

Towards Process Intensification in Homogeneous Catalysis

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Applications of Polyhedral Oligomeric Silsesquioxane as Molecular Weight Enlargement Unit.

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List of Symbols and Abbreviations

2-EH	2-ethylhexanol
acac	Acetylacetonate
ATR-IR	Attenuated total reflectance infrared
b-aldehyde	Branched aldehyde
BASF	Badische Anilin- und Soda-Fabrik
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BISBIS	2,2'-Bis(diphenylphosphinomethyl)-1,1'-biphenyl sulfonate
ACN	Acetonitrile
CFC	Cross-flow chamber
CHO	Cyclohexene oxide
DCM	Dichloromethane
DEHP	Bis(2-ethylhexyl) phthalate
DLS	Dynamic light scattering
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)- ethane
DTBG	Di-tert-butyl glycerol
DVX	Di-vinyl-xanthene
EDS	Energy-dispersive X-ray spectroscopy
FCC	Fluid catalytic cracking
GC-FID	Gas chromatography flame ionization detector
GC-MS	Gas chromatography mass spectrometry
HALS	Hindered amine light stabilisers
HASPO	Heteroatom-substituted phosphine oxide
HPLC	High pressure liquid chromatography
HSP	Hansen solubility parameter
ICP-OES	Inductive coupled plasma optical emission spectrophotometers
IEC	Ion exchange capacity
IL	Ionic liquid
IR	Infrared
IS	Internal standard
l/b-ratio	Linear to branched ratio
l-aldehyde	Linear aldehyde
LPO	Low-pressure oxo processes
MALDI-MS	Matrix assisted laser desorption/ionization mass spectrometry
MCC	Mitsubishi Chemical Corporation
MFC	Mass flow controller
MO	Molecular orbital
MTO	Methanol to olefin
MW	Molecular weight
MWCO	Molecular weight cut-off
MWE	Molecular weight enlargement
NHC	N-heterocyclic carbene

NMP	N-methylpyrrolidone
NMR	Nuclear magnetic resonance
OP-POSS	Octaphenyl-POSS
OSN	Organic solvent nanofiltration
PDMS	Polydimethylsiloxane
PDP	Pressure de-pressure
PEG	Poly(ethylene glycol)
PG	Polyglycerol
PIB	Polyisobutylene
POSS	Polyhedral oligomeric silsesquioxane
PS	Polystyrene
PTSA	Paratoluenesulfonic acid
PVC	Polyvinyl chloride
RCH/RP	Ruhrchemie/Rhône-Poulenc
SAPO	Silicoaluminophosphate
SBA	Sec-butyl alcohol
scCO ₂	Supercritical carbon dioxide
SEM	Scanning electron microscope
SHOP	Shell higher olefin process
SILP	Supported ionic liquid phase
SPOS	Sulfonated polyorganosiloxanes
STY	Space time yield
Sulfoxantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene-2,7-disulfonic acid disodium salt
TEA	Triethylamine
THF	Tetrahydrofuran
TM	Transition metal
T _{melt}	Melting point
TMP	2,2,6,6-tetramethylpiperidine
TMS	Thermomorphing multicomponent solvent system
TOF	turnover frequency
TON	Turnover number
TPP	Triphenylphosphine
TPPMS	Triphenylphosphine monosulfonate
TPPTS	Triphenylphosphine trisulfonate

Abstract

The central theme of this thesis is to enhance the recyclability of homogeneous catalysts of the type phosphine/phosphite/transition-metal-complexes as well as Brønsted acids to make processes based on such catalysts ever more feasible. The initial approach was to apply organic solvent nanofiltration (OSN) membranes in conjunction with molecular weight enlargement (MWE) of the catalyst/ligands. Specifically, polyhedral oligomeric silsesquioxane (POSS) was the MWE-unit of choice. It is important to have control over the ligands/catalyst's stability under typical reaction conditions for extended periods of time in order to justify such modifications. The stability of phosphine ligands and Brønsted acids is relatively unproblematic and so POSS modifications of such ligands was directly attempted. The stability of phosphite ligands was known to be more difficult and so this was explored more deeply. Hence, in this thesis one chapter is dedicated to study the long-term stability of the phosphite ligand Biphephos when in solution, exposed to elevated temperature and under typical Rh-catalysed hydroformylation reaction conditions. It was concluded that the way a Biphephos/Rh solution is prepared has a major impact, the use of stabilising additives is important and that using an O₂-free hydroformylation system is decisive in order to achieve long-term stability of such ligands. Two chapters of this thesis were dedicated to the POSS modification of phosphine ligands. One chapter presents a set of TPP-POSS ligands bearing 1, 2 or 3 POSS cages, highlighting that grafting a POSS cage so close to the phosphorus atom can have significant effects upon the ligand's catalytic activity. The other chapter presents work on POSS modification of Xantphos-type ligands in the rear of their ligand backbone. The synthesis of NixantPOSS, a POSS modified version of Nixantphos, was realised in a one-pot reaction at ambient temperature giving the desired ligand at 94% isolated yield. When NixantPOSS was applied in the Rh-catalysed hydroformylation reaction of 1-octene it showed the same selectivity and only an 18% reduction in TOF as compared to the unmodified Nixantphos. NixantPOSS was rejected at 99% by a ceramic nanofiltration membrane during continuous hydroformylation. The last chapter of this thesis explores the application of sulfonated octaphenyl-POSS as a Brønsted acid catalyst in the ketalisation reaction of glycerol with butanone. The H-S-POSS catalysts were almost as active as PTSA and significantly more active than Amberlyst-36. The solubility of H-S-POSS was poor in all common laboratory solvents and so a recycling strategy based upon centrifugation and sedimentation was explored that turned out successful for H-S-POSS catalyst with a lower degree of sulfonation.

Chapter 1: Preