the remaining aqueous and organic phases after extraction support this (Table 3. 4). On average, rhodium concentrations of 11.4 ppm were detected in the aqueous phase while only 0.55 ppm were detected in the organic phase. High rhodium leaching was also found for the hydroformylation of 1-octene where an identical ten-fold excess ligand was used, albeit in the opposite phase (Table 3. 2). The gas uptake profile recorded when using the recycled catalyst was very similar to those obtained with fresh catalyst (Figure 3. 13).

$^{13}C\{^1H\}$-NMR analysis of the aqueous phases recovered after extraction with toluene under nitrogen bubbling was used for the analysis of the reaction products. While the gas uptake curves obtained with fresh and recycled catalyst were very similar, the amount of products detected varied considerably. From cycles 1a and 1b, 23 % of aldehydes were detected while 62 % aldehydes for cycle 2 (Table 3. 4). This disagrees with the

Table 3. 4 *Hydroformylation of allyl alcohol using a 10-fold excess of mono-SwitchPhos*[a].

Entry	Catalyst	Aldehydes[b] (%)	Aldehydes[c] (%)	l/b[c]	$[Rh]_{aq}$ (ppm)	$[Rh]_{org}$ (ppm)
1	Cycle 1a	37	23	10	12.9	0.8
2	Cycle 1b	37				
3	Cycle 2	31	62	- [d]	9.9	0.3

a: Reaction conditions: 75 °C, 20 bar, CO:H_2 = 1:1, stirring rate = 1000 rpm, [Rh] = 1 10^{-3} mol dm^{-3}, P/Rh = 10, water : 4 cm^3, allyl alcohol : 1 cm^3. b: Calculated from the total gas uptake. c: Calculated from the $^{13}C\{^1H\}$-NMR spectra of the aqueous phase after separation of the catalyst. d: the branched product could not be detected by $^{13}C\{^1H\}$-NMR.

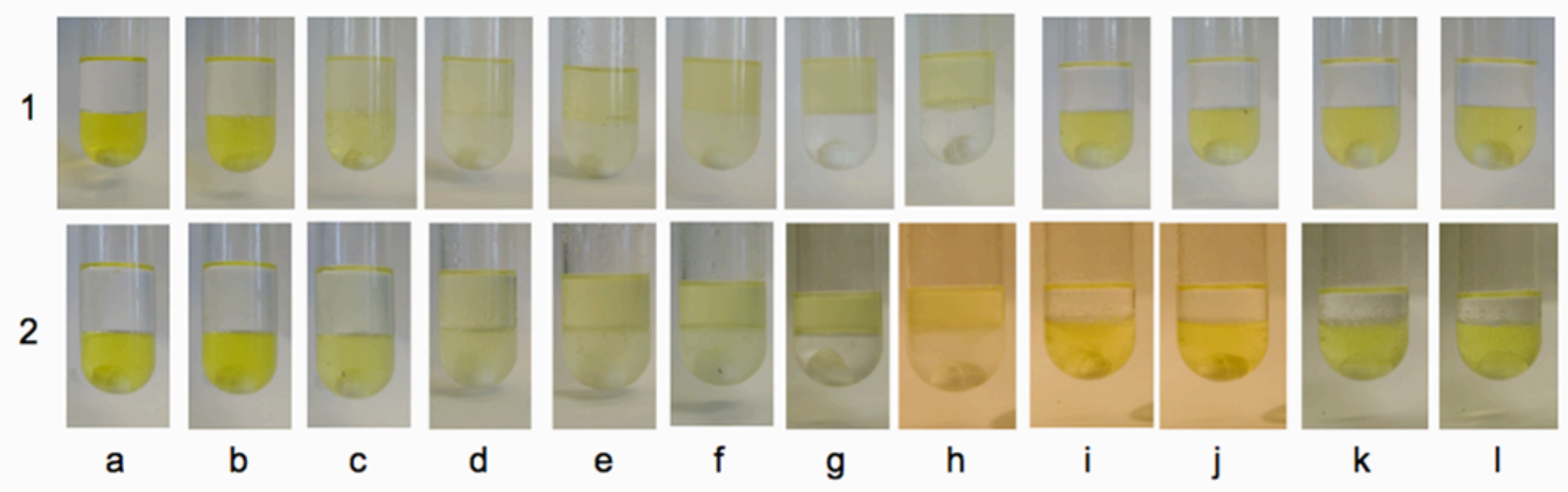
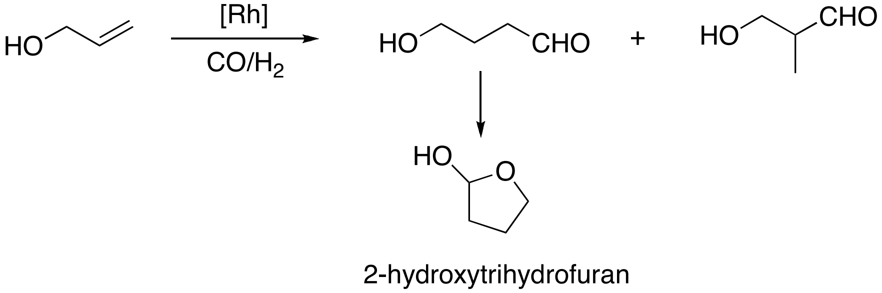


Figure 3. 14 *Pictures obtained during the catalyst recycling process for hydroformylation of allyl alcohol. (a) The crude product from cycle n with added toluene; (b) after 10 min stirring; (c) after 10 min stirring at room temperature with N_2 bubbling; (d) after 30 min stirring at 60°C with N_2 bubbling; (e) after 1h stirring at 60°C with N_2 bubbling; (f) after 1.5 h stirring at 60°C with N_2 bubbling; (g) after the aqueous phase had been separated and fresh water added; (h) after 10 min stirring without CO_2; (i) after 10 min stirring with CO_2 bubbling;(j) after 30 min stirring with CO_2 bubbling; (k) after 1h stirring with CO_2 bubbling; (l) after 1.5 h stirring with CO_2 bubbling*

theoretical amount of product calculated from the syngas consumption (Table 3. 4). However, it might be possible that part of the product is extracted with the catalyst leading to an underestimation of the yield when analyzing the aqueous phase for products. The product could then be re-extracted in the aqueous phase and so reintroduced in the reactor. This would lead this time to an overestimate yield for the second cycle. This would be especially true if the partitioning of the product between the phases depends on the pH of the system. A careful analysis of both phases using HPLC or LC-MS and GC would greatly help in understanding the observed discrepancies in yield.

Regarding the linear selectivity, to our surprise, almost only 2-hydroxytrihydrofuran, arising from intramolecular cyclisation of the linear product was detected (Table 3. 4 and Scheme 3. 3). This very high linear selectivity for monodentate triaryl phosphines could be due to the formation of the cyclic hemiacetal, which is promoted in the slightly acidic water.

CO_2-switchable catalysts seem to be suitable to carry out catalyst recycling in a reverse system. However, the catalyst is found to be less efficient for the hydroformylation of allyl alcohol than for the hydroformylation of 1-octene. A careful analysis of the products would be highly desirable to further evaluate this system.



Scheme 3. 3 *Hydroformylation of allyl alcohol.*

3.4 Conclusion

We have developed a new methodology for the separation of the products from the catalyst in homogeneous catalytic reactions. It involves using ligands that can be protonated by carbonic acid, generated from dissolution of gaseous CO_2 in water, thereby switching the catalyst from being organic soluble to water soluble. The catalyst can be returned to the organic phase by flushing the CO_2 with nitrogen under gentle heating. No residues, *i.e.* salt by-product, accumulate during the process and all phase switchings proceed under mild conditions.

Providing the ligand bears enough “switchable moieties”, the transfer from and to both phases is complete allowing almost full recovery of the high initial catalyst activity.

We have also used this methodology for the reverse system, *i.e.* aqueous reaction followed by recycling. However, optimization and further studies are needed.

Although we only tested this catalytic system for hydroformylation, we do believe it could be advantageously apply to numerous other catalytic reactions.

3.5 Experimental

3.5.1. General

All experiments were carried out under dry argon on a vacuum line using standard Schlenk techniques.

Gases; argon, nitrogen, carbon dioxide and syngas, were purshased from BOC gases. Water was distilled, degassed by vacuum and stored under argon. $[Rh(acac)(CO)_2]$, and diphenylphosphine were obtained from Strem chemical in the highest purity and were used as received. 3-iodoaniline, dimethylacetamide, phenyl dichlorophosphine, 3-[Bis(trimethylsilyl)amino]-phenylmagnesium chloride (1.0 M solution in tetrahydrofuran), potassium acetate and palladium acetate were obtained from Aldrich in the highest purity and were used as received. Phosphorus trichloride (Aldrich, 99 %) and dimethylacetamide dimethylacetal (Aldrich, 90 % or prepared according to [31]) were distilled under argon and stored under argon. 1-octene (Aldrich, 98 %) was purified from peroxides by extraction with aqueous $(NH_4)_2Fe(SO_4)_2.6H_2O$ followed by filtration trough basic alumina and stored in the dark under Argon. Allyl alcohol (Aldrich, 99 %) was degassed and stored under argon. Solvents; diethylether, tetrahydrofuran, hexane, petroleum ether 40-60, toluene, dicholoromethane, methanol, isopropanol, were distilled over the appropriate drying agent, degassed and stored under argon.

Gas chromatography analyses were carried out using a Hewlett-Packard 5890 series gas chromatograph equiped with a flame ionisation detector (FID) fitted with a Supelco MDN-35 (35 % phenyl/65 % methyl-polysiloxane) capillary column for quantitative analysis. The temperature programme used was: 50 C (4 min), Δ 20 °C/min to 130°C (2 min), Δ 20°C/min to 260 (13.5 min). The temperature of the injector and the detector were both 250 °C. The split ratio used was 100/1. Helium was used as the carrier gas with a flow of 1 ml min^{-1}.

^{13}C, ^{1}H and ^{31}P NMR spectra were recorded on Bruker AM 300/400 NMR spectrometers or a Varian 300 NMR spectrometer. Broadband decoupling was used for ^{13}C and ^{31}P NMR spectra. ^{1}H and ^{13}C NMR spectra were referenced internally to deuterated solvents, which were referenced relative to TMS at $\delta = 0$: $CDCl_3$: ^{1}H, $\delta = 7.27$ ppm, ^{13}C, $\delta = 77.23$ ppm; D_2O: $^{1}H = 4.53$ ppm. ^{31}P NMR spectra were referenced externally to 85 % H_3PO_4. Coupling constants are given in Hz.

3.5.2. Ligand synthesis

Synthesis of 3-(diphenylphosphino)aniline (adapted procedure from[32]*)*

In a round bottom-flask equipped with a magnetic stirrer and a dry argon inlet, 3-iodoaniline (5.04 g, 23 mmol) was introduced. Dimethylacetamide (25 cm^3), potassium acetate (2.7 g, 27.5 mmol) and Pd(II)acetate (52.7 mg, 0.23 mmol) were added. The suspension obtained was degassed *in vacuo*. After addition of diphenyl phosphine (4 cm^3, 23 mmol), the round-bottom flask was equipped with a reflux condenser topped with a dry argon bubbler. The mixture was heated under reflux for 4.5 h. Water (125 cm^3) and CH_2Cl_2 (50 cm^3) were added to the reaction mixture. The water phase was discharged and the organic phase was washed with water (3 x 15 cm^3), dried over Na_2SO_4 and evaporated *in vacuo.* The brown solid obtained was purified by column chromatography over silica using CH_2Cl_2 as eluant. After evaporation of the solvent, the product was obtained as a white solid (2.7 g, 42 %).

^{1}H-NMR (300 MHz; $CDCl_3$) δ 3.64 (2H, s, broad, NH_2), 6.68 - 7.35 (14H,m); $^{31}P\{^1H\}$-NMR (300 MHz, $CDCl_3$) δ 4.87 (s). In agreement with literature data[32]

MonoSwitchPhos - (N'-(3-(diphenylphosphino)phenyl)-N,N- dimethylacetimidamide)

3-(diphenylphosphino)aniline (2.7 g, 9.7 mmol), dimethylacetamide dimethylacetal (1.6 cm^3, 11 mmol) and toluene (10 cm^3) were introduced into a Schlenk tube equipped with a dry argon inlet, a magnetic stirrer and a reflux condenser topped with a dry argon bubbler. The solution obtained was heated under reflux for 14 h. After the reaction mixture had cooled to room temperature the reflux condenser was exchanged for a distillation head and the solvent; the methanol by-product and the unreacted dimethylacetamide dimethyl acetal were removed from the crude product by atmospheric pressure distillation. The light yellow oil obtained was further purified by column chromatography over silica using a gradient elution [$CH_2Cl_2 \rightarrow CH_2Cl_2:Et_2O$ (4:1)$\rightarrow$ $CH_2Cl_2:Et_2O$ (2:1)]. After evaporation of the solvent, a colorless oil that solidified as a white solid overnight was obtained. (0.7 g, 21%).

^{1}H-NMR (300 MHz; $CDCl_3$) δ 1.72 (3H, s, CMe), 2.91 (6H, s, NMe_2), 6.62 - 7.24 (14H, m, Ar). $^{31}P\{^1H\}$-NMR (300 MHz, $CDCl_3$) δ -4.81 (s). MS (ES) *m/z* $[M+H]^+$: 347.09. Anal. Calcd for $C_{22}H_{23}N_2P$: C, 76.28; H, 6.69; N, 8.09. Found: C, 75.62; H, 6.49; N, 8.54.

Phenyl bis(3-aminophenyl)-phosphine (adapted procedure from[33])

In a Schlenk tube, phenyl dichlorophosphine (2 cm^3, 2.638 g, 14.74 mmol) and tetrahydrofuran (30 cm^3) were introduced. This solution was added drop wise at room temperature to a round-bottom flask equipped with a dry argon inlet containing a solution of 3-[Bis(trimethylsilyl)amino]phenylmagnesium chloride in tetrahydrofuran (1 mol dm^{-3}, 33 cm^3, 33 mmol). The system was stirred for 1 h. The solvent was evaporated and the residue was further dried under vacuum (20°C, 0.01 mbar). The residue was then extracted with diethyl ether (40 cm^3). The ether phase was filtered via canula and evaporated to yield a waxy solid (9.75 g). In a round-bottom flask equipped with a dry argon inlet and a stirrer, the waxy solid was dissolved in methanol (40 cm^3). The flask was equipped with a reflux condenser topped by a dry nitrogen bubbler and the solution was refluxed for 14 h. Once the reaction mixture had cooled to room temperature the product precipitated from the reaction mixture. The product was collected on a sintered glass funnel, washed with methanol and dried under vacuum (20°C, 0.01 mbar) (1.79 g, 40%).

^{1}H-NMR (300 MHz; DMSO-d_6) δ 5.11 (4H, s, broad, NH_2), 6.34 (4H, t, arom.), 6.47 - 6.56 (4H, m, arom.), 6.95 – 7.04 (2H, m, arom.), 7.19- 7.39 (5H, m, arom.). $^{31}P\{^1H\}$-NMR (300 MHz; DMSO-d_6) δ -4.66 (s). In agreement with literature data[33].

MS (ES) m/z $[M+H]^+$: 293.18

bis-SwitchPhos - (N',N''-(3,3'-(phenylphosphinediyl)bis(3,1-phenylene))bis(N,N-dimethylacetimidamide)

Phenyl bis(3-aminophenyl)phosphine (0.403 g, 1.36 mmol) was introduced into a microwave reaction vessel equipped with a magnetic stirrer. The tube was sealed with a septum and purged with alternate vacuum/Ar (3 times). Dimethylacetamide dimethylacetal (4 cm^3, 3.644 g, 27.3 mmol) was added and the tube was heated at 160°C for 1 h in the microwave. The crude reaction solution was transferred to a Schlenk tube. The operation was repeated and the two crude reaction products were combined. The excess dimethylacetamide dimethylacetal and the produced methanol were removed under reduced pressure (20°C, 24 mbar). The residue was further dried under vacuum. Impurities were precipitated upon addition of toluene (15 cm^3). The toluene phase was washed with water (10 cm^3). Water was added (15 cm^3) and CO_2 was bubbled trough the biphasic system under stirring for 1.5 h. The toluene phase was discharged and fresh toluene was added (15 cm^3). Nitrogen was bubbled trough the biphasic system under stirring for 1.5 h at 60°C. The toluene was evaporated and the obtained waxy yellow solid further dried under vacuum (20°C, 0.01 mbar)(0.45g, 38%).

^{1}H-NMR (400 MHz; $CDCl_3$) δ 1.77 (6H, s, Me) 2.97 (12H, s, NMe_2), 6.64 – 6.71 (4H, m, arom.), 6.90 (2H, t, arom.), 7.15 – 7.20 (2H, m, arom.), 7.25- 7.36 (5H, m, arom.). $^{31}P\{^1H\}$-NMR (400 MHz; $CDCl_3$) δ -4.27 (s). MS (ES) m/z $[M+H]^+$: 431.29; $[M+2H]^{2+}$: 216.14. Anal. Calcd for $C_{26}H_{31}N_4P$: C, 72.53; H, 7.26; N, 13.01. Found: C, 71.98; H, 7.72; N, 12.93.

tris(3-aminophenyl)-phosphine (adapted procedure from[33])

In a Schlenk tube, phosphorus trichloride (0.55 cm^3, 0.8657 g, 6.30 mmol) and tetrahydrofuran (25 cm^3) were introduced. This solution was added dropwise at room temperature to a round-bottom flask equipped with a dry argon inlet containing a solution of 3-[Bis(trimethylsilyl)amino]phenylmagnesium chloride in tetrahydrofuran (1 mol dm^{-3}, 23 cm^{-3}, 23 mmol). The system was stirred for 1 h. Water (25 cm^3) and petroleum ether 40-60 (60 cm^3) were added. The phases were allowed to separate, the upper organic phase was collected and dried over $MgSO_4$. The solvent was evaporated and the residue was further dried under vacuum (20°C, 0.01 mbar) to yield a pale yellow solid (5.38 g). In a round-bottom flask equipped with a dry nitrogen inlet and a stirrer, the pale yellow solid was dissolved in methanol (15 cm^3) and tetrahydrofuran (20 cm^3). The flask was equipped with a reflux condenser topped by a dry argon bubbler and the solution was refluxed for 18 h. The solvents were evaporated and the residue further dried under vacuum (20°C, 0.01 mbar) to yield a white solid. The solid was washed with petroleum ether 40-60 (2 x 15 cm^3) and dried under vacuum. The solid was further washed with isopropanol (50 cm^3) and dried under vacuum (20°C, 0.01 bar) to yield a finely dispersed white solid (1g, 28%).

^{1}H-NMR (400 MHz; DMSO-d_6) δ 5.07 (6H, s, broad, NH_2), 6.36 (3H, t, arom.), 6.51 (6H, d, arom.), 6.94 – 7.01 (3H, m, arom.). ^{31}P{^{1}H}-NMR (400 MHz; DMSO-d_6) δ -3.45 (s). In agreement with literature data[33].

Tris-SwitchPhos.

Tris(3-aminophenyl)-phosphine (0.2478 g, 0.81 mmol) was introduced into a microwave reaction vessel equipped with a magnetic stirrer. The tube was sealed with a septum and purged with alternate vacuum/Ar (3 times). Dimethylacetamide dimethylacetal (3.5 cm^3, 3.188 g, 23.9 mmol) was added and the tube was heated at 160°C for 1 h in the microwave. The crude reaction product, in which the product had precipitated, was transferred to a Schlenk tube. The operation was repeated 3 times (0.2493 g, 0.81 mmol; 0.2524g, 0.82 mmol; 0.2042g, 0.66 mmol) and the four crude reaction products were combined. The mixture was filtered through a sintered glass funnel, washed with hexane (3 x 10 cm^3) and dried under vacuum (20°C, 0.01 mbar). The solid was taken into toluene (20 cm^3) and washed with water (20 cm^3). Fresh water was added (20 cm^3) and CO_2 was bubbled trough the mixture for 1.5 h. The organic phase was discharged, fresh toluene (20 cm^3) was added and N_2 was bubbled trough the mixture at 60°C for 1.5 h. The toluene phase was collected and evaporated to yield a white solid. The solid was dried under vacuum (20°C, 0.01 mbar)(0.96 g , 61%).

^{1}H-NMR ($CDCl_3$) δ 1.77 (s, 9H, $N{=}C(CH_3)N(CH_3)_2$) 2.97 (s, 18H, $N(CH_3)_2$) 6.66 (m, 6H) 6.92 (m, 3H, PCC*H*CH) 7.16 (m, 3H, PCCHC*H*).

$^1H\{^{31}P\}$-NMR ($CDCl_3$) δ 1.77 (s, 9H, N=C(CH_3)N(CH_3)$_2$) 2.97 (s, 18H, N(CH_3)$_2$) 6.66 (m, 6H) 6.92 (d, 3H,$^3J_{HH}$= 7.6 Hz, PCC*H*CH) 7.16 (t, 3H, $^3J_{HH}$= 7.6 Hz, PCCHC*H*).

$^{31}P\{^1H\}$-NMR ($CDCl_3$) δ -3.83 (s, P).

$^{13}C\{^1H\}$-NMR ($CDCl_3$) δ 15.18 (CH_3, N=C(*C*H_3)N) 38.15 (CH_3, N(*C*H_3)$_2$) 123.07 (CH, N*C*HCH) 127.32 (CH, $^2J_{CP}$ = 21.1 Hz, PC*C*HCH) 127.85 (CH, $^2J_{CP}$ = 17.0 Hz, PC*C*HCN) 128.72 (CH, $^3J_{CP}$ = 8.3 Hz, PCCH*C*H) 138.01 (C, $^1J_{CP}$ = 10.8 Hz, P*C*) 152.01 (C, *C*N=C(CH_3)N) 157.60 (C, N=*C*(CH_3)N).

HRMS-ESI+ (*m/z*) $[M+H]^+$ calcd for $C_{30}H_{40}N_6P$ 515.3052 found 515.3051.

Anal. Calcd for $C_{30}H_{39}N_6P$: C, 70.0; H, 7.6; N, 16.3. Found: C, 70.4; H, 8.0; N, 16.3.

3.5.3. Typical catalyst solution preparation

For organic phase reaction.

In a Schlenk tube, [Rh(acac)(CO)$_2$] (3.2 mg, 12.4 μmol) and the ligand (mono- or tris-Switchphos) were introduced and degassed. After addition of toluene (10 cm^3) a yellow solution was obtained and syngas was bubbled through for 1 h at 60°c

$^{31}P\{^1H\}$-NMR (300 MHz; $CDCl_3$) δ -3.47 (s, broad, P) 26.10 (s, P=O) 36.10 (d, $J_{P\text{-}Rh}$ = 148 Hz).

For aqueous phase reaction

In a Schlenk tube, tris-Switchphos (87.6 mg, 170.3 μmol) and [Rh(acac)(CO)$_2$] (3.2 mg, 12.4 μmol) were introduced and degassed. Water was added (10 cm^3) and a slurry was obtained. CO_2 was bubbled through the slurry under ultrasonic irradiation for 30 min yielding a yellow solution.

$^{31}P\{^1H\}$-NMR (400 MHz; C_6D_6 capillary) δ -6.57 (s, broad, P) 34.04 (s, P=O) 40.81 (d, $J_{P\text{-}Rh}$ = 154 Hz).

3.5.4. Typical procedure for hydroformylation of 1-octene and allyl alcohol

An autoclave fitted with a mechanical stirrer, thermocouple pocket, pressure transducer and attached to a ballast vessel *via* a catalyst injector and mass flow controller was degassed by pressurizing three times with CO/H_2 and releasing the pressure. Catalyst solution (for 1-octene hydroformylation: 8 cm^3, for allyl alcohol hydroformylation: 4 cm^3) was transferred into the autoclave and degassed by pressurizing three times with CO/H_2 and releasing the pressure. The autoclave was pressurized with CO/H_2 (1:1, 16 bar) and heated (100 °C for 1-octene hydroformylation and 75 °C for allyl alcohol hydroformylation)(Stirrer speed = 1000 rpm). Meanwhile, the substrate injector was charged with substrate (1-octene = 2 cm^3, allyl alcohol = 1 cm^3). Once the reactor had reached the desired temperature, the substrate was injected using an overpressure of CO/H_2 and the pressure brought to 20 bar. CO/H_2 was then fed from the ballast vessel so as to maintain the pressure in the autoclave at 20 bar and the pressure in the ballast vessel was monitored electronically. At the end of the reaction (once no gas was consumed anymore), the autoclave was cooled and depressurized.

3.5.5. Typical procedure for catalyst recycling

1-octene hydroformylation

The content of the autoclave (yellow liquid) was transferred via canula into a Schlenk tube. The second catalyst solution was then injected into the autoclave and another run in a constant pressure batch reactor was carried out.

The content of the autoclave (yellow liquid) was transferred via canula into the Schlenk tube containing the solution from the first run. The combined solutions were transferred via canula into a Schlenk tube equipped with a magnetic stirrer containing degassed water (20 cm^3). The biphasic system obtained was stirred for 10 min and left standing for 10 min. Visual observation showed no colouration of the aqueous phase. CO_2 was bubbled through the system with stirring for 10 min. The aqueous phase quickly changed from colourless to yellow while the toluene phase completely lost its yellow colouration. The bubbling was continued for 20 min leaving the aqueous phase with the same yellow colouration and the toluene phase colourless. CO_2 bubbling was continued for 30 min, no further change in colouration was observed. The bubbling was continued for a further 30 min, again no further change in colouration was observed. The organic phase was separated and analyzed by Gas Chromatography for the organic content and by ICP-MS for the rhodium content. Fresh toluene (16 cm^3) was added to the remaining yellow-orange aqueous phase and the biphasic system obtained was stirred for 10 min and left standing for 5 min. Visual observation showed no change in colouration for any of the phases. Nitrogen was bubbled through the system for 10 min. Visual inspection revealed that the toluene phase turned slightly yellow. Nitrogen was bubbled at 60°C for 30 min. The aqueous phase had become colourless, while the toluene phase had turned yellow. N_2 bubbling was continued for 30 min at 60°C; no further change in colouration was observed. The bubbling was continued for more 30 min at 60°C, again no further change in colouration was observed. The volume of the toluene phase was measured using a syringe and the solution was transferred to a Schlenk tube. Fresh toluene was added to bring the volume back to 16 cm^3. The aqueous phase was collected and analyzed by ICP-OES for the rhodium content.

Part of the recovered catalyst solution (8 cm^3) was transferred to the reactor and another run in a constant pressure batch reactor was carried out. The contents of the autoclave were transferred via canula to a Schlenk tube containing the remainder of the previously recovered catalyst solution.

The same recycling procedure was followed, as described above. Part of the recovered catalyst solution (8 cm^3) was transferred to the reactor and another run in a constant pressure batch reactor was carried out. The contents of the autoclave were transferred via canula to a Schlenk tube containing the remaining of the previously recovered catalyst solution.

The same recycling procedure was once again followed. At the end of the third recycling, the catalyst solution was analyzed by ^{31}P NMR spectroscopy.

$^{31}P\{^1H\}$-NMR (400 MHz; $CDCl_3$) δ -3.59 (s, broad, P) 27.52 (s, P=O) 39.98 (d, $J_{P\text{-}Rh}$ = 153.5 Hz).

For every visual observation of the system photographs were taken.

Allyl alcohol hydroformylation

The content of the autoclave (yellow liquid) was transferred via canula into a Schlenk tube. Catalyst solution (4 cm^3) was then injected into the autoclave and another run in a constant pressure batch reactor was carried out.

The content of the autoclave (yellow liquid) was transferred via canula into the Schlenk tube containing the crude solution from the first run. The combined crude solutions were transferred via canula into a Schlenk tube equipped with a magnetic stirrer containing toluene (10 cm^3). The biphasic system obtained was stirred for 10 min and left standing for 10 min. Visual observation showed no colouration of the toluene phase. N_2 was bubbled through the system with stirring for 10 min. The toluene phase changed from colourless to slight yellow. The bubbling was continued for 30 min at 60°C. The yellow colouration of the toluene phase intensified while the aqueous phase had discoloured and turned cloudy. N_2 bubbling was continued for 30 min at 60°C, no further change in colouration was observed. The bubbling was continued for a further 30 min at 60°C, again no further change in colouration was observed. The organic phase was transferred to another Schlenk tube containing degassed water (8 cm^3). The remaining aqueous phase was analyzed by ^{13}C-NMR spectroscopy for organic products and by ICP-OES for its rhodium content. The biphasic system obtained was stirred for 10 min and left standing for 5 min. Visual observation showed no change in colouration for any of the phases. CO_2 was bubbled through the system for 10 min. Visual inspection revealed that the aqueous phase turned bright yellow while the toluene phase had become completely colourless. CO_2 was bubbled for more 20 min. No further change in colouration was observed. CO_2 bubbling was continued for 30 min, no further change in colouration was observed. The bubbling was continued for 30 min more, again no further change in colouration was observed. The toluene phase was separated and the volume of the aqueous phase was measured using a syringe and the solution was transferred to a Schlenk tube. Fresh water was added to bring the volume back to 8 cm^3.

Part of the recovered catalyst solution (4 cm^3) was transferred to the reactor and another run in a constant pressure batch reactor was carried out.

The contents of the autoclave were transferred via canula to a Schlenk tube containing the remainder of the previously recovered catalyst solution.

The same recycling procedure was followed as described above.

For every visual observation of the system photographs were taken.

3.6 References

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Chapter
FOUR

Aqueous-biphasic hydroformylation using an oscillatory baffled reactor.

4.1 Introduction

Aqueous-biphasic organometallic catalysis is, as illustrated by hydroformylation of propene and butene via the Ruhrchemie/Rhône-Poulenc process, one of the most promising ways to overcome the intrinsic problem of catalyst separation in organometallic catalysis[1]. In this process, the catalyst is dissolved in an aqueous phase by the use of sulfonated ligands, whilst the starting material and products form a separate phase. This methodology allows fast and efficient separation of the product from the catalyst by simple decantation. The aqueous phase containing the catalyst can then be reused for further operation.

While the introduction of a second phase ensures efficient catalyst separation and recycling, it induces mass transfer limitations that reduce the reaction rate. For higher alkenes ($>C_5$), which display poor solubility in water, mass transport limitations render the reaction rate to be lower than any that could be economically viable, greatly limiting the scope of this elegant technology.

As described in the first chapter, several methods have been developed to extend the scope of the aqueous-biphasic methodology to more hydrophobic substrates. None of the investigated new systems has so far led to new commercial applications.

Surprisingly, very few studies have been devoted to the engineering aspect of aqueous-biphasic catalysis. However, since mass transfer of the reactant to the catalytic phase seems to be the limiting factor, new reactor designs aiming at increasing the mass transfer and the interfacial area could offer enhanced reaction rates while maintaining the inherent strength of the RCH/RP process. The use of ultrasonic irradiation and of a Cavitron reactor has been studied for the aqueous-biphasic hydroformylation of 1-hexene[2, 3]. Ultrasonic irradiation, provided via a dipping probe fitted to an autoclave, resulted in a 2-fold increase of the hexene conversion. When the reaction was carried in a Cavitron reactor only slight improvement of the conversion could be observed. Another approach was to use a tubular reactor with an internal static mixer. In this system, both phases are pumped through the reactor at high velocity causing the mixture to break into fine bubbles and droplets generating a high interfacial area. With such a system, a 10-fold increase in reaction rate could be obtained for the aqueous-biphasic hydroformylation of propene[4]. According to the authors, economically viable space time yields for the octene hydroformylation could be obtained with this new process design[5, 6].

4.1.1. Oscillatory baffled reactor (OBR)

Recently, a new reactor type, so-called oscillatory baffled reactor (OBR), has received increasing attention as an efficient alternative to classical stirred tank reactors for many applications.

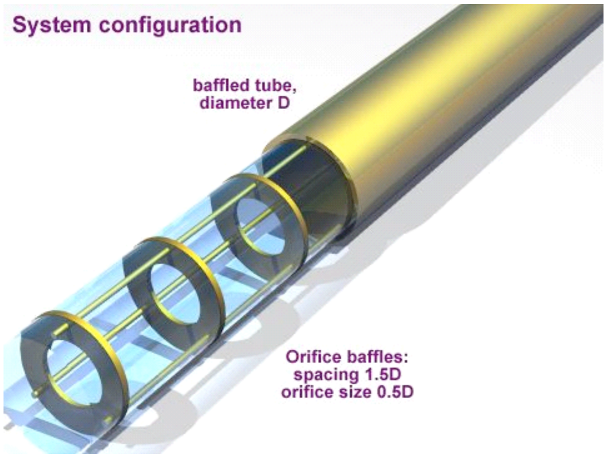

Figure 4. 1 *Section of an oscillatory baffled reactor. Reproduced from*[7]

An OBR is a tube containing annular orifices (baffles) at regular intervals (Figure 4. 1). The liquid in the tube can be oscillated back and forth relative to the baffles. Alternatively, the baffles can be oscillated relative to the liquid (Figure 4. 2). The interaction between the oscillating fluid and the baffles generates vortices in the space between two baffles, leading to efficient mixing where the radial and axial velocity components are of comparable magnitude (Figure 4. 3)[8]. This efficient mixing can significantly improve heat transfer in batch and continuous operation. High heat transfer

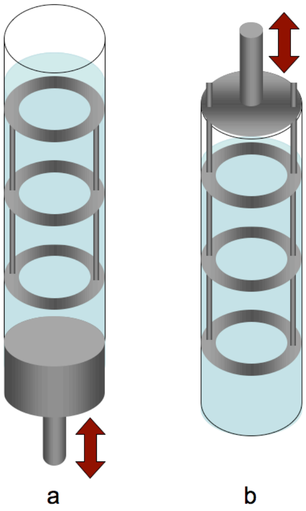

Figure 4. 2 *Different arrangement for an oscillatory baffled reactor. (a) Fixed baffles with oscillatory fluid. (b) Standing fluid with oscillatory baffles.*

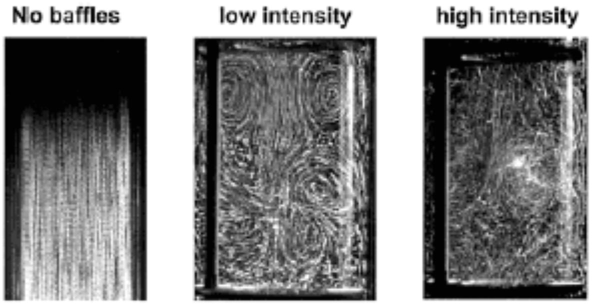

Figure 4. 3 *Flow patterns observed for an oscillating fluid with or without baffles. Reproduced from* [9]

coefficients can be obtained in an OBR at considerably lower Reynolds number than in conventional tubular reactor[10]. When considering continuous flow operation, plug flow conditions can be obtained in an OBR when the bulk flow is laminar, *i.e.* at low Reynolds number. This makes the OBR ideal for continuous flow operation in chemical, pharmaceutical and biochemical processes where long residence times are required[11].

When a gas is present, very efficient mixing of the gas into the liquid occurs to give a very high interfacial area. Considerable gas hold-up can be obtained so that the gas is recycled through the solution many times before escaping leading to high gas-liquid mass transfer coefficients[12, 13]. For example, when using an OBR for the production of pullulan, a biopolymer, higher rate of pullulan formation compared to a classical stirred fermenter could be obtained due to a better transfer of oxygen in the reactor[14].

When a biphasic liquid system is present, the oscillating movement, transverse to the baffles, causes one phase to break into the other forming droplets with diameters as low as 5 μm[15]. This allows complete dispersion of one phase into the other after only a few oscillation cycles[16]. So, the use of an OBR was studied for liquid-liquid biphasic reactions such as phase transfer catalysis and suspension polymerization. Higher conversions at lower power input and better particle size distribution could be obtained, respectively[15a, 17, 18].

There is considerable evidence that this new reactor design is particularly suited for multiphasic applications. However, rather few practical applications have been tested and none under pressure.

In this chapter we report our preliminary results regarding the use of a pressurized OBR (POBR) for the rhodium-catalysed hydroformylation of alkenes.

4.2 Results and discussion

We carried out the hydroformylation of 1-octene in a closed POBR and a closed continuously stirred tank reactor (CSTR) under the same reaction conditions to allow for comparison (Table 4. 1). The reaction carried in the POBR proceeded to a lower conversion than the reaction carried in the CSTR (Table 4. 1, entry 1 and 2). Regarding the linear selectivity, no major difference was observed between both types of reactor.

Table 4. 1 *Aqueous-biphasic hydroformylation of alkenes in a POBR and a CSTR*[a].

Entry	Substrate	Reactor	Stirring	Aldehydes (%)	Isomerised octenes (%)	l/b	<TOF> (h^{-1})
1	1-octene	CSTR	1000 rpm	4.9	n.d.	3.9	30
2	1-octene	POBR	7 mm, 4Hz	2.2	n.d.	4.1	14
3	1-hexene	CSTR	1000 rpm	32.7	3.3	4.6	256
4	1-hexene	POBR	7 mm, 4Hz	11.8	0.8	4.7	94
5	1-hexene	POBR	7 mm, 8Hz	31.8	2.3	4.5	254

a Reaction conditions: 100 °C, 20 bar, CO:H_2 = 1:1, 2h, $[Rh]_{aq}$ = 1.25 10^{-3} mol dm^{-3}, P/Rh = 10, V_{aq}/V_{alk} = 4, V_{tot} (POBR) = 60 cm^3, V_{tot} (CSTR) = 10 cm^3.

However, due to the low conversion obtained, no real conclusions can be drawn. So, we carried out the hydroformylation of 1-hexene, which is known to proceed to higher conversion due to its slightly higher water solubility. At low oscillation frequency, the reaction in the POBR was found to be *ca.* three times slower than in the CSTR. However, doubling the oscillation frequency increased the reaction rate and similar conversion could be obtained in the CSTR and the POBR. For any set of reaction conditions, no significant difference in linear selectivity was observed.

From the different results, it can be seen that, under the investigated conditions, carrying out the reaction with a POBR did not lead to rate improvements under the conditions that we employed. It allows, at the maximum, to reach conversion levels similar to those observed in with a CSTR. The increase in conversion observed with the POBR when increasing oscillation frequency is in line with studies showing enhancement of the mass transfer in multiphasic system (liquid-liquid, gas-liquid) upon increasing oscillation frequency and amplitude[12a, 14a-b, 16b]. It suggests that at low oscillation frequency, the reaction is strongly mass transfer limited but this can be overcome by intensifying the stirring. The one advantage may be in the energy input into the stirrer. In the OBR the baffles are oscillated at a linear frequency of 8 Hz, whilst in the CSTR there is a rotation rate of 16.7 Hz for similar conversions.

4.3 Conclusion

Few conclusions can be drawn from this very short investigation. At first sight, the use of a POBR seems not to be a prime solution on its own to tackle the strong mass transfer limitation encountered in the aqueous-biphasic hydroformylation of alkenes. There surely is room for improvements, changing the oscillation amplitude should be attempted. Increasing further the oscillation frequency also should be attempted but that was not possible with our apparatus. However, it would be possible with another apparatus to pass beyond that limit.

The main strength of this new reactor technology relies on the low energy input required to obtain similar or slightly improved performances compared to CSTR. Therefore, it could be used in already optimized system to add extra energy saving. For example, the use of a POBR for homogeneous hydroformylation or hydrogenation could lead to a decrease in the operating pressure or the energy required for stirring. By using a continuous flow OBR, it may be possible to integrate the separation with the reaction. In a flow system, the liquid column is oscillated in a snake like reactor. Gas could be added at every other turn to allow for gas depletion and baffles could be omitted from the final section so that phase separation could occur. Removal of the product and recycling of the catalyst phase could then lead to a genuine flow system for aqueous biphasic systems. This concept is illustrated in Figure 4.4.

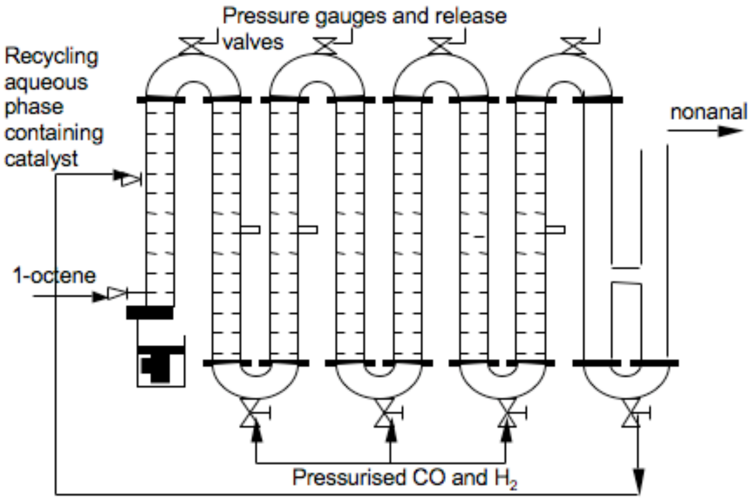

Figure 4. 4 *Schematic diagram of an oscillatory baffled reactor system for aqueous-biphasic catalysis.*

For the aqueous-biphasic hydroformylation, testing of the additives we developed in Chapter 2 could maybe lead to further improvement since the system seemed to be limited by the gas-transfer.

4.4 Experimental

4.4.1. General

All experiments were carried out under dry argon on a vacuum line using standard Schlenk techniques.

Gases; argon and syngas, were purshased from BOC gases. Water was distilled, degassed by vacuum. and stored under argon. Triphenylphosphine trisulfonate sodium salt, TPPTS, (Aldrich, 96 % or prepared according to [19]), [Rh(acac)(CO)$_2$] (Strem Chemicals, 99 %) and deuterium oxide (Aldrich, 99.9 atom % D) were used as received. Alkenes, 1-hexene (Aldrich, 99 %), 1-octene (Aldrich, 98 %) were purified from peroxide by extraction with aqueous $(NH_4)_2Fe(SO_4)_2.6H_2O$ followed by filtration trough basic alumina and stored in the dark under Ar.

Gas chromatography analyses were carried out using a Hewlett-Packard 5890 series gas chromatograph equiped with a flame ionisation detector (FID) fitted with a Supelco MDN-35 (35 % phenyl/65 % methyl-polysiloxane) capillary column for quantitative analysis. The temperature programme used was: 50 ^{o}C (4 min), Δ 20 °C/min to 130°C (2 min), Δ 20°C/min to 260 (13.5 min). The temperature of the injector and the detector were both 250 °C. The split ratio used was 100/1. Helium was used as the carrier gas with a flow of 1 ml min^{-1}.

^{13}C, ^{1}H and ^{31}P NMR spectra were recorded on Bruker AM 300/400 NMR spectrometers or a Varian 300 NMR spectrometer. Broadband decoupling was used for ^{13}C and ^{31}P NMR spectra. ^{1}H and ^{13}C NMR spectra were referenced internally to deuterated solvents, which were referenced relative to TMS at $\delta = 0$: $CDCl_3$: ^{1}H, $\delta = 7.27$ ppm, ^{13}C, $\delta = 77.23$ ppm; D_2O: $^{1}H = 4.53$ ppm. ^{31}P NMR spectra were referenced externally to 85 % H_3PO_4. Coupling constants are given in Hz.

4.4.2. Catalyst preparation

Catalyst solutions were prepared as follows: weighed amounts of $[Rh(acac)(CO)_2]$ and TPPTS were dissolved in a known volume of water. $CO-H_2$ was then gently bubbled through the resulting yellow solution at 60°C for 1 h. δ_P (300MHz; D_2O;) -4.55 (s, broad).

4.4.3. Hydroformylation of alkenes

Typical procedure for hydroformylation of alkenes in a closed reactor (CSTR or POBR):

The reactor, fitted with a mechanical stirrer or a set of 3 baffles connected to the shaft of a piston through a supporting plate and driven by an electrical motor together with an inverter, thermocouple pocket, pressure transducer, gas inlet and injection port, was degassed by 3 alternate vacuum -. N_2 cycles. The stock catalyst solution (CSTR: 8 cm^3; POBR: 48 cm^3) and alkene (CSTR: 2 cm^3, POBR: 12 cm^3) were transferred into the autoclave. The autoclove was purged three times with pressurised $CO-H_2$. The autoclave was pressurized with $CO-H_2$ (1:1, 20 bar) and heated with stirring, to 100 °C. After 2 h, the autoclave was quickly cooled, depressurised and the contents analysed using GC for the organic products. The results presented (Table 4. 1) are the average of at least 2 runs under each set of conditions.

4.5 References

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Chapter
FIVE

Conclusions and future work

5.1 Introduction

Rhodium catalyzed aqueous-biphasic hydroformylation has been successfully used for commercial application since 1984. From this milestone in biphasic catalysis process, an impressive growth in the number of multiphasic catalysis applications was expected. However, very few commercial applications went on stream but the amount of academic and industrial research in the field literally exploded. Numerous new biphasic systems have been explored (involving *inter alia* ionic liquids, supercritical carbon dioxide, fluorous solvents). Nevertheless, their complexity, both molecular and technological, together with their cost have so far impeded their widespread use.

Aqueous-organic systems are very much simpler (which undergraduate organic chemistry laboratory experiment does not have a water-diethyl ether extraction step?), but mass transfer brings the reaction rate of the poorly water-soluble substrates below any that is viable for commercial production. Numerous and varied new approaches have been developed to tackle this limitation. However, this important body of work has not, so far, led to new practical applications. Two main reasons can account for this disappointing performance. The new methodologies developed do not meet the efficiency requirement in terms of catalyst immobilization, ease of phase separation or reaction rate. When those requirements are met, it is the cost of the new technology that impedes its application. For example, very efficient systems have been developed using cyclodextrins or surface-active ligands but that might be at a prohibitive cost.

However, owing to the advantages of aqueous-biphasic technology in terms of efficiency and “greenness”, new strategies aiming at commercial application should be developed.

So, we studied three different new approaches for the aqueous-biphasic hydroformylation of medium alkenes. We focused on the development of new additives, the use of CO_2 phase switching catalysts and the use of a new reactor design. We have tried, as far as possible, to keep those new systems simple so that, if efficient, they could be practically used.

5.2 “Weak” Surfactants

We have used ammonium salts ,bearing one medium-length alkyl chain, as additives for the aqueous-biphasic hydroformylation of medium alkenes (C_6-C_{10}). High reaction rates have been obtained with additives bearing an alkyl chain of sufficient length ($\geq C_8$) and having a methylimidazolium or a triethylammonium head group. More importantly, the ease of phase separation was little affected when additives having an octyl chain were used. Additives having a longer alkyl chain (C_{10}) led to the formation of stable emulsions rendering the separation of the catalyst impossible. The nature of the anion showed little influence on the reaction rate and the ease of phase separation. High retention of the metal in the aqueous phase was found in the presence of all the studied additives and typical levels of rhodium leaching were below 1 ppm providing enough ligand excess was used.

1-octyl-3-methylimidazolium bromide offered the best balance between high reaction rate, efficient phase separation and low rhodium leaching. Evidence gathered through the investigation indicates that these additives act as “weak” surfactants, forming emulsions with poor stability that improve the contact between the substrate and the catalyst but break after settling for a short time.

In order to fully appreciate the potential of these additives for aqueous-biphasic hydroformylation, several important parameters need to be further evaluated.

Careful study of the additive leaching in the product phase is of the utmost importance. Carrying away part of the additive means that constant replenishment would be required to maintain the promoting effect. Moreover, the presence of the additive in the product could considerably complicate their separation. During the investigation, the presence of additive in the product phase could not be detected by ^{1}H-NMR spectroscopy. However, analysis of the product phase by a more sensitive method such as HPLC or LC-MS would be highly desirable to quantify more precisely the possible leaching of the additive.

So far promising results have been obtained in batch systems. Carrying the reaction continuously would provide a better evaluation, under more realistic conditions, of the influence of the additive on the phase separation. Moreover, this would allow the stability of the system on stream to be evaluated and hence indirectly the extent of additive and metal leaching together with the stability of the catalyst in the presence of additive.

One limitation of the developed additive is the discrepancies in rate observed with substrates of different water solubility. This means that the studied additives could only be used for a narrow range of substrates (C_6-C_{10}) for which the reaction rate meets the requirement for commercial application. One has also to keep in mind that the formation of an emulsion depends on all the constituents of the mixture and their relative amounts. Therefore, different substrates might require different additives to conserve the promoting effect together with efficient phase separation.

The results obtained so far are very promising. The additives used are simple and readily available, especially since the booming interest in ionic liquids. Moreover, they could be used in existing plants for processing other feeds without requiring major modifications of the process. The rather large amount of additive required may, however, add too much extra cost.

We believe that the concept of unstable emulsions is very attractive for aqueous-biphasic catalysis in general, not only for hydroformylation, since switching between a pseudo monophasic system (enabling high reaction rate) and a biphasic system (enabling efficient catalyst separation) is just a matter of switching the stirrer on and off.

5.3 CO_2 induced phase switching

We have developed new ligands that can be protonated by carbonic acid (aqueous solution of CO_2) hence making them water-soluble. Deprotonation can be achieved simply by flushing the CO_2 using nitrogen under gentle heating. Using these ligands for the rhodium based hydroformylation of 1-octene allows the reaction to be carried out in a homogeneous system, only limited by intrinsic kinetics, and the catalyst to be separated from the reaction products by aqueous extraction in the presence of CO_2. The catalyst can be recovered by re-extraction in the organic phase with nitrogen under gentle heating. No residues accumulate during the process and all the extractions are carried out under mild conditions.

The new ligands were found to yield very active catalysts for hydroformylation of 1-octene. Initial turnover frequencies in the range of 7000 to 14000 h^{-1} were observed. The recycling of the catalyst could be efficiently performed providing the ligand bears enough "switchable" moieties and that a 50-fold excess of ligand relative to the metal is used. In this way, 92 % of the initial catalyst activity could be recovered. The rhodium leaching was found to be very low, typically below 1 ppm, *i.e.* less than 0.5 % of the initial rhodium charged, was lost in the organic and aqueous phases. The reverse system, *i.e.* aqueous reaction in the presence of CO_2 with subsequent organic extraction with N_2, was studied for the hydroformylation of allyl alcohol. The catalyst was found to be less active than for the hydroformylation of 1-octene, although the reactions were carried out at lower temperature. Reproducible gas uptake curves were obtained, indicating that catalyst recycling was possible also for the reverse system. Leaching of the metal was found to be consistent with the leaching observed during the hydroformylation of 1-octene with a 10-fold excess ligand. However, analysis of the reaction product suggested that the product was partially soluble in the organic phase.

These CO_2-switchable catalysts constitute one of the few examples of a catalytic system that displays a high reaction rate together with efficient catalyst recycling. Moreover, compared with already developed systems for catalyst phase switching, using a benign trigger such as CO_2 does not required extensive energy input and does not induce the formation of by-products.

The present studies have so far demonstrate the proof of principle of the methodology. Several unknowns remain that need careful study to further assess the potential of this new catalyst. We, so far, only have an indirect indication that the switching is almost complete (recovered activity, rhodium leaching), direct quantification of the switching using spectroscopic methods would be highly desirable. Moreover this would allow a better understanding of the parameters affecting the transport of the catalyst from one phase to another. Optimization of the extraction procedure could then be made. Regarding the reverse system, different analytical methods such as HPLC or LC-MS should be used for the quantification of the reaction products in the aqueous phase. Moreover, analysis of the organic phase should be made in order to evaluate the extent of product and starting material partitioning between the phases.

We believe that the use of CO_2 phase switching catalysts is a general methodology for catalyst recycling and could be use for several other catalytic reactions. However, care should be taken that the reaction does not require the use of acids or bases since they could interact with the ligand and render the recycling of the catalyst impossible. Interaction of the metal with CO_2 could also be an issue. The design of new switchable ligands, especially bidentate, could improve the retention of the metal and improve the reaction selectivity.

5.4 Oscillatory baffled reactor

We investigated the use of an oscillatory baffled reactor (OBR) for the rhodium aqueous-biphasic hydroformylation of 1-octene and 1-hexene. At low oscillation frequency, the reaction proceeded to lower conversion than with a continuously stirred tank reactor (CSTR). However, at higher oscillation frequency, similar levels of conversion were found for both reactors.

The OBR seems not to be especially suited to enhance mass transfer in aqueous-biphasic hydroformylation. However, variation of the oscillation amplitude should be attempted since it could lead to some improvement. The use of an OBR could be tested in conjunction with the use of additives. In the study regarding the use of additives, under certain conditions, the reactions appeared to be limited by the gas transfer. The OBR could be used to improve the gas transfer and hence accelerate further the reaction.

One of the advantages of the OBR is the low energy input required to achieve efficient mixing. It could be advantageously used for homogeneous hydroformylation, enabling efficient gas transfer, while decreasing the energy consumption.

Appendices

1. Crystallographic data for mono-SwitchPhos

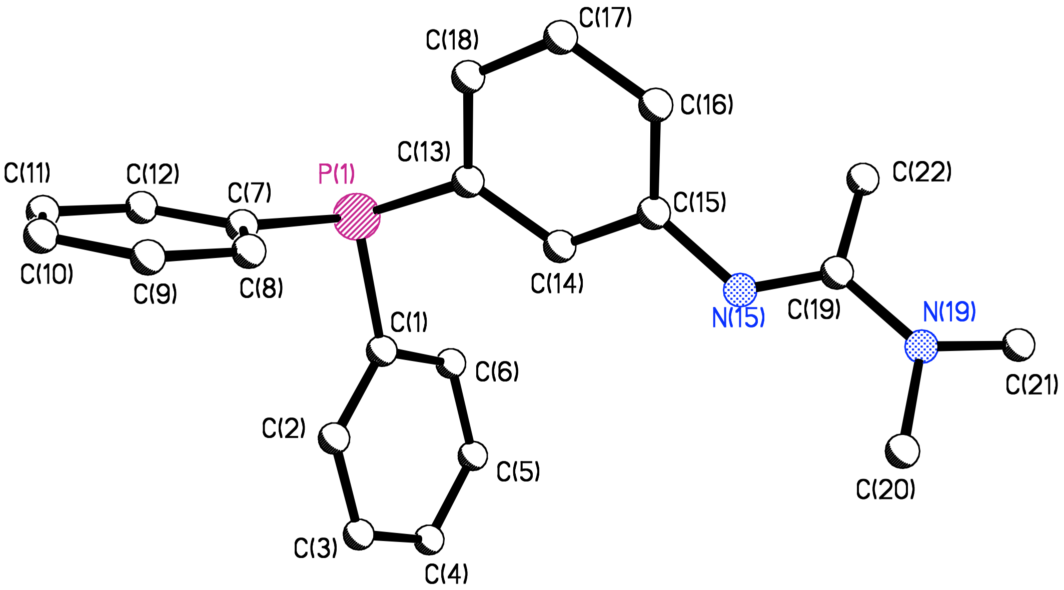

Figure 1 *Molecular structure (ORTEP plot) of mono-SwitchPhos (hydrogen atoms are omitted for clarity).*

Table 1. Crystal data and structure refinement for mono-SwitchPhos.

Empirical formula	C22 H23 N2 P	
Formula weight	346.39	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 11.561(3) Å	α= 90°.
	b = 16.199(4) Å	β= 115.775(5)°.
	c = 11.349(3) Å	γ = 90°.
Volume	1913.9(8) $Å^3$	
Z	4	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	0.150 mm^{-1}	
F(000)	736	
Crystal size	0.1000 x 0.0500 x 0.0500 mm^3	
Theta range for data collection	2.33 to 25.32°.	
Index ranges	-13<=h<=13, -19<=k<=16, -13<=l<=12	
Reflections collected	12285	
Independent reflections	3414 [R(int) = 0.0908]	
Completeness to theta = 25.00°	97.9 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9822	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3414 / 0 / 231	
Goodness-of-fit on F^2	1.129	
Final R indices [I>2sigma(I)]	R1 = 0.0854, wR2 = 0.2057	
R indices (all data)	R1 = 0.1209, wR2 = 0.2331	
Extinction coefficient	0.014(3)	
Largest diff. peak and hole	0.458 and -0.490 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for mono-SwitchPhos. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	5969(1)	247(1)	7623(1)	33(1)
C(1)	5682(3)	-851(2)	7758(3)	32(1)
C(2)	6258(4)	-1322(2)	8885(4)	39(1)
C(3)	5963(4)	-2151(3)	8883(4)	45(1)
C(4)	5084(4)	-2518(3)	7747(4)	46(1)
C(5)	4491(4)	-2059(3)	6618(4)	44(1)
C(6)	4763(3)	-1229(2)	6609(4)	37(1)
C(7)	7019(3)	531(2)	9327(3)	33(1)
C(8)	8348(4)	386(3)	9941(4)	40(1)
C(9)	9063(4)	623(3)	11215(4)	44(1)
C(10)	8496(4)	1015(2)	11911(4)	42(1)
C(11)	7200(4)	1155(2)	11324(4)	45(1)
C(12)	6451(4)	918(2)	10032(4)	38(1)
C(13)	7093(3)	246(2)	6889(3)	33(1)
C(14)	7387(3)	-454(2)	6349(3)	34(1)
C(15)	8184(3)	-416(2)	5719(3)	34(1)
N(15)	8569(3)	-1157(2)	5358(3)	37(1)
C(16)	8703(4)	354(2)	5622(4)	38(1)
C(17)	8408(4)	1052(2)	6148(4)	40(1)
C(18)	7626(4)	1003(2)	6778(3)	38(1)
C(19)	8344(3)	-1320(2)	4165(4)	35(1)
N(19)	8864(3)	-2016(2)	3909(3)	36(1)
C(20)	9604(4)	-2585(2)	4962(4)	47(1)
C(21)	8433(4)	-2335(3)	2597(4)	49(1)
C(22)	7518(4)	-796(3)	3000(4)	45(1)

Table 3. Bond lengths [Å] and angles [°] for mono-SwitchPhos.

