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Towards continuous Rh-hydroformylation of long chain alkenes: handling methodology for the long-term stability of Biphephos in a continuous reactor with an attached membrane separation unit†

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Diphosphites like Biphephos are known for their combination of high activity and high linear selectivity in the Rh-catalyzed hydroformylation of terminal alkenes. However, like most phosphite-type ligands, Biphephos is prone to hydrolysis under acidic conditions and oxidation in the presence of oxygen, resulting in detrimental catalyst performance loss. In this work, we identified practical aspects that safeguard the long-term stability of Biphephos during the Rh-catalyzed hydroformylation of alkenes. Furthermore, different additives (amines and one epoxide) were explored as stabilizers for Biphephos. The Biphephos/Rh/stabilizer system was first extensively investigated *via* ^{31}P-NMR, followed by batch autoclave experiments (100 ml reactors), and finally applied in an upscaled reactor (300 ml) with an attached nanofiltration membrane unit for catalyst retention. With cyclohexene oxide (CHO) as a stabilizer for the ligand, stable operation with high catalyst retention (95%) was achieved for over 100 h at high product selectivity (l/b = 78).

Introduction

Rh-catalyzed hydroformylation of alkenes is widely applied in industry, whereby alkenes are reacted with synthesis gas (CO/H_2) to form aldehydes, see Fig. 1 right side for a reaction overview. In this reaction, various ligands can be applied with varying stability, activity, and selectivity results. One group of industrially relevant ligands are bidentate phosphite ligands which are highly active and selective towards the linear aldehyde.[1] One of the more established derivatives of such bidentate phosphite ligands is Biphephos (Fig. 1, left side), first presented in the patent literature in the mid-1980s.[2,3] It has a wide bite-angle (β_n = 123°) and is known for high activity (TOF = 2000–6000 h^{-1}) and excellent selectivity towards the linear aldehyde in the Rh-catalyzed hydroformylation of terminal alkenes. The reported l/b ratios have been close to 100.[4–6]

The Rh–Biphephos catalyst is also known for the fast double bond isomerization of alkenes, allowing for its use in the hydroformylation of internal alkenes towards the linear aldehydes.[5,7] A high l/b ratio is only realized as long as a sufficiently large quantity of intact Biphephos ligand is present in the reaction system. More recent patents concerning the improved synthesis of Biphephos prove that industry is maintaining a keen interest in this type of ligands.[8–15] Furthermore, other patents focus on purification procedures for such diphosphite ligands to safeguard their long-term stability, *e.g.*, by reducing residual chloride content.[16–20] It is known that phosphites can undergo various (autocatalytic) decomposition reactions, many of which are catalyzed by acids. Notably, in many cases, the decomposition products are acids themselves.[21–26] Hydrolysis is one of the more prominent decomposition reactions of phosphites. The hydrolysis products are pentavalent phosphorus compounds, also known as phosphonic acid diesters or secondary phosphine oxides (SPO) or as pentavalent heteroatom-substituted phosphine oxides (HASPO),[27] see ESI 2.† These exist in a tautomeric equilibrium with trivalent phosphorus species, able to coordinate to transition metals such as rhodium to form active but unselective hydroformylation catalysts.[28] Oxidation of the phosphorus atoms in Biphephos is also possible in the presence of oxygen, but also introducing alkenes will significantly accelerate the oxidation.[29] See ESI 1† for further information about phosphite decomposition and its effect on

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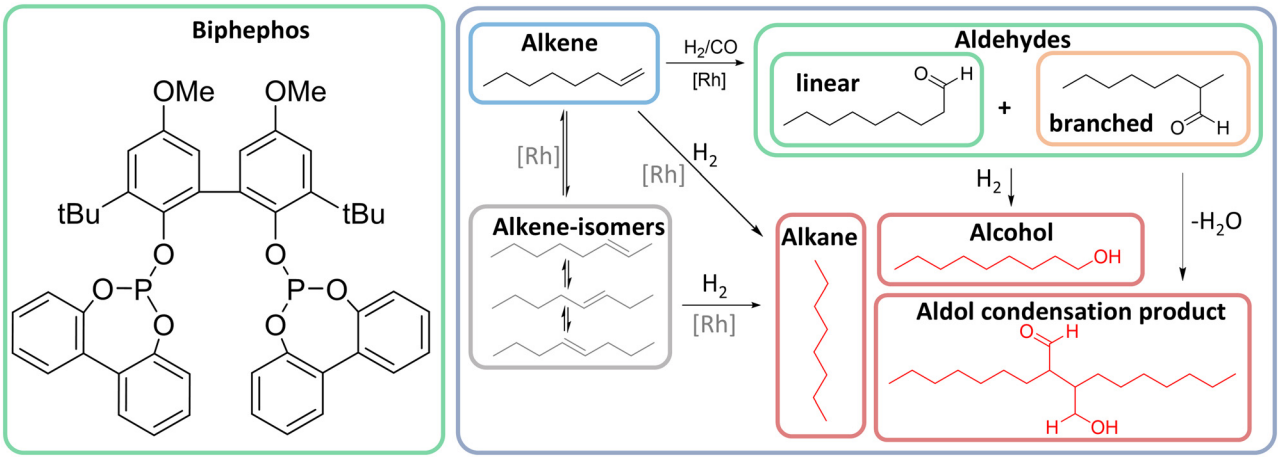

Fig. 1 On the left side: the ligands Biphephos; on the right side: a reaction overview of Rh-catalyzed hydroformylation of a terminal alkene where the most desired product is the linear aldehyde. Hydrogenation products such as alkane and alcohols can be produced. Aldol condensation products from aldehydes can be formed.

catalyst selectivity. Despite the delicate nature of phosphite ligands, several stable, continuously operated Rh/phosphite-catalyzed hydroformylation systems for gaseous short-chained alkenes have been reported.[2,3,8,22,30–33] However, continuously operated systems using liquid mid- to long-chained alkene substrates have so far been unstable and/or require a constant ligand make-up stream to maintain stable operation.[34–36] Different measures have been described as suitable for creating more robust hydroformylation systems. Most literature concerning phosphite ligands applied in hydroformylation reactions emphasizes the importance of excluding air by using Schlenk techniques and degassed solvents and reactants, as well as the removal of peroxides from alkene feeds.[37] This is because Biphephos can be oxidized, albeit slow by oxygen itself, but significantly faster by peroxides that can form from alkenes that have reacted with oxygen.[29,38] Liquid alkene substrates can be purified from peroxides by percolating through alumina,[39] and distillation.[37] It has also been suggested that the addition of certain stabilizers to a phosphite-based hydroformylation system is beneficial. Two more commonly discussed types of stabilizers are amines and epoxides. Their function is to neutralize any acidic species (*e.g.* decomposition by-products) from further destabilizing remaining phosphites in the system. See ESI 3† for more detail about the reaction mechanism of these stabilizers. Those stabilizers that have shown better effect of stabilizing phosphite systems include tetramethylpiperidine (TMP) and derivatives thereof (*e.g.*, bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate, Tinuvin® 770),[33,40] triethylamine (TEA)[41] and cyclohexene oxide (CHO),[32] all presented in Fig. 2. The initial purity of the Biphephos used is important as impurities often are acidic decomposition products that can then destabilize the catalytic system.[29]

Research gap

So far, there has not been a single academic publication on a long-term (>10 h) continuously operated stable diphosphite-based hydroformylation system for mid- to long-chained alkene substrates, without the need of catalyst/ligand make-up streams. This is surprising, considering the number of publications and patents showing the long-term stability of such systems for short-chained alkenes. This work thus sets out to identify and explore the crucial parameters to achieve predictable long-term stability of a Biphephos/Rh-based hydroformylation system.

Approach

Experimental procedures and catalyst preformation routines were systematically varied to map out their influence on long-term catalyst stability and performance and to identify critical

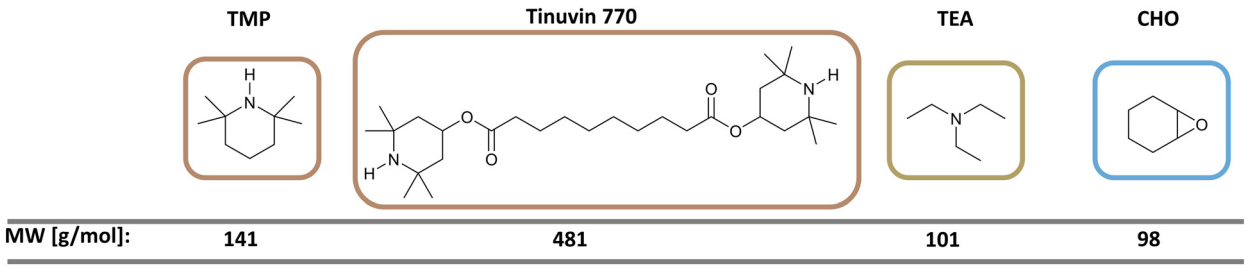

Fig. 2 Three different stabilizers studied for their stabilizing effect on Biphephos. 2,2,6,6-Tetramethylpiperidine (TMP) and Tinuvin® 770 are sterically hindered secondary amines, Et_3N (TEA), and cyclohexene oxide (CHO).

parameters. The impact of stabilizing agents on Biphephos decomposition was studied for extended periods at different relevant temperatures and followed by ^{31}P-NMR spectroscopy, both in the presence and absence of the Rh precursor. Hydroformylation reactions were carried out to identify parameters crucial for achieving a predictably stable Rh/Biphephos-based reaction system. Finally, under optimized conditions for higher ligand stability, hydroformylation of 1-octene was carried out in a continuous reactor combined with a nanofiltration membrane unit for catalyst retention and operated for more than 100 hours.

Results and discussion

^{31}P-NMR investigation of Biphephos/Rh/stabilizer solutions

A set of Biphephos/Rh/stabilizer solutions were prepared to investigate the relative stability of Biphephos in toluene having different stabilizers at a different ratio to the BP. Three different stabilizers, triethylamine, cyclohexene oxide and tetramethylpiperidine, were chosen due to their small size and good solubility in the reaction medium. Tinuvin® 770 was excluded because it is prone to precipitation, which caused problems in the initial membrane experiment (see ESI 6.f†). A method of co-dissolving the solids of Rh-precursor and Biphephos was used for preparing a stock solution of Rh/Biphephos. This method for preparing a Rh/Biphephos solution has been described by several different authors before.[1,7,11,29,40,42–52] In the preparation of the solution for this investigation it was decided that air was not to be excluded as it was believed that Biphephos would be stable against oxygen in the absence of any alkenes. Also, no care was taken to dry glassware or chemicals from water as it was believed the presence of the stabilizers would neutralize any acids and thus prevent any hydrolysis of the phosphites from happening. The Rh/Biphephos solution was distributed into test tubes to which the stabilizers were added. The prepared solutions were then analyzed by ^{31}P-NMR 3 days after preparation. The results are presented in Fig. 3, left side. Large quantities of Biphephos decomposition products[53] believed to be oxidized phosphites were observed (−4.3 and −4.8 ppm)[29] in all of the solutions already after three days of storage at room temperature. The solutions were then heated at 90 °C for 14 h before being resubmitted for analysis by ^{31}P-NMR; the results are presented in Fig. 3, right side. Clearly, after 14 h at 90 °C, all solutions now contained mainly Biphephos decomposition products meaning that the stabilizers had been unable to prevent further decomposition under these conditions. The cause for the decomposition was suspected to be a combination of Rh together with oxygen.

Rh-free stabilizer containing Biphephos solutions

To prove that it was not the stabilizers nor the oxygen alone that caused the decomposition by oxidation, Rh-free Biphephos solutions containing the stabilizers were prepared under a non-

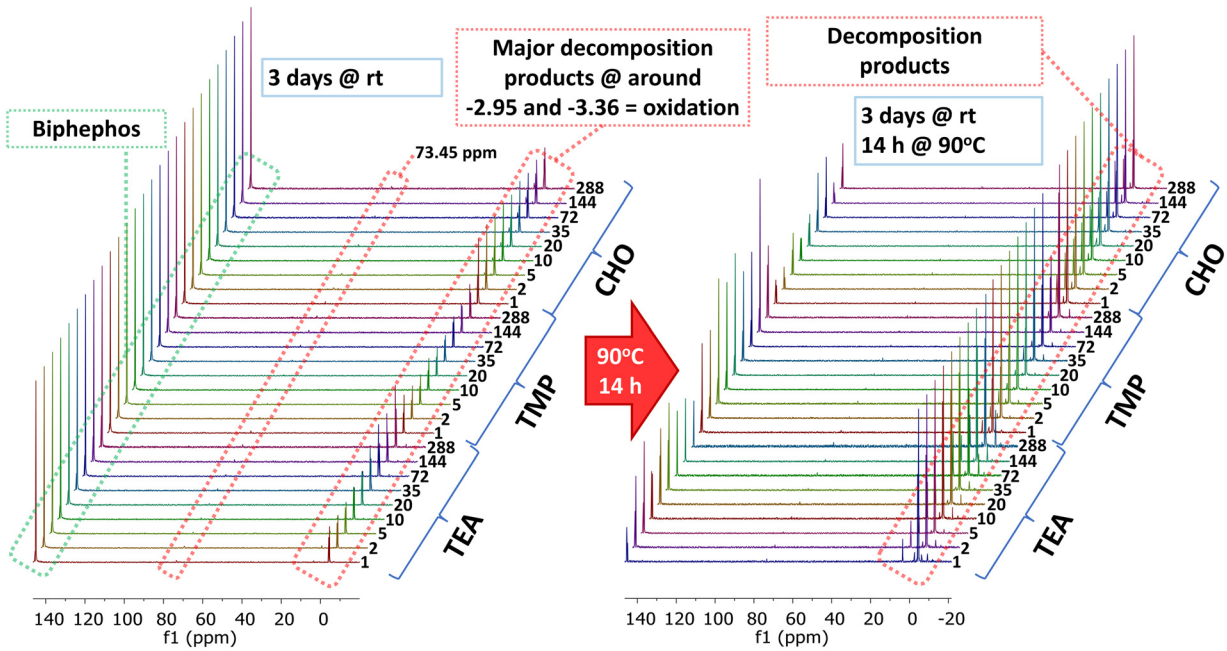

Fig. 3 The effect of Biphephos : stabilizer ratio upon Biphephos stability in the presence of Rh. Solutions were prepared without using any precaution to exclude oxygen or water from the system. Unexpected decomposition of Biphephos (145 ppm) resulted in oxidation decomposition products (−4.3 and −4.8 ppm). The stabilizers are Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene oxide (CHO). The numbers (1, 2, 5, 10, 20, 35, 72, 144, 288) represent the number of stabilizer's molar equivalences relative to Biphephos. NMR samples were prepared with d-toluene. For the stacked spectra on the left the peaks associated with undecomposed Biphephos (145 ppm) were integrated and set to 100 and the decomposition peaks were scaled accordingly. For the stacked spectra on the right the largest peak associated with decomposition products (~−4 ppm) were set to 100 and the Biphephos peaks were scaled accordingly.

inert atmosphere (with regards both to oxygen and water) and analyzed three days after preparation by ^{31}P-NMR. The result from that set of experiments is presented in Fig. 4 left side. As can be seen, only minimal quantities of decomposition products can be identified in the absence of the rhodium while in the presence of the stabilizers and air. However, a trend is observed for the two amines; an increased amount of Biphephos oxidation with an increased amount of amine stabilizer. The amount of oxidized Biphephos that each sample contained was estimated relative to the integral of all the ^{31}P-NMR peaks; this is presented in Fig. 4 right side. These results are indicating that co-dissolving Rh(acac)(CO)$_2$ and Biphephos is causing significant oxidation of the Biphephos in the presence of air. During the co-dissolution of the solid Biphephos and the solid Rh-precursor, for a moment, there will be a very high concentration of Rh-species present. It has been suggested in patent literature that certain Rh-clusters (*e.g.*, $Rh_6(CO)_{16}$) can catalyze the hydrolysis of phosphites.[54] Although it is not likely that such clusters could have been formed during the co-dissolution of the Rh(acac)(CO)$_2$ and Biphephos in this system as that would require the Rh(I) species to be reduced to Rh(0) species and there were no reducing agents present during the dissolution stage. It is likely that certain rhodium species catalyzed the oxidation of Biphephos,[55,56] but the exact nature of those rhodium species is currently not known.

Investigating a proper order of mixing

Different methods of preparing a Rh/Biphephos solution can be found in the literature. One approach is first to dissolve the Rh-precursor separately and then to add it to Biphephos[57] or add Biphephos to a Rh-solution[58,59] or add a Rh-solution to a Biphephos-solution.[5,53,60–62] The last method of preparing a catalyst solution would minimize the risk of exposing Biphephos to unfavorably high rhodium concentrations. The next set of Rh/Biphephos solutions were prepared using this last method. A Biphephos solution was split up into four fractions, to three of which the appropriate amount of stabilizer and Rh-solution was added to give a ratio of Rh : Biphephos : stabilizer = 1 : 5 : 25. The fourth Biphephos solution only got Rh-solution added to it, hence being a stabilizer free solution. The stacked ^{31}P-NMR spectra of those solutions before heating are presented in Fig. 5, left side. Only smaller quantities of oxidation and hydrolysis decomposition products were observed within all the samples directly after they had been prepared. The solutions were then exposed to elevated temperature (90 °C) for 3 h and analyzed by ^{31}P-NMR (Fig. 5, right side). All Biphephos solutions containing stabilizers showed no signs of decomposition, while the stabilizer-free Biphephos solution was completely decomposed having decompositions peaks at 17.2, 15.3 and 3.5 ppm, which is suggesting hydrolysis product. Clearly, by separately dissolving the Rh(acac)(CO)$_2$ and Biphephos there was much less oxidation of the Biphephos compared to co-dissolving Rh(acac)(CO)$_2$ and Biphephos. O_2 did not affect the stability of Biphephos on its own, and the presence of any of the three stabilizers significantly improves the stability of Biphephos at elevated temperature against hydrolysis.

Investigating the long-term effect of Biphephos : stabilizer ratio by ^{31}P-NMR

A set of Rh-containing solutions with varying Biphephos : stabilizer ratios were prepared. The solutions were then

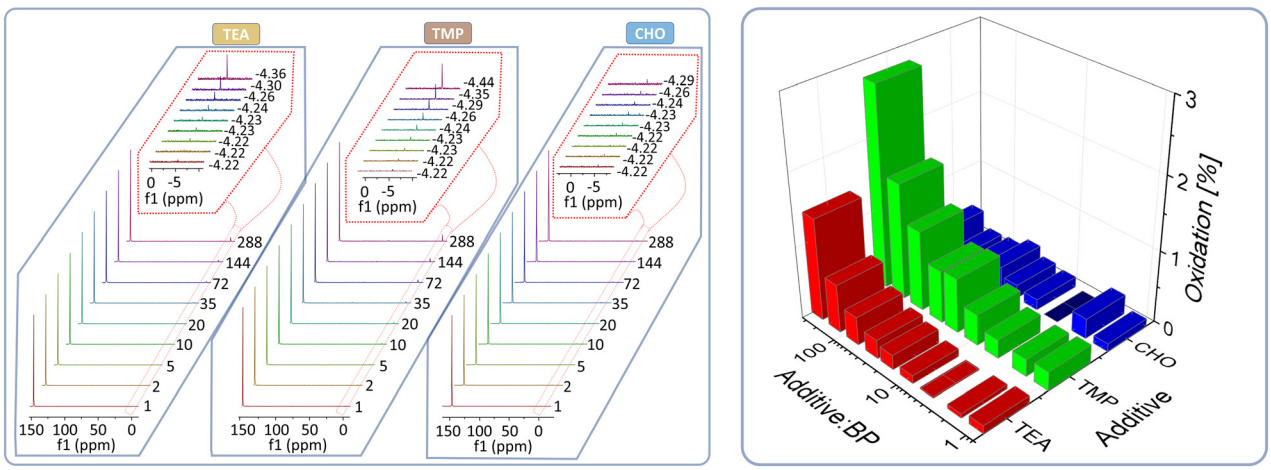

Fig. 4 Left side: A set of Biphephos : stabilizer solutions prepared under non-inert conditions regarding both oxygen and water, investigated by ^{31}P-NMR 3 days after preparation. The stabilizers are Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene oxide (CHO). The numbers (1, 2, 5, 10, 20, 35, 72, 144, 288) represent the number of molar equivalences of stabilizer present relative to Biphephos. NMR samples were prepared with d-toluene. The region around −4 ppm is zoomed in on and the chemical shift of the oxidized Biphephos decomposition product is relative to the chemical shift of the Biphephos peak which was defined to be 145 ppm. Right side: The amount of oxidized Biphephos decomposition product in various stabilizer containing Biphephos solutions after three days of storage at room temperature. Samples contained no rhodium and were prepared with no care taken to exclude air or water.

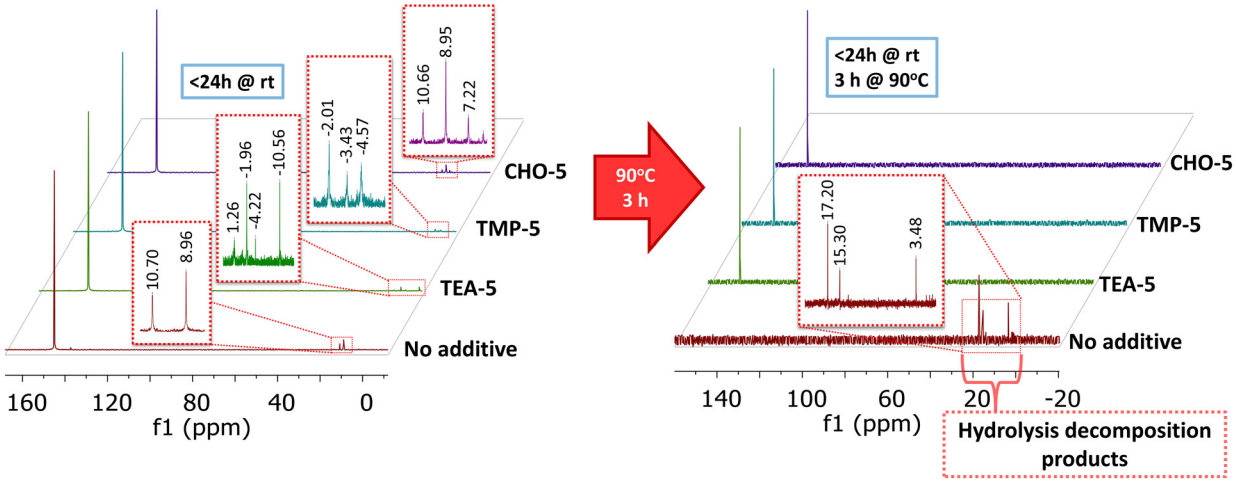

Fig. 5 Correct order of solvating Biphephos and Rh(acac)$(CO)_2$. Biphephos and Rh(acac)$(CO)_2$ were dissolved separately under non-inert conditions with regards to both oxygen and water. The Rh solution was then added dropwise to the Biphephos solution while stirring. Finally, the combined Rh/Biphephos solution was divided into four separate ones, to three of which a stabilizer was added to give Rh : BP : stabilizer = 1 : 5 : 25. The solutions were analysed by ^{31}P-NMR and then subjected to 90 °C for 3 h before being analysed by ^{31}P-NMR again. NMR samples were prepared with d-toluene. The chemical shift of the decomposition products is relative to the chemical shift of the Biphephos peak which was defined to 145 ppm.

intermittently analyzed by ^{31}P-NMR and exposed to elevated temperature. The results from this investigation are presented in Fig. 6. When the Biphephos is intact, only one peak at around +145 ppm is visible. Upon decomposition of one of the two arms of Biphephos, a new peak slightly upshift of +145 ppm starts to take shape. This is thought to be the undecomposed phosphite arm of a Biphephos ligand with the other arm deactivated. The relative integral between the two peaks at around +145 ppm can thus be used to quickly give an idea of the progress of decomposition. The most stable solutions were those containing CHO at any of the concentrations applied or TMP at the lower concentrations applied with a significant increase in decomposition with higher concentrations of TMP.

Summary for the ^{31}P NMR experiments

The ligand Biphephos and the metal precursor Rh(acac)$(CO)_2$ must be dissolved separately before being mixed to not jeopardize the stability of Biphephos. All three stabilizers (TMP, CHO and Et_3N) can stabilize Biphephos dissolved in toluene against hydrolysis compared to a stabilizer-free solution. Increasing concentrations of the amine-based stabilizers resulted in an increasing amount of oxidation decomposition products, which is not necessarily the case for CHO. The presence of oxygen did not cause any oxidation or other decomposition effect of the Biphephos when rhodium and Biphephos were dissolved separately and then combined as determined from the ^{31}P-NMR experiments.

Effect of oxygen on a Biphephos/Rh catalyzed hydroformylation system

The presence of oxygen was clearly not causing any stability issues for the Biphephos in the Biphephos/Rh/additive solutions when being prepared correctly. But oxygen can cause an issue for the stability of Biphephos when also alkenes are present in a system. The combination of alkenes and oxygen will result in the formation of peroxides which are known to oxidize Biphephos much faster.[50,63] To improve exclusion of oxygen from the reaction system, the application of a "pressurize de-pressurize" (PDP) cycle system of a reactor was investigated. After the reactor has been loaded with reaction mass, any residual oxygen left inside the reactor and dissolved in the liquid should be removed. The O_2 equilibrium between the liquid- and gas phase can be offset by applying high pressure, high purity gas to the reactor. When the reactor system's pressure is released, a large part of O_2 present inside the reactor will be purged from the system together with the other gasses. For high efficiency, a high purity gas is recommended. This concept of using PDP-cycles is illustrated in Fig. 7.