P(1)-C(13)	1.824(4)
P(1)-C(1)	1.828(4)
P(1)-C(7)	1.840(4)
C(1)-C(2)	1.385(5)
C(1)-C(6)	1.414(5)
C(2)-C(3)	1.385(5)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.382(6)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.378(6)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.382(5)
C(5)-H(5A)	0.9500
C(6)-H(6A)	0.9500
C(7)-C(12)	1.386(5)
C(7)-C(8)	1.404(5)
C(8)-C(9)	1.372(5)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.381(6)
C(9)-H(9A)	0.9500
C(10)-C(11)	1.367(6)
C(10)-H(10A)	0.9500
C(11)-C(12)	1.394(5)
C(11)-H(11A)	0.9500
C(12)-H(12A)	0.9500
C(13)-C(14)	1.401(5)
C(13)-C(18)	1.402(5)
C(14)-C(15)	1.391(5)
C(14)-H(14A)	0.9500
C(15)-N(15)	1.402(5)
C(15)-C(16)	1.409(5)
N(15)-C(19)	1.290(5)
C(16)-C(17)	1.388(5)
C(16)-H(16A)	0.9500

C(17)-C(18)	1.378(5)
C(17)-H(17A)	0.9500
C(18)-H(18A)	0.9500
C(19)-N(19)	1.367(5)
C(19)-C(22)	1.511(5)
N(19)-C(21)	1.445(5)
N(19)-C(20)	1.456(5)
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(13)-P(1)-C(1)	103.26(17)
C(13)-P(1)-C(7)	101.79(17)
C(1)-P(1)-C(7)	102.52(16)
C(2)-C(1)-C(6)	118.7(3)
C(2)-C(1)-P(1)	125.5(3)
C(6)-C(1)-P(1)	115.7(3)
C(3)-C(2)-C(1)	120.9(3)
C(3)-C(2)-H(2A)	119.6
C(1)-C(2)-H(2A)	119.6
C(2)-C(3)-C(4)	119.9(4)
C(2)-C(3)-H(3A)	120.0
C(4)-C(3)-H(3A)	120.0
C(5)-C(4)-C(3)	120.1(4)
C(5)-C(4)-H(4A)	119.9
C(3)-C(4)-H(4A)	119.9
C(4)-C(5)-C(6)	120.6(4)
C(4)-C(5)-H(5A)	119.7
C(6)-C(5)-H(5A)	119.7
C(5)-C(6)-C(1)	119.7(3)

C(5)-C(6)-H(6A)	120.1
C(1)-C(6)-H(6A)	120.1
C(12)-C(7)-C(8)	118.7(3)
C(12)-C(7)-P(1)	117.3(3)
C(8)-C(7)-P(1)	124.0(3)
C(9)-C(8)-C(7)	120.2(4)
C(9)-C(8)-H(8A)	119.9
C(7)-C(8)-H(8A)	119.9
C(8)-C(9)-C(10)	120.9(4)
C(8)-C(9)-H(9A)	119.6
C(10)-C(9)-H(9A)	119.6
C(11)-C(10)-C(9)	119.3(4)
C(11)-C(10)-H(10A)	120.3
C(9)-C(10)-H(10A)	120.3
C(10)-C(11)-C(12)	120.9(4)
C(10)-C(11)-H(11A)	119.5
C(12)-C(11)-H(11A)	119.5
C(7)-C(12)-C(11)	119.9(3)
C(7)-C(12)-H(12A)	120.1
C(11)-C(12)-H(12A)	120.1
C(14)-C(13)-C(18)	118.0(3)
C(14)-C(13)-P(1)	123.9(3)
C(18)-C(13)-P(1)	118.0(3)
C(15)-C(14)-C(13)	122.0(4)
C(15)-C(14)-H(14A)	119.0
C(13)-C(14)-H(14A)	119.0
C(14)-C(15)-N(15)	118.5(3)
C(14)-C(15)-C(16)	118.6(4)
N(15)-C(15)-C(16)	122.4(4)
C(19)-N(15)-C(15)	122.5(3)
C(17)-C(16)-C(15)	119.6(4)
C(17)-C(16)-H(16A)	120.2
C(15)-C(16)-H(16A)	120.2
C(18)-C(17)-C(16)	121.1(4)
C(18)-C(17)-H(17A)	119.5
C(16)-C(17)-H(17A)	119.5

C(17)-C(18)-C(13)	120.7(4)
C(17)-C(18)-H(18A)	119.7
C(13)-C(18)-H(18A)	119.7
N(15)-C(19)-N(19)	119.1(3)
N(15)-C(19)-C(22)	124.5(4)
N(19)-C(19)-C(22)	116.5(3)
C(19)-N(19)-C(21)	121.9(3)
C(19)-N(19)-C(20)	120.1(3)
C(21)-N(19)-C(20)	115.9(3)
N(19)-C(20)-H(20A)	109.5
N(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
N(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
N(19)-C(21)-H(21A)	109.5
N(19)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
N(19)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(19)-C(22)-H(22A)	109.5
C(19)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(19)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å^{2}x 10^3) for mono-SwitchPhos. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	36(1)	26(1)	38(1)	1(1)	18(1)	1(1)
C(1)	35(2)	23(2)	42(2)	-1(2)	22(2)	-2(2)
C(2)	43(2)	29(2)	44(2)	-1(2)	19(2)	-2(2)
C(3)	51(2)	30(3)	57(3)	8(2)	28(2)	4(2)
C(4)	52(2)	21(2)	75(3)	-5(2)	36(2)	-4(2)
C(5)	46(2)	40(3)	52(3)	-8(2)	26(2)	-5(2)
C(6)	37(2)	31(2)	44(2)	-5(2)	19(2)	-4(2)
C(7)	41(2)	21(2)	42(2)	-3(2)	22(2)	-4(2)
C(8)	37(2)	45(3)	40(2)	-3(2)	20(2)	-1(2)
C(9)	38(2)	49(3)	43(2)	-1(2)	15(2)	-7(2)
C(10)	52(2)	31(2)	46(2)	-3(2)	24(2)	-9(2)
C(11)	60(3)	37(3)	49(2)	-8(2)	32(2)	5(2)
C(12)	43(2)	32(2)	43(2)	1(2)	22(2)	4(2)
C(13)	31(2)	33(2)	37(2)	3(2)	17(2)	2(2)
C(14)	41(2)	28(2)	37(2)	3(2)	22(2)	1(2)
C(15)	35(2)	33(2)	34(2)	4(2)	14(2)	4(2)
N(15)	46(2)	33(2)	41(2)	3(1)	27(2)	5(1)
C(16)	39(2)	34(3)	44(2)	2(2)	21(2)	-2(2)
C(17)	40(2)	33(2)	48(2)	3(2)	19(2)	-1(2)
C(18)	41(2)	34(3)	41(2)	-1(2)	21(2)	-1(2)
C(19)	37(2)	32(2)	46(2)	1(2)	27(2)	-3(2)
N(19)	43(2)	31(2)	41(2)	-5(1)	23(2)	-1(1)
C(20)	53(2)	35(3)	58(3)	-3(2)	30(2)	5(2)
C(21)	62(3)	42(3)	52(3)	-13(2)	33(2)	-8(2)
C(22)	51(2)	42(3)	45(2)	1(2)	21(2)	-1(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10 ^{3}) for mono-SwitchPhos.

	x	y	z	U(eq)
H(2A)	6863	-1073	9669	47
H(3A)	6365	-2467	9662	54
H(4A)	4888	-3087	7743	56
H(5A)	3889	-2315	5840	53
H(6A)	4335	-913	5833	44
H(8A)	8754	122	9472	48
H(9A)	9960	517	11625	53
H(10A)	9000	1186	12788	51
H(11A)	6805	1418	11804	54
H(12A)	5552	1020	9636	46
H(14A)	7032	-971	6414	40
H(16A)	9252	396	5199	45
H(17A)	8750	1571	6071	48
H(18A)	7446	1487	7141	45
H(20A)	9924	-2294	5802	71
H(20B)	10331	-2798	4829	71
H(20C)	9054	-3044	4965	71
H(21A)	7576	-2578	2309	74
H(21B)	9034	-2759	2588	74
H(21C)	8397	-1885	2005	74
H(22A)	7168	-330	3292	68
H(22B)	6810	-1131	2376	68
H(22C)	8039	-588	2576	68

Table 6. Torsion angles [°] for mono-SwitchPhos.

C(13)-P(1)-C(1)-C(2)	99.9(3)
C(7)-P(1)-C(1)-C(2)	-5.6(4)
C(13)-P(1)-C(1)-C(6)	-82.0(3)
C(7)-P(1)-C(1)-C(6)	172.5(3)
C(6)-C(1)-C(2)-C(3)	1.4(6)
P(1)-C(1)-C(2)-C(3)	179.5(3)
C(1)-C(2)-C(3)-C(4)	0.0(6)
C(2)-C(3)-C(4)-C(5)	-0.6(6)
C(3)-C(4)-C(5)-C(6)	-0.1(6)
C(4)-C(5)-C(6)-C(1)	1.5(6)
C(2)-C(1)-C(6)-C(5)	-2.1(5)
P(1)-C(1)-C(6)-C(5)	179.6(3)
C(13)-P(1)-C(7)-C(12)	153.9(3)
C(1)-P(1)-C(7)-C(12)	-99.5(3)
C(13)-P(1)-C(7)-C(8)	-25.7(4)
C(1)-P(1)-C(7)-C(8)	81.0(4)
C(12)-C(7)-C(8)-C(9)	0.0(6)
P(1)-C(7)-C(8)-C(9)	179.6(3)
C(7)-C(8)-C(9)-C(10)	-0.7(6)
C(8)-C(9)-C(10)-C(11)	1.1(6)
C(9)-C(10)-C(11)-C(12)	-0.8(6)
C(8)-C(7)-C(12)-C(11)	0.2(6)
P(1)-C(7)-C(12)-C(11)	-179.4(3)
C(10)-C(11)-C(12)-C(7)	0.2(6)
C(1)-P(1)-C(13)-C(14)	11.4(3)
C(7)-P(1)-C(13)-C(14)	117.4(3)
C(1)-P(1)-C(13)-C(18)	-173.2(3)
C(7)-P(1)-C(13)-C(18)	-67.2(3)
C(18)-C(13)-C(14)-C(15)	0.2(5)
P(1)-C(13)-C(14)-C(15)	175.6(3)
C(13)-C(14)-C(15)-N(15)	171.7(3)
C(13)-C(14)-C(15)-C(16)	-0.3(5)
C(14)-C(15)-N(15)-C(19)	122.4(4)
C(16)-C(15)-N(15)-C(19)	-66.0(5)

C(14)-C(15)-C(16)-C(17)	-0.2(5)
N(15)-C(15)-C(16)-C(17)	-171.8(3)
C(15)-C(16)-C(17)-C(18)	0.8(5)
C(16)-C(17)-C(18)-C(13)	-0.9(5)
C(14)-C(13)-C(18)-C(17)	0.4(5)
P(1)-C(13)-C(18)-C(17)	-175.3(3)
C(15)-N(15)-C(19)-N(19)	173.2(3)
C(15)-N(15)-C(19)-C(22)	-7.6(6)
N(15)-C(19)-N(19)-C(21)	165.9(4)
C(22)-C(19)-N(19)-C(21)	-13.3(5)
N(15)-C(19)-N(19)-C(20)	3.2(5)
C(22)-C(19)-N(19)-C(20)	-176.0(3)

Symmetry transformations used to generate equivalent atoms:

2. Crystallographic data for tris-SwitchPhos

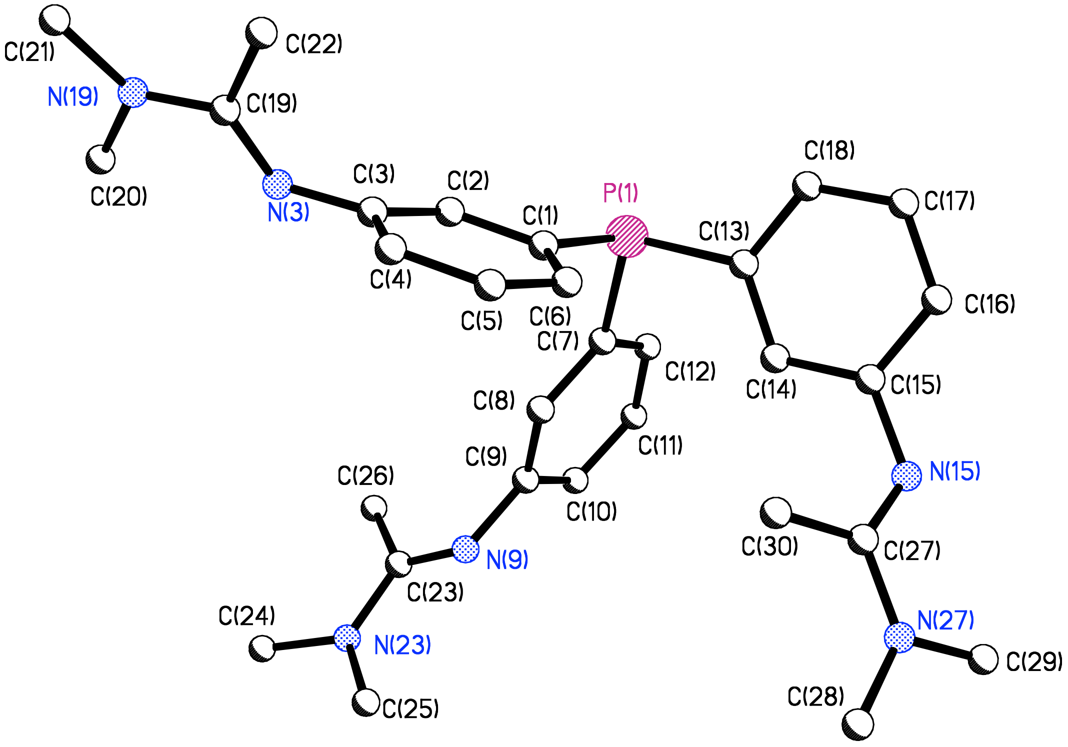

Figure 2 *Molecular structure (ORTEP plot) of tris-SwitchPhos (hydrogen atoms are omitted for clarity).*

Table 1. Crystal data and structure refinement for tris-SwitchPhos.

Empirical formula	C30 H39 N6 P	
Formula weight	514.64	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.7016(8) Å	α= 113.256(5)°.
	b = 13.3035(15) Å	β= 91.826(7)°.
	c = 15.1797(17) Å	γ = 95.123(7)°.
Volume	1419.4(3) Å^3	
Z	2	
Density (calculated)	1.204 Mg/m^3	
Absorption coefficient	0.126 mm^{-1}	
F(000)	552	
Crystal size	0.200 x 0.200 x 0.100 mm^3	
Theta range for data collection	2.93 to 25.35°.	
Index ranges	-9<=h<=9, -16<=k<=15, -15<=l<=18	
Reflections collected	12403	
Independent reflections	4935 [R(int) = 0.0423]	
Completeness to theta = 25.00°	95.6 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9648	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4935 / 0 / 344	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.0478, wR2 = 0.1245	
R indices (all data)	R1 = 0.0518, wR2 = 0.1287	
Largest diff. peak and hole	1.176 and -0.229 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for tris-SwitchPhos. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	4887(1)	2144(1)	6377(1)	23(1)
C(1)	3032(2)	1461(1)	6737(1)	22(1)
C(2)	3340(2)	1278(1)	7573(1)	24(1)
C(3)	2047(2)	747(1)	7914(1)	24(1)
N(23)	969(2)	6533(1)	10272(1)	31(1)
N(3)	2390(2)	670(1)	8801(1)	29(1)
C(4)	413(2)	391(1)	7393(1)	28(1)
C(5)	97(2)	564(2)	6561(1)	29(1)
C(6)	1391(2)	1093(1)	6227(1)	26(1)
C(7)	4738(2)	3618(1)	7094(1)	22(1)
C(8)	3427(2)	4029(1)	7709(1)	21(1)
C(9)	3454(2)	5164(1)	8259(1)	23(1)
N(9)	2064(2)	5538(1)	8839(1)	26(1)
C(10)	4786(2)	5883(2)	8148(1)	28(1)
C(11)	6087(2)	5482(2)	7528(1)	31(1)
C(12)	6079(2)	4352(2)	7015(1)	28(1)
C(13)	4124(2)	1995(1)	5169(1)	21(1)
C(14)	2989(2)	2675(1)	5007(1)	22(1)
C(15)	2432(2)	2534(1)	4073(1)	21(1)
N(15)	1287(2)	3195(1)	3876(1)	23(1)
C(16)	3136(2)	1731(2)	3300(1)	25(1)
C(17)	4242(2)	1042(2)	3455(1)	28(1)
C(18)	4734(2)	1158(1)	4382(1)	25(1)
C(19)	2297(2)	-270(2)	8877(1)	27(1)
N(19)	2574(3)	-264(2)	9769(1)	43(1)
C(20)	2865(4)	787(2)	10595(2)	51(1)
C(21)	2269(3)	-1217(2)	9999(2)	45(1)
C(22)	2003(3)	-1382(2)	8042(1)	31(1)
C(23)	2336(2)	6091(1)	9758(1)	25(1)
C(24)	1030(3)	6941(2)	11320(2)	43(1)
C(25)	-748(3)	6368(2)	9778(2)	38(1)

C(26)	4070(3)	6296(2)	10327(1)	35(1)
C(27)	-271(2)	3234(1)	4185(1)	22(1)
N(27)	-1302(2)	3925(1)	4009(1)	26(1)
C(28)	-3071(2)	4068(2)	4309(2)	32(1)
C(29)	-605(2)	4558(2)	3486(1)	29(1)
C(30)	-1052(2)	2528(2)	4676(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for tris-SwitchPhos.

P(1)-C(13)	1.8360(18)
P(1)-C(1)	1.8377(18)
P(1)-C(7)	1.8451(17)
C(1)-C(2)	1.400(2)
C(1)-C(6)	1.401(2)
C(2)-C(3)	1.398(3)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.402(3)
C(3)-N(3)	1.410(2)
N(23)-C(23)	1.365(2)
N(23)-C(25)	1.454(3)
N(23)-C(24)	1.462(3)
N(3)-C(19)	1.296(2)
C(4)-C(5)	1.388(3)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.391(3)
C(5)-H(5A)	0.9500
C(6)-H(6A)	0.9500
C(7)-C(8)	1.395(2)
C(7)-C(12)	1.398(2)
C(8)-C(9)	1.405(2)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.400(3)
C(9)-N(9)	1.407(2)
N(9)-C(23)	1.294(2)
C(10)-C(11)	1.390(3)
C(10)-H(10A)	0.9500
C(11)-C(12)	1.393(3)
C(11)-H(11A)	0.9500
C(12)-H(12A)	0.9500
C(13)-C(14)	1.394(2)
C(13)-C(18)	1.403(2)
C(14)-C(15)	1.402(2)
C(14)-H(14A)	0.9500

C(15)-C(16)	1.402(2)
C(15)-N(15)	1.405(2)
N(15)-C(27)	1.300(2)
C(16)-C(17)	1.385(3)
C(16)-H(16A)	0.9500
C(17)-C(18)	1.390(3)
C(17)-H(17A)	0.9500
C(18)-H(18A)	0.9500
C(19)-N(19)	1.361(2)
C(19)-C(22)	1.512(2)
N(19)-C(21)	1.444(3)
N(19)-C(20)	1.456(3)
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-C(26)	1.510(3)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
C(27)-N(27)	1.363(2)
C(27)-C(30)	1.509(2)
N(27)-C(29)	1.450(2)
N(27)-C(28)	1.455(2)
C(28)-H(28A)	0.9800

C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800
C(30)-H(30A)	0.9800
C(30)-H(30B)	0.9800
C(30)-H(30C)	0.9800

C(13)-P(1)-C(1)	102.72(8)
C(13)-P(1)-C(7)	101.86(7)
C(1)-P(1)-C(7)	103.03(8)
C(2)-C(1)-C(6)	119.04(16)
C(2)-C(1)-P(1)	115.91(13)
C(6)-C(1)-P(1)	125.02(13)
C(3)-C(2)-C(1)	121.59(16)
C(3)-C(2)-H(2A)	119.2
C(1)-C(2)-H(2A)	119.2
C(2)-C(3)-C(4)	118.30(16)
C(2)-C(3)-N(3)	118.81(16)
C(4)-C(3)-N(3)	122.69(16)
C(23)-N(23)-C(25)	119.43(16)
C(23)-N(23)-C(24)	122.61(17)
C(25)-N(23)-C(24)	116.34(17)
C(19)-N(3)-C(3)	121.89(15)
C(5)-C(4)-C(3)	120.55(17)
C(5)-C(4)-H(4A)	119.7
C(3)-C(4)-H(4A)	119.7
C(4)-C(5)-C(6)	120.77(17)
C(4)-C(5)-H(5A)	119.6
C(6)-C(5)-H(5A)	119.6
C(5)-C(6)-C(1)	119.74(16)
C(5)-C(6)-H(6A)	120.1
C(1)-C(6)-H(6A)	120.1
C(8)-C(7)-C(12)	119.21(16)
C(8)-C(7)-P(1)	124.77(13)

C(12)-C(7)-P(1)	116.01(13)
C(7)-C(8)-C(9)	121.01(16)
C(7)-C(8)-H(8A)	119.5
C(9)-C(8)-H(8A)	119.5
C(10)-C(9)-C(8)	118.58(16)
C(10)-C(9)-N(9)	122.54(16)
C(8)-C(9)-N(9)	118.66(15)
C(23)-N(9)-C(9)	121.20(15)
C(11)-C(10)-C(9)	120.79(17)
C(11)-C(10)-H(10A)	119.6
C(9)-C(10)-H(10A)	119.6
C(10)-C(11)-C(12)	119.89(17)
C(10)-C(11)-H(11A)	120.1
C(12)-C(11)-H(11A)	120.1
C(11)-C(12)-C(7)	120.45(16)
C(11)-C(12)-H(12A)	119.8
C(7)-C(12)-H(12A)	119.8
C(14)-C(13)-C(18)	119.37(16)
C(14)-C(13)-P(1)	123.10(12)
C(18)-C(13)-P(1)	117.53(13)
C(13)-C(14)-C(15)	121.44(15)
C(13)-C(14)-H(14A)	119.3
C(15)-C(14)-H(14A)	119.3
C(14)-C(15)-C(16)	117.98(15)
C(14)-C(15)-N(15)	123.39(15)
C(16)-C(15)-N(15)	118.53(15)
C(27)-N(15)-C(15)	119.75(14)
C(17)-C(16)-C(15)	120.78(16)
C(17)-C(16)-H(16A)	119.6
C(15)-C(16)-H(16A)	119.6
C(16)-C(17)-C(18)	120.78(16)
C(16)-C(17)-H(17A)	119.6
C(18)-C(17)-H(17A)	119.6
C(17)-C(18)-C(13)	119.47(16)
C(17)-C(18)-H(18A)	120.3
C(13)-C(18)-H(18A)	120.3