There are sources in the literature that describe that they perform a purge/degassing/flush[2,5,31,42,45,48,50,60,61,63–67] after loading the reactor with all reaction mass and before starting to heat. But it is important to stress that flushing the reactor is not the same as applying the PDP. Flushing will be less effective at removing unwanted dissolved gases and gases present in restricted spaces of the reactor piping. The effect of using PDP cycles was measured by the final l/b ratio of Rh/Biphephos catalyzed hydroformylation of 1-octene reaction mixtures after 1000 min (16.7 h) of reaction time in a batch autoclave. The assumption was that a higher l/b ratio in the final reaction mixture indicates that enough Biphephos was left intact to prevent the formation of unselective Rh-species that would then lower the l/b ratio. Thus, a higher final l/b ratio means that the system contained less oxygen at the onset of the reaction. The results from these experiments are presented in Fig. 8.

There was a significant improvement in the l/b ratio by applying only one PDP cycle. The best results were obtained

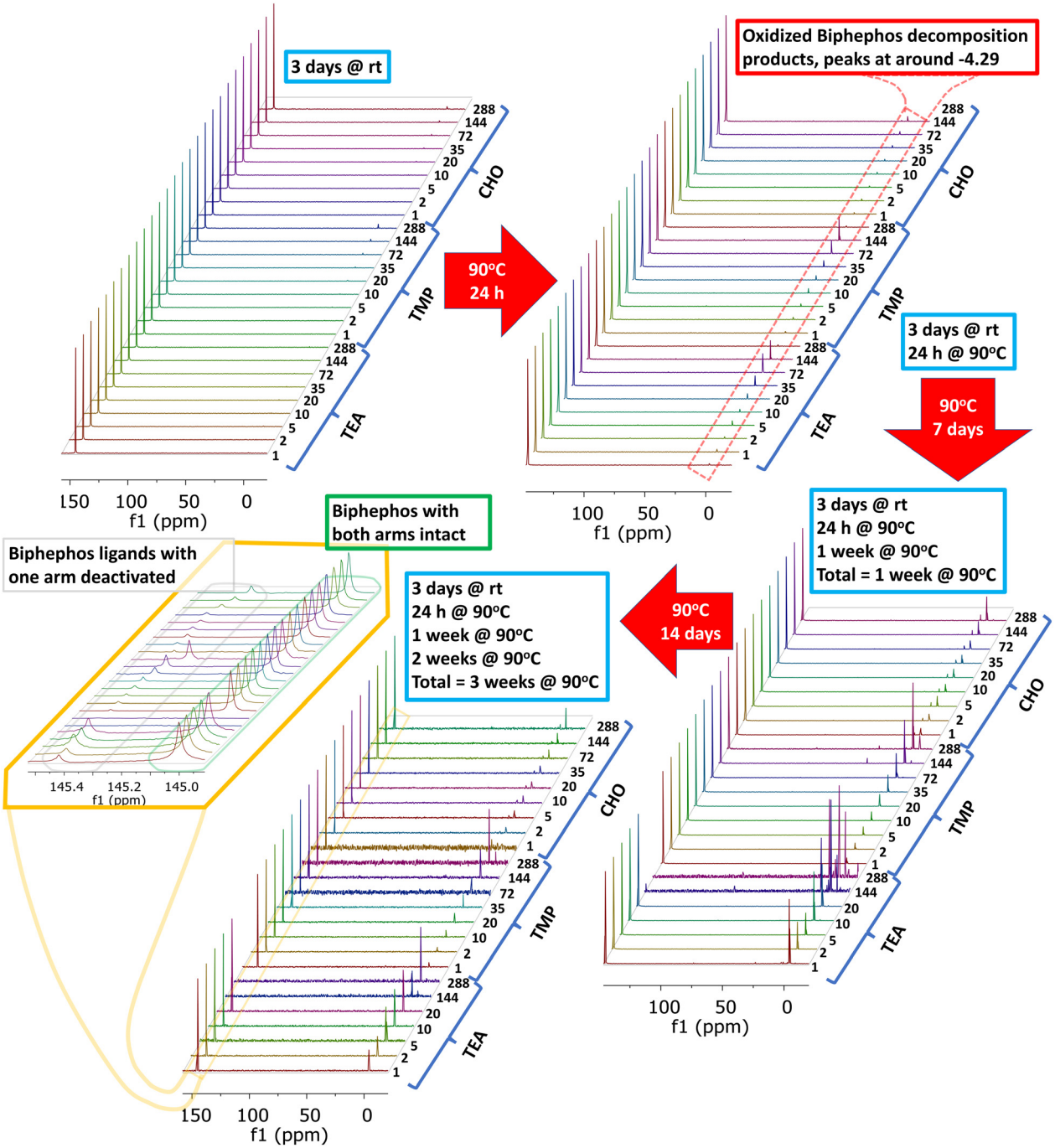

Fig. 6 Different Biphephos : stabilizer ratios and the resulting stability of Biphephos. The solutions were made up into NMR tubes which were exposed to 90 °C for various lengths of time with intermittent ^{31}P-NMR analysis. The stabilizers are Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene oxide (CHO). The numbers (1, 2, 5, 10, 20, 35, 72, 144, 288) represent the number of stabilizer's molar equivalences relative to Biphephos. Rh : BP = 1 : 5. NMR samples were prepared with d-toluene.

by applying three PDP cycles. These PDP-cycle experiments must conclude that a Rh/Biphephos hydroformylation process is very sensitive to oxygen contamination in the reaction system and feed. Therefore, apart from using standard Schlenk technique to prepare the reactors with previously degassed solvents, catalyst- and substrate-solutions, the application of three PDP-cycles will significantly improve the long-term stability and selectivity of the system.

Summary of measures to safeguard against phosphite decomposition

It is worth listing the points required to safeguard the longevity of Biphephos when applied in a Rh-catalyzed hydroformylation reaction system:

- Separate dissolution of (Rh) metal-precursor and phosphite ligand before combining.

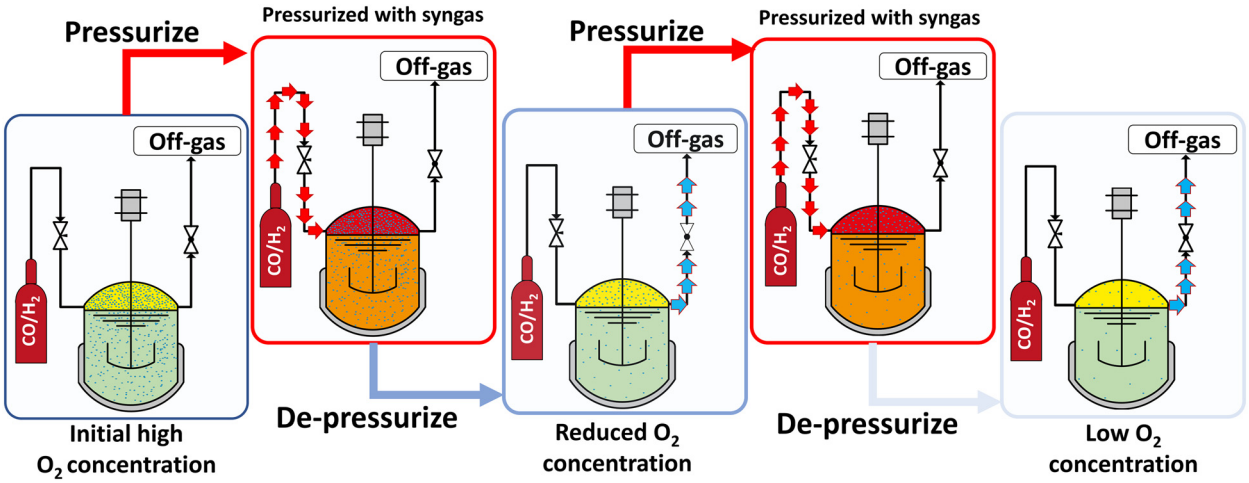

Fig. 7 A schematic representation of how a "pressure-de-pressure" cycle helps to reduce the concentration of O_2 present within the autoclave reactor after being charged with all the reaction mass.

- Removal of peroxides in alkene substrate by percolation over alumina or distillation.
- Use of suitable stabilizers at a proper concentration.
- Apply PDP cycles after loading reaction mass into the reactor and before the start of the reaction.

Continuous flow reaction

To validate all the lessons on how to practically handle Biphephos to establish a long-term stable Rh-catalyzed hydroformylation system, a continuous flow experiment was performed using a nanofiltration membrane reactor miniplant (NEMO 2.0). In this setup an organic solvent nanofiltration membrane (OSN) would allow for a continuous recycling of the catalyst for several hours of operation, see Fig. 9 for a simplified basic scheme. The P&ID and a photo of this miniplant are both in the ESI 6.b.†

The reaction system included a feed solution of 1-octene (25 wt%), toluene (75 wt%) and cyclohexene oxide as a stabilizer, and a catalyst solution of Rh and Biphephos.

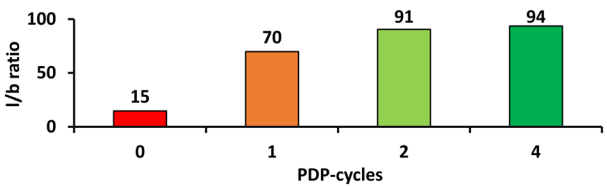

Fig. 8 The effect of PDP-cycles upon the l/b ratio of the final reaction mixture after 1000 min (16.7 h) of reaction in the Rh/Biphephos catalysed hydroformylation of 1-octene in batch autoclaves reactors. Preparation of reaction media and reactors was done using standard Schlenk technique. Conditions: PDP-cycle: 30 bar synthesis gas, 10 min, 700 rpm, degas (and repeat). Rh : L : TMP : 1-octene = 1 : 5 : 5 : 6000. $Rh(acac)(CO)_2$ (2.9 mg, 0.01 mmol); Biphephos (43.8 mg, 0.06 mmol); TMP (0.06 mmol); 1-octene (10.5 ml, 67.4 mmol); CO/H_2 = 1 : 1; P = 20 bar; solvent = toluene 41 ml; 2 h preformation (80 °C, 18 bar).

The screening for a suitable membrane was executed in several pre-experiments (described in detail in the ESI 6.d†). As a result, the SOLSEP BV (NF030105) membrane was chosen for the long-term continuous experiment with a rhodium retention of >95% and an acceptable flux of around 10 g cm^{-2} h^{-1}.

The experiment was carried out for over 100 h and the main results are presented in Fig. 10. During the experiment an average l/b ratio of 78 could be achieved. After 75 h the feed ratio was switched to a higher load of substrate (75 wt% 1-octene and 25 wt% toluene), which directly lead to an accelerated formation of *n*-nonanal.

These results clearly support the validity of all previously discussed methods to obtain a stable Biphephos complex for the hydroformylation of mid-chain aldehydes for longer duration. After 100 h the experiment was terminated by bubbling air through the feed flask leading to a direct drop in the l/b ratio and a coloration of the permeate.

Final NMRs

At the end of the experiment NMR samples were taken before and after oxidizing the feed stream. Fig. 11 clearly shows, that there was plenty of Biphephos that had not decomposed

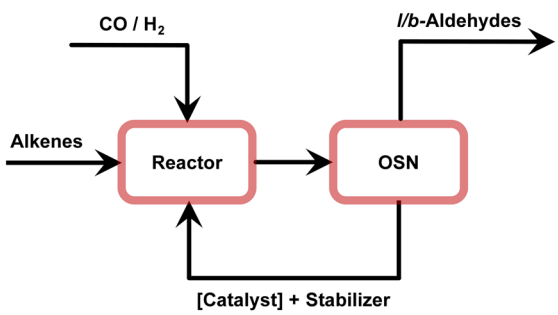

Fig. 9 Basic scheme of the nanofiltration membrane reactor miniplant. The catalyst complex remains in the reaction system.

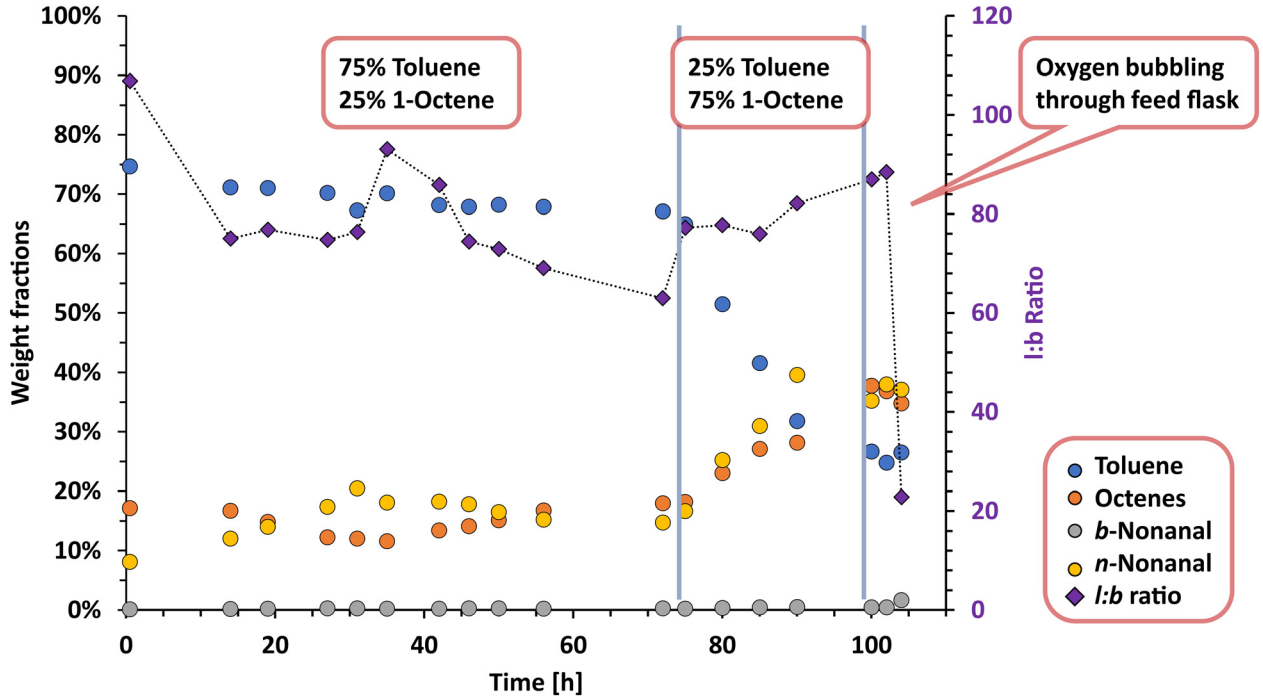

Fig. 10 Weight fractions and l/b ratio over time in hydroformylation of 1-octene in toluene. Reaction conditions: toluene : 1-octene = 75 : 25 up to 75 h then reversed; 1-octene : Rh = 2000 : 1 ($Rh(acac)(CO)_2$ = 144 mg), BP : Rh = 5 : 1 (BP = 2.19 g), CHO : BP = 5 : 1, CO/H_2 = 1 : 1, p = 20 bar, T = 80 °C, n = 200 rpm, no catalyst/ligand make-up. Membrane conditions: SOLSEP (applied in 2.5″ MET-cell), Δ = 40 bar, T = 40 °C.

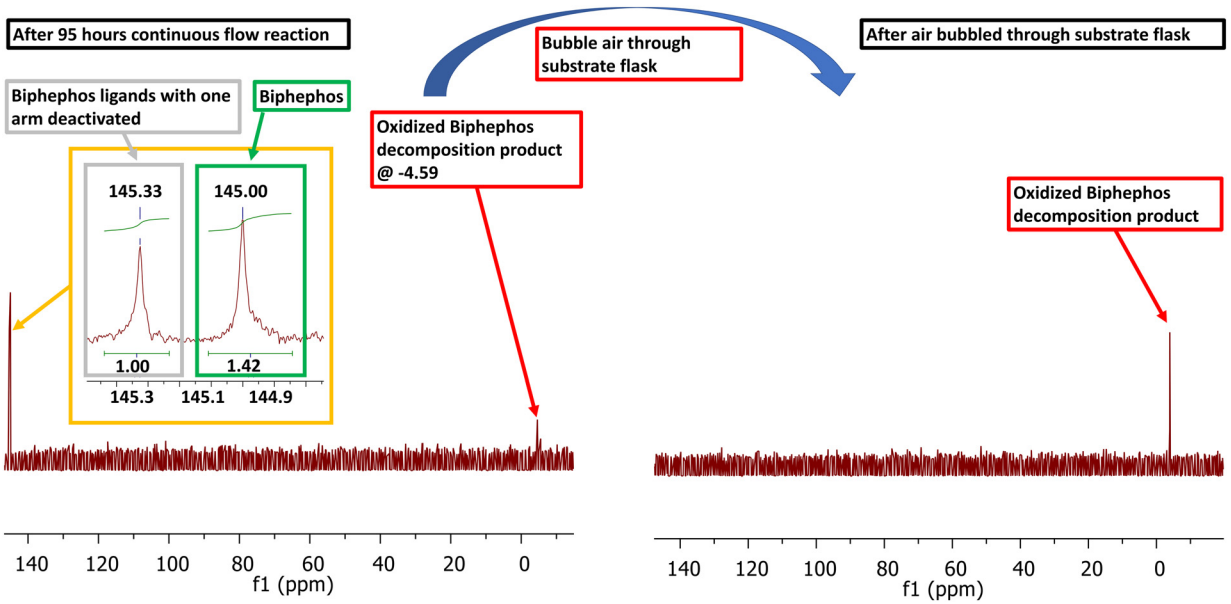

Fig. 11 ^{31}P-NMR analysis before (95 h) and after oxidizing the feed stream (104 h). NMR samples were prepared with d-toluene.

just before starting to bubble air through the substrate solution. And it is clear that all Biphephos had been decomposed in the second NMR sample.

$$R = 1 - \frac{c_{\text{permeate}}}{c_{\text{retentate}}}[\%] \quad (1)$$

Retention and flux

The concentration of Rh and P was measured in the permeate and in the retentate. The retention was calculated according to formula (1) for a given time.

The average retention for rhodium was 95% and for phosphorus 91% (see Fig. 12) and hence lower than expected

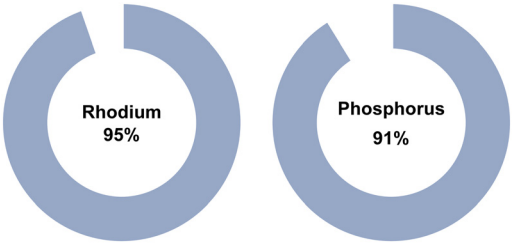

Fig. 12 Average retention for Rh and P, measured by ICP-OES. A table with all results is given in the ESI 6.e.†

from the initial membrane screenings but in a high range for a single stage OSN unit. Nevertheless, leaching was observed and resulted in a lower catalyst loading at the end of the experiment. The result is in line with the other findings. The formed Biphephos–Rh complex is more retainable than uncoordinated rhodium or decomposition products of the catalyst complex. Since the Rh retention is higher than the one from phosphorus, the stability of the complex is again indicated. It must be noted, that for industrial purposes probably a higher retention would be necessary to operate economically.

The flux in the experiment was on average 1.1 g h^{-1} m^{-2}) (see diagram in ESI 6.e†) which was around 5 to 10 times smaller than in the screening experiments leading to a total of 7 to 8 exchanged reactor volumes during the 100 h of the semi-batch experiment. This is the longest time published for a mid-chain hydroformylation with Biphephos.

Comparing the methodologies applied in preparing phosphite-based catalytic systems

The findings of suitable measures recommended to be included in the preparation of phosphite-based catalytic systems can be compared to the various preparation methodologies described in multiple publications/patents concerning phosphite-based systems. A collection of such publications and what preparation steps they included is presented in the ESI 5.† No single source included all the four (recommended) preparation steps/elements, and overall, there is a significant inconsistency in the methodologies used. Nevertheless, the fact that publications did not include such measures does not necessarily mean that the reaction systems were compromised. But it is still surprising how inconsistent the various preparation methodologies have been up until now. That is especially true for Biphephos, which is seemingly rather sensitive towards unfavorable environments and treatment.

Experimental

All experiments used very pure Biphephos (99.9%, see ESI 4†) where purity was determined by ^{31}P-NMR. Toluene (>95%) was a technical grade that was used as received without any prior drying unless specified and had a water content of 131.5 ppm (Karl-Fischer titration).

Premature hydrolysis of Biphephos

A total of 27 NMR samples were prepared, all containing Rh : Biphephos = 1 : 5 and one out of three stabilizers (TMP, Et_3N or CHO) in different ratios Biphephos : stabilizer = 1 : 1, 1 : 2, 1 : 5, 1 : 10, 1 : 20, 1 : 35, 1 : 72, 1 : 144 and 1 : 288. The samples were prepared accordingly:

$Rh(acac)(CO)_2$ (37.14 mg, 0.14 mmol) and Biphephos (566.16 mg, 0.72 mmol) were each weighed out into a round bottom flask containing a stirrer-bar, no care was taken to inertness from air or water. Toluene (90 ml) was added to the solids in the round bottom flasks to dissolve them while stirring for about 1 h until (almost) everything had dissolved. A series of 27 test tubes (3 × 9) with screw caps were prepared with 2 ml each of the Biphephos/Rh solution and 0.5 so that each test tube contained Biphephos (12.58 mg, 0.016 mmol). The three different stabilizers were then added to the test tubes so that the relevant ratio of Biphephos : stabilizer was established. These solutions were then used for preparing the NMR samples using d-toluene. After the NMR tubes had been analyzed by ^{31}P-NMR they were subjugated to heating at 90 °C for 14 h and then again analyzed by ^{31}P-NMR.

Rh-free stabilizer-containing solutions

A total of 27 NMR samples were prepared, all containing Biphephos and one out of three stabilizers (TMP, Et_3N or CHO) in different ratios Biphephos : stabilizer = 1 : 1, 1 : 2, 1 : 5, 1 : 10, 1 : 20, 1 : 35, 1 : 72, 1 : 144 and 1 : 288. The samples were prepared accordingly:

Biphephos (566.16 mg, 0.72 mmol) was weighed out into a round bottom flask containing a stirrer-bar, no care was taken to inertness from air or water. Toluene (90 ml) was added to the round bottom flasks while stirring for about 1 h until everything had dissolved. A series of 27 test tubes (3 × 9) with screw caps were prepared with 2 ml each of the Biphephos solution so that each test tube contained Biphephos (12.58 mg, 0.016 mmol). The three different stabilizers were then added to the test tubes so that the relevant ratio of Biphephos : stabilizer was established. These solutions were then used for preparing the NMR samples according to standard procedure previously described above.

Correct order of mixing $Rh(acac)(CO)_2$ and Biphephos

A total of 4 NMR samples were prepared, all containing Rh : Biphephos = 1 : 5, one of which had no stabilizer and the other three had one out of the three stabilizers TMP, Et_3N or CHO present in a ratio Biphephos : stabilizer = 1 : 5. The samples were prepared accordingly:

Biphephos (134.80 mg, 0.17 mmol) and $Rh(acac)(CO)_2$ (8.80 mg, 0.034 mmol) were weighed out separately and added to two separate round bottom flasks containing stirrer-bars, no care was taken to inertness (exclusion of air or water). To each flask was added toluene (10 ml) to dissolve all solids. The $Rh(acac)(CO)_2$ solution was slowly added to the Biphephos solution while stirring. The resulting solution was then added (2 ml) into each of 4 test-tubes with screw

cap, each tube now containing Biphephos (13.48 mg, 0.017 mmol). Stabilizers were then added to 3 of the test tubes according to Table 1.

These solutions were then used for preparing the NMR samples according to standard procedure previously described above. After the NMR tubes had been analyzed by ^{31}P-NMR they were subjugated to heating at 90 °C for 3 h and then again analyzed by ^{31}P-NMR.

The long-term effect of Biphephos : stabilizer ratio

A total of 27 NMR samples were prepared, all containing Rh : Biphephos = 1 : 5 and one out of three stabilizers (TMP, Et_3N or CHO) in different ratios Biphephos : stabilizer = 1 : 1, 1 : 2, 1 : 5, 1 : 10, 1 : 20, 1 : 35, 1 : 72, 1 : 144 and 1 : 288. The samples were prepared accordingly:

Rh(acac)$(CO)_2$ (37.14 mg, 0.14 mmol) and Biphephos (566.16 mg, 0.72 mmol) were separately weighed out into two separate round bottom flasks containing stirrer-bars, no care was taken to inertness from air or water. Toluene (45 ml) was added to each of the 6 round bottom flasks to dissolve all the solids, they were left stirring for about 1 h until everything was fully dissolved. The Rh(acac)$(CO)_2$ solution was then added dropwise to the Biphephos solution. A series of 27 test tubes (3 × 9) with screw caps were prepared with 2 ml each of the Biphephos/Rh solution so that each test tube contained Biphephos (4.19 mg, 0.005 mmol). The three different stabilizers were then added to the test tubes according to the Table 2 and vigorously shaken.

These solutions were then used for preparing the NMR samples using d-toluene. After the NMR tubes had been prepared, they waited 3 days at room temperature before they were first analyzed by ^{31}P-NMR. After this they were subjected to heating cycles with intermittent ^{31}P-NMR analysis accordingly: 90 °C for 24 h; 90 °C for 7 days; 90 °C for 14 days.

PDP-cycle experiments in the presence of TMP

Three reactors (reactor 1, 3 and 4) were used in parallel during these experiments. A stock catalyst solution was prepared scaled for 3.05 reactions. The metal precursor Rh(acac)$(CO)_2$ (8.75 mg, 0.034 mmol) and Biphephos (133.59 mg, 0.17 mmol) were weighed out into two separate Schlenk-flasks fitted with a stirrer-bar. The Rh(acac)$(CO)_2$ was dissolved in 10 ml toluene, while the Biphephos was dissolved in 60 ml toluene. The solutions were left to stir for about 20 min or until everything had dissolved. The Rh(acac)$(CO)_2$ solution was added dropwise to the Biphephos solution while stirring, no solids or turbidity could be observed after this. The stabilizer TMP (94.4 μL, 0.06 mmol) was added to the Biphephos/rhodium solution while stirring. The Rh/Biphephos/TMP solution was transferred using a syringe to the autoclave pot using Schlenk technique. 1-Octene (10.5 ml, 67.4 mmol) was transferred to dropping funnel of the autoclave using Schlenk technique.

Table 1 Prepared solutions in test-tubes for correct order of mixing

Test tube [−]	Add : BP [−]	Add [mmol]	V_{CHO} [μL]	V_{TMP} [μL]	V_{Et_3N} [μL]
1	5	0.09	8.9	—	—
2	5	0.09	—	14.5	—
3	5	0.09	—	—	11.9
4	—	—	—	—	—

Table 2 Prepared solutions in test-tubes for long-term effect

Tube [−]	Add : BP [−]	Add [mmol]	V_{TMP} [μL]	V_{CHO} [μL]	V_{Et_3N} [μL]
1	288	4.6	777	477	642
2	144	2.3	389	238	321
3	72	1.2	194	119	161
4	35	0.6	94	58	78
5	20	0.3	54	33	45
6	10	0.2	27	17	22
7	5	0.1	14	8	11
8	2	0.03	5	3	5
9	1	0.02	3	2	2

After filling the autoclaves with these solutions, and before heating, the reactors were cycled through various number of "pressure de-pressure" (PDP) cycles using synthesis gas.

One PDP-cycle constitute: 30 bar synthesis gas (H_2/CO = 1 : 1) introduced to the reactor, stirring is applied (700 rpm) for 15 min. The reactor is then very slowly depressurized. The PDP-cycle was then repeated the number of times the experiment requested. After the PDP-cycle preformation was done (700 rpm, 80 °C at 18 bar H_2 : CO = 1 : 1) for 1 hours. The start of the experiment was when the valve to the dropping funnel was opened and the 1-octene substrate got released into the pot. At the end of the experiment (t = 16.7 h) a sample from the reaction mixture was taken and analyzed by GC-FID using the method of internal standard (IS = dodecane).

Continuous hydroformylation in nanofiltration membrane miniplant (type: NEMO 2.0)

Preparation of the substrates: 1-octene was cleaned over Al_2O_3-column to remove traces of peroxides, toluene was cleaned over Al_2O_3-column to remove traces of water. The substrate solution was prepared by weighing out 1-octene (25 wt%) and toluene (75 wt%), then CHO was added to maintain a ratio of CHO : BP of 5. The ratio of 1-octene to toluene was switched after 75 h.

Preparation of the miniplant: miniplant incl. reactor, valves and glassware was cleansed with acetone to remove any residues in the pipes and afterwards with toluene to remove any acetone. Three PDP-cycles were applied (2× nitrogen (<10 bar), 1× argon, each followed by vacuum to remove any air and low boiling solvents.

Preparation of the membrane: cutting membrane, insertion of membrane in membrane module (2.5″ MET-cell),

low pressure argon flushing of the module, connection to miniplant. Further flushing of miniplant with nitrogen (<2 bar) and argon (<2 bar) to remove further air. Filling in a solution containing toluene (275 g), 1-octene (125 g) as well as CHO (0.68 g) for conditioning of membrane (4 h total; reactor: T = 40 °C, p = 20 bar; membrane part: T = 40 °C, Δp = 40 bar; glass flask: T = 40 °C, p = 1 bar, stripped with argon).

Preparation of catalyst, BP and CHO: solving of Biphephos (2.19 g) and CHO (0.68 g) in toluene (50 ml) as well as solving of Rh (144 mg) in toluene (50 ml) in a separate flask in ultrasonic bath under argon stream. Inserting both mixtures into the reactor *via* gear pump (both flasks are topped with argon). Preforming for 1 h (T = 40 °C, p = 20 bar).

Start-up for longtime run: HPLC pump starts to feed the membrane cycle (time = 0) and the other pump is starting to feed the reactor from the glass flask again. Heating to 80 °C (reactor). Depending on flux the substrates and the CHO were replenished to maintain a constant reaction volume.

Conclusions and outlook

The stability of Biphephos under reaction conditions was thoroughly investigated using ^{31}P-NMR analysis. It was shown that it is important to dissolve Biphephos and Rh(acac)$(CO)_2$ separately and then combine the two solutions in order to not risk decomposition of Biphephos. Stabilizer-free Biphephos/Rh solutions are completely hydrolyzed within a couple of hours when heated at 90 °C. Biphephos solutions in toluene containing stabilizers can, on the other hand, maintain stability while heated at 90 °C for more than 3 weeks. The amine-based stabilizers provided better stability when applied at lower concentrations. Meanwhile CHO showed superior stabilizing properties regardless of its concentration.

Through the ^{31}P-NMR experiments, it was concluded that Biphephos is not directly at risk by the presence of oxygen in a solution. However, oxygen will harm a Rh/Biphephos catalyzed hydroformylation system, probably by oxidizing the alkene substrate into peroxides which in turn oxidizes the Biphephos. This was concluded from batch autoclave experiments prepared using "standard Schlenk technique" *vs.* those further treated with "pressure-de-pressure" cycles.

Rh/Biphephos catalyzed hydroformylation of terminal alkenes like 1-octene is a suitable reaction that can be used for indirectly determining the inertness from oxygen and stability of a system through the l/b ratio under process conditions. Due to the catalyst complex size, a nanofiltration membrane reactor miniplant allows the complex's long-term behavior to be studied over several hours. The nanofiltration offers a separation technique without various decomposition possibilities like thermal stress on the ligand. In such a miniplant, the continuous hydroformylation of 1-octene could be demonstrated with a stable l/b ratio at around 78 for over 100 h which is 10 times more than any publication on continuous hydroformylation of 1-octene with a Biphephos/Rh system to date. Despite the high l/b ratio and good retention results, this proof of concept could be further optimized for even better results. To improve the yield of aldehyde, it would be necessary to optimize the gas/liquid mixing properties for an increased phase contacting area and the residence time. Following those improvements, the process could be further investigated. Regarding the effectiveness of the whole reaction system, it would be an improvement to identify a membrane able to retain 99.9% of the catalyst while also giving a higher flux. Since Biphephos is a main player in the conversion of internal alkenes it would be of interest to extend studies to mixtures of alkenes and even longer chain alkenes.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 A. Van Rooy, P. C. J. Kamer, P. W. N. M. Van Leeuwen, K. Goubitz, J. Fraanje, N. Veldman and A. L. Spek, *Organometallics*, 1996, **15**, 835–847.
2 E. Billig, A. G. Abatjoglou, D. R. Bryant and Union Carbide Corporation, *EP Pat.*, 0214622A2, 1987.
3 E. Billig, A. G. Abatjoglou, D. R. Bryant and Union Carbide Corporation, *US Pat.*, 4769498, 1988.
4 A. Rost, Y. Brunsch, A. Behr and R. Schomäcker, *Chem. Eng. Technol.*, 2014, **37**, 1055–1064.
5 C. Vogl, E. Paetzold, C. Fischer and U. Kragl, *J. Mol. Catal. A: Chem.*, 2005, **232**, 41–44.
6 Y. Brunsch and A. Behr, *Angew. Chem., Int. Ed.*, 2013, **52**, 1586–1589.
7 A. Behr, D. Obst, C. Schulte and T. Schosser, *J. Mol. Catal. A: Chem.*, 2003, **206**, 179–184.
8 E. Billig, A. G. Abatjoglou, D. R. Bryant and Union Carbide Corporation, *EP Pat.*, 0213639B1, 1991.
9 T. A. Puckette, G. E. Struck and Eastman Chemical Company, *US Pat.*, 005840647A, 1998.
10 G. S. Tolleson, T. A. Puckette and Eastmann Chemical Company, *US Pat.*, 006130358A, 2000.

11 D. Röttger, D. Hess, K.-D. Wiese, C. Borgmann, A. Börner, D. Selent, R. Schumutzer, C. Kunze and Oxeno Olefinchemie GmbH, *US Pat.*, 006570033B2, 2003.
12 D. Ortmann, K.-D. Wiese, O. Moeller, D. Fridag and Oxeno Olefinchemie GmbH, *US Pat.*, 007345185B2, 2008.
13 D. Ortmann, K.-D. Wiese, O. Moller, D. Fridag and Evonik Oxeno GmbH, *US Pat.*, 007767861B2, 2010.
14 D. Fridag, R. Franke, B. Schemmer, B. Kreidler, B. Wechsler and Evonik Oxeno GmbH, *US Pat.*, 008729287B2, 2014.
15 B. Kreidler, D. Fridag, B. Schemmer, B. Wechsler, A. Christiansen, D. Neumann and Evonik Degussa GmbH, *US Pat.*, 009127030B2, 2015.
16 B. Kreidler, D. Fridag, B. Schemmer, B. Wechsler, A. Christiansen, D. Neumann and Evonik Oxeno GmbH, *US Pat.*, 20130317246A1, 2013.
17 J. M. Maher, E. Billig, D. R. Bryant and Union Carbide Corporation, *US Pat.*, 4835299, 1989.
18 K. M. Dyballa, R. Franke and Evonik Degussa GmbH, *US Pat.*, 009650401B2, 2017.
19 K. M. Dyballa, F. Robert, D. Fridag, M. Priske and Evonik Degussa GmbH, *US Pat.*, 009676805B2, 2017.
20 K. M. Dyballa, R. Franke and Evonik Degussa GmbH, *US Pat.*, 010011619B2, 2018.
21 P. W. N. M. Van Leeuwen, *Appl. Catal., A*, 2001, **212**, 61–81.
22 E. Billig, A. G. Abatjoglou, D. R. Bryant, R. E. Murray, J. M. Maher and Union Carbide Corporation, *US Pat.*, 4789753, 1988.
23 S. K. McIntyre and T. M. Alam, *Magn. Reson. Chem.*, 2007, **45**, 1022–1026.
24 F. H. Westheimer, S. Huang and F. Covitz, *J. Am. Chem. Soc.*, 1988, **110**, 181–185.
25 M. Papanastasiou, A. W. McMahon, N. S. Allen, B. W. Johnson, K. Keck-Antoine, L. Santos and M. G. Neumann, *Int. J. Mass Spectrom.*, 2008, **275**, 45–54.
26 K. Schwetlick, J. Pionteck, A. Winkler, U. Hähner, H. Kroschwitz and W. D. Habicher, *Polym. Degrad. Stab.*, 1991, **31**, 219–228.
27 A. Christiansen, D. Selent, A. Spannenberg, M. Köckerling, H. Reinke, W. Baumann, H. Jiao, R. Franke and A. Börner, *Chem. – Eur. J.*, 2011, **17**, 2120–2129.
28 A. Christiansen, C. Li, M. Garland, D. Selent, R. Ludwig, R. Franke and A. Börner, *ChemCatChem*, 2010, **2**, 1278–1285.
29 J. T. Vossen, F. Patzina, W. Leitner and A. J. Vorholt, *ACS Sustainable Chem. Eng.*, 2024, **12**, 10665–10677.
30 A. J. Dennis, G. E. Harrison, J. P. Wyber and Davy Mckee (London) Limited, *US Pat.*, 4567306, 1986.
31 E. Billig, A. G. Abatjoglou, D. R. Bryant, R. E. Murray, J. M. Maher and Union Carbide Corporation, *US Pat.*, 4717775, 1988.
32 J. E. Babin, J. M. Maher, E. Billig and Union Carbide Corporation, *US Pat.*, 5364950A, 1994.
33 M. Jakuttis, A. Schönweiz, S. Werner, R. Franke, K. D. Wiese, M. Haumann and P. Wasserscheid, *Angew. Chem., Int. Ed.*, 2011, **50**, 4492–4495.
34 J. Dreimann, P. Lutze, M. Zagajewski, A. Behr, A. Górak and A. J. Vorholt, *Chem. Eng. Process.*, 2016, **99**, 124–131.
35 J. M. Dreimann, H. Warmeling, J. N. Weimann, K. Künnemann, A. Behr and A. J. Vorholt, *AIChE J.*, 2016, **62**, 4377–4383.
36 M. Jokiel, K. H. G. Rätze, N. M. Kaiser, K. U. Künnemann, J.-P. Hollenbeck, J. M. Dreimann, D. Vogt and K. Sundmacher, *Ind. Eng. Chem. Res.*, 2019, **58**, 2471–2480.
37 R. Paciello, L. Siggel, H. J. Kneuper, N. Walker and M. Röper, *J. Mol. Catal. A: Chem.*, 1999, **143**, 85–97.
38 M. Gerlach, F. Jameel, A. Seidel-Morgenstern, M. Stein and C. Hamel, *Catal. Sci. Technol.*, 2023, **13**, 1788–1801.
39 P. W. N. M. van Leeuwen and C. F. Roobeek, *J. Organomet. Chem.*, 1983, **258**, 343–350.
40 D. Hess, D. Ortmann, O. Moeller, K.-D. Wiese, D. Fridag, W. Bueschken and Evonik Oxeno GmbH, *US Pat.*, 007495134B2, 2009.
41 A. J. Dennis, G. E. Harrison, J. P. Wyber and Davy McKee (London) Limited, *EP Pat.*, 0149894A2, 1985.
42 G. D. Cuny and S. L. Buchwald, *J. Am. Chem. Soc.*, 1993, **115**, 2066–2068.
43 A. Behr, G. Henze, D. Obst and B. Turkowski, *Green Chem.*, 2005, **7**, 645–649.
44 A. Behr, D. Obst and A. Westfechtel, *Eur. J. Lipid Sci. Technol.*, 2005, **107**, 213–219.
45 G. Ionescu, J. I. Van Der Vlugt, H. C. L. Abbenhuis and D. Vogt, *Tetrahedron: Asymmetry*, 2005, **16**, 3970–3975.
46 R. Jana and J. A. Tunge, *Org. Lett.*, 2009, **11**, 971–974.
47 J. Fang, R. Jana, J. A. Tunge and B. Subramaniam, *Appl. Catal., A*, 2011, **393**, 294–301.
48 A. C. J. Koeken and N. M. B. Smeets, *Catal. Sci. Technol.*, 2013, **3**, 1036–1045.
49 G. Kiedorf, D. M. Hoang, A. Müller, A. Jörke, J. Markert, H. Arellano-Garcia, A. Seidel-Morgenstern and C. Hamel, *Chem. Eng. Sci.*, 2014, **115**, 31–48.
50 M. Gerlach, D. Abdul Wajid, L. Hilfert, F. T. Edelmann, A. Seidel-Morgenstern and C. Hamel, *Catal. Sci. Technol.*, 2017, **7**, 1465–1469.
51 A. Behr, A. Kämper, R. Kuhlmann, A. J. Vorholt and R. Franke, *Catal. Sci. Technol.*, 2015, **6**, 208–214.
52 A. Jörke, *PhD thesis*, Otto von Guericke Universität Magdeburg, 2018.
53 B. Zhang, H. Jiao, D. Michalik, S. Kloß, L. M. Deter, D. Selent, A. Spannenberg, R. Franke and A. Börner, *ACS Catal.*, 2016, **6**, 7554–7565.
54 A. G. Abatjoglou, D. R. Bryant, J. M. Maher and Union Carbide Corporations, *US Pat.*, 005756855A, 1998.
55 A. Morvillo and M. Bressan, *J. Mol. Catal.*, 1986, **37**, 63–74.
56 C. E. Bibby, R. Grigg and R. Price, *J. Chem. Soc., Dalton Trans.*, 1977, 872–876.
57 L. Le Goanvic, J. Ternel, J.-L. Couturier, J.-L. Dubois and J.-F. Carpentier, *Catalysts*, 2018, **8**, 1–9.
58 M. Haumann, M. Jakuttis, R. Franke, A. Schönweiz and P. Wasserscheid, *ChemCatChem*, 2011, **3**, 1822–1827.
59 S. Walter, M. Haumann, P. Wasserscheid, H. Hahn and R. Franke, *AIChE J.*, 2015, **61**, 893–897.
60 R. Paciello, L. Siggel, H. J. Kneuper, N. Walker and M. Röper, *J. Mol. Catal. A: Chem.*, 1999, **143**, 85–97.

61 J. I. Van Der Vlugt, J. Ackerstaff, T. W. Dijkstra, A. M. Mills, H. Kooijman, A. L. Spek, A. Meetsma, H. C. L. Abbenhuis and D. Vogt, *Adv. Synth. Catal.*, 2004, **346**, 399–412.
62 D. Selent, R. Franke, C. Kubis, A. Spannenberg, W. Baumann, B. Kreidler and A. Börner, *Organometallics*, 2011, **30**, 4509–4514.
63 R. P. J. Bronger, J. P. Bermon, J. Herwig, P. C. J. Kamer and P. W. N. M. Van Leeuwen, *Adv. Synth. Catal.*, 2004, **346**, 789–799.
64 P. B. Webb, M. F. Sellin, T. E. Kunene, S. Williamson, A. M. Z. Slawin and D. J. Cole-Hamilton, *J. Am. Chem. Soc.*, 2003, **125**, 15577–15588.
65 B. Hamers, P. S. Bäuerlein, C. Müller and D. Vogt, *Adv. Synth. Catal.*, 2008, **350**, 332–342.
66 S. Yu, X. Zhang, Y. Yan, C. Cai, L. Dai and X. Zhang, *Chem. – Eur. J.*, 2010, **16**, 4938–4943.
67 C. Chen, P. Li, Z. Hu, H. Wang, H. Zhu, X. Hu, Y. Wang, H. Lv and X. Zhang, *Org. Chem. Front.*, 2014, **1**, 947–951.