N(3)-C(19)-N(19)	117.86(16)
N(3)-C(19)-C(22)	125.07(16)
N(19)-C(19)-C(22)	116.97(16)
C(19)-N(19)-C(21)	124.82(18)
C(19)-N(19)-C(20)	119.01(17)
C(21)-N(19)-C(20)	115.03(17)
N(19)-C(20)-H(20A)	109.5
N(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
N(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
N(19)-C(21)-H(21A)	109.5
N(19)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
N(19)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(19)-C(22)-H(22A)	109.5
C(19)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(19)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
N(9)-C(23)-N(23)	118.77(16)
N(9)-C(23)-C(26)	125.20(16)
N(23)-C(23)-C(26)	116.03(16)
N(23)-C(24)-H(24A)	109.5
N(23)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
N(23)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
N(23)-C(25)-H(25A)	109.5
N(23)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5

N(23)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(23)-C(26)-H(26A)	109.5
C(23)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
C(23)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
N(15)-C(27)-N(27)	117.33(15)
N(15)-C(27)-C(30)	124.88(15)
N(27)-C(27)-C(30)	117.71(15)
C(27)-N(27)-C(29)	118.30(14)
C(27)-N(27)-C(28)	124.21(15)
C(29)-N(27)-C(28)	117.49(15)
N(27)-C(28)-H(28A)	109.5
N(27)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
N(27)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
N(27)-C(29)-H(29A)	109.5
N(27)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
N(27)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5
C(27)-C(30)-H(30A)	109.5
C(27)-C(30)-H(30B)	109.5
H(30A)-C(30)-H(30B)	109.5
C(27)-C(30)-H(30C)	109.5
H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for tris-SwitchPhos. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[h^2 $a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	23(1)	21(1)	23(1)	8(1)	1(1)	2(1)
C(1)	26(1)	15(1)	22(1)	5(1)	2(1)	3(1)
C(2)	28(1)	16(1)	23(1)	4(1)	-1(1)	2(1)
C(3)	35(1)	15(1)	20(1)	3(1)	2(1)	3(1)
N(23)	35(1)	27(1)	29(1)	8(1)	7(1)	8(1)
N(3)	43(1)	22(1)	20(1)	6(1)	0(1)	-1(1)
C(4)	32(1)	21(1)	26(1)	8(1)	5(1)	-2(1)
C(5)	28(1)	28(1)	29(1)	9(1)	-3(1)	-2(1)
C(6)	29(1)	25(1)	25(1)	11(1)	-2(1)	1(1)
C(7)	23(1)	22(1)	19(1)	8(1)	-2(1)	1(1)
C(8)	21(1)	23(1)	20(1)	9(1)	-3(1)	-1(1)
C(9)	23(1)	25(1)	20(1)	8(1)	-3(1)	3(1)
N(9)	26(1)	25(1)	24(1)	7(1)	1(1)	3(1)
C(10)	31(1)	21(1)	27(1)	6(1)	-2(1)	0(1)
C(11)	31(1)	26(1)	32(1)	9(1)	3(1)	-5(1)
C(12)	26(1)	27(1)	26(1)	7(1)	5(1)	0(1)
C(13)	19(1)	20(1)	23(1)	7(1)	3(1)	-1(1)
C(14)	21(1)	20(1)	21(1)	4(1)	5(1)	2(1)
C(15)	18(1)	22(1)	22(1)	8(1)	3(1)	-2(1)
N(15)	22(1)	24(1)	20(1)	9(1)	2(1)	1(1)
C(16)	24(1)	29(1)	18(1)	4(1)	3(1)	-2(1)
C(17)	25(1)	24(1)	26(1)	1(1)	7(1)	2(1)
C(18)	21(1)	20(1)	30(1)	6(1)	5(1)	2(1)
C(19)	31(1)	26(1)	22(1)	9(1)	4(1)	1(1)
N(19)	75(1)	33(1)	23(1)	13(1)	2(1)	3(1)
C(20)	84(2)	44(1)	20(1)	9(1)	0(1)	5(1)
C(21)	63(1)	43(1)	39(1)	26(1)	9(1)	8(1)
C(22)	43(1)	23(1)	27(1)	8(1)	1(1)	3(1)
C(23)	32(1)	17(1)	25(1)	8(1)	2(1)	5(1)
C(24)	58(1)	36(1)	30(1)	6(1)	14(1)	14(1)
C(25)	29(1)	33(1)	50(1)	14(1)	7(1)	7(1)

C(26)	41(1)	33(1)	24(1)	5(1)	-5(1)	11(1)
C(27)	21(1)	22(1)	18(1)	4(1)	-2(1)	-1(1)
N(27)	23(1)	29(1)	26(1)	12(1)	3(1)	5(1)
C(28)	23(1)	34(1)	39(1)	16(1)	1(1)	5(1)
C(29)	32(1)	29(1)	28(1)	13(1)	0(1)	4(1)
C(30)	22(1)	30(1)	29(1)	13(1)	3(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for tris-SwitchPhos

	x	y	z	U(eq)
H(2A)	4454	1521	7916	28
H(4A)	-484	29	7612	33
H(5A)	-1016	317	6216	35
H(6A)	1163	1205	5656	31
H(8A)	2502	3535	7756	26
H(10A)	4802	6654	8499	33
H(11A)	6980	5977	7455	37
H(12A)	6991	4078	6609	33
H(14A)	2584	3245	5541	26
H(16A)	2851	1658	2663	30
H(17A)	4670	483	2921	33
H(18A)	5478	674	4482	30
H(20A)	3483	1338	10405	76
H(20B)	3571	705	11106	76
H(20C)	1738	1025	10829	76
H(21A)	1186	-1181	10327	67
H(21B)	3249	-1229	10421	67
H(21C)	2164	-1887	9406	67
H(22A)	869	-1758	8074	47
H(22B)	2933	-1826	8075	47
H(22C)	2018	-1282	7436	47
H(24A)	931	6316	11511	64
H(24B)	59	7382	11556	64
H(24C)	2141	7398	11597	64
H(25A)	-617	6362	9136	57
H(25B)	-1425	6968	10146	57
H(25C)	-1359	5664	9719	57
H(26A)	4935	5898	9902	52
H(26B)	3936	6035	10845	52
H(26C)	4465	7086	10605	52

H(28A)	-3378	3607	4662	48
H(28B)	-3890	3851	3741	48
H(28C)	-3138	4842	4726	48
H(29A)	529	4957	3796	43
H(29B)	-1416	5086	3486	43
H(29C)	-458	4060	2822	43
H(30A)	-365	1909	4564	40
H(30B)	-2260	2247	4413	40
H(30C)	-1039	2970	5368	40

Table 6. Torsion angles [°] for tris-SwitchPhos.

C(13)-P(1)-C(1)-C(2)	169.65(13)
C(7)-P(1)-C(1)-C(2)	-84.77(13)
C(13)-P(1)-C(1)-C(6)	-8.49(16)
C(7)-P(1)-C(1)-C(6)	97.09(15)
C(6)-C(1)-C(2)-C(3)	-0.5(2)
P(1)-C(1)-C(2)-C(3)	-178.79(13)
C(1)-C(2)-C(3)-C(4)	0.3(2)
C(1)-C(2)-C(3)-N(3)	-174.80(15)
C(2)-C(3)-N(3)-C(19)	-122.76(19)
C(4)-C(3)-N(3)-C(19)	62.4(2)
C(2)-C(3)-C(4)-C(5)	0.0(3)
N(3)-C(3)-C(4)-C(5)	174.89(16)
C(3)-C(4)-C(5)-C(6)	0.0(3)
C(4)-C(5)-C(6)-C(1)	-0.2(3)
C(2)-C(1)-C(6)-C(5)	0.5(3)
P(1)-C(1)-C(6)-C(5)	178.59(13)
C(13)-P(1)-C(7)-C(8)	103.69(15)
C(1)-P(1)-C(7)-C(8)	-2.54(16)
C(13)-P(1)-C(7)-C(12)	-77.84(14)
C(1)-P(1)-C(7)-C(12)	175.93(13)
C(12)-C(7)-C(8)-C(9)	-1.1(2)
P(1)-C(7)-C(8)-C(9)	177.28(12)
C(7)-C(8)-C(9)-C(10)	2.8(2)
C(7)-C(8)-C(9)-N(9)	177.55(15)
C(10)-C(9)-N(9)-C(23)	-63.7(2)
C(8)-C(9)-N(9)-C(23)	121.79(18)
C(8)-C(9)-C(10)-C(11)	-2.0(3)
N(9)-C(9)-C(10)-C(11)	-176.55(16)
C(9)-C(10)-C(11)-C(12)	-0.4(3)
C(10)-C(11)-C(12)-C(7)	2.1(3)
C(8)-C(7)-C(12)-C(11)	-1.4(3)
P(1)-C(7)-C(12)-C(11)	-179.91(14)
C(1)-P(1)-C(13)-C(14)	79.94(15)
C(7)-P(1)-C(13)-C(14)	-26.54(15)

C(1)-P(1)-C(13)-C(18)	-100.44(14)
C(7)-P(1)-C(13)-C(18)	153.08(13)
C(18)-C(13)-C(14)-C(15)	0.5(2)
P(1)-C(13)-C(14)-C(15)	-179.87(12)
C(13)-C(14)-C(15)-C(16)	-3.9(2)
C(13)-C(14)-C(15)-N(15)	179.78(15)
C(14)-C(15)-N(15)-C(27)	-60.0(2)
C(16)-C(15)-N(15)-C(27)	123.76(17)
C(14)-C(15)-C(16)-C(17)	4.9(2)
N(15)-C(15)-C(16)-C(17)	-178.62(15)
C(15)-C(16)-C(17)-C(18)	-2.5(3)
C(16)-C(17)-C(18)-C(13)	-1.1(3)
C(14)-C(13)-C(18)-C(17)	2.0(2)
P(1)-C(13)-C(18)-C(17)	-177.61(13)
C(3)-N(3)-C(19)-N(19)	-177.16(18)
C(3)-N(3)-C(19)-C(22)	6.5(3)
N(3)-C(19)-N(19)-C(21)	170.4(2)
C(22)-C(19)-N(19)-C(21)	-12.9(3)
N(3)-C(19)-N(19)-C(20)	3.3(3)
C(22)-C(19)-N(19)-C(20)	179.9(2)
C(9)-N(9)-C(23)-N(23)	173.22(15)
C(9)-N(9)-C(23)-C(26)	-6.8(3)
C(25)-N(23)-C(23)-N(9)	0.3(3)
C(24)-N(23)-C(23)-N(9)	165.25(18)
C(25)-N(23)-C(23)-C(26)	-179.65(17)
C(24)-N(23)-C(23)-C(26)	-14.7(3)
C(15)-N(15)-C(27)-N(27)	177.24(14)
C(15)-N(15)-C(27)-C(30)	-6.2(2)
N(15)-C(27)-N(27)-C(29)	0.5(2)
C(30)-C(27)-N(27)-C(29)	-176.26(15)
N(15)-C(27)-N(27)-C(28)	-179.80(16)
C(30)-C(27)-N(27)-C(28)	3.4(2)

Symmetry transformations used to generate equivalent atoms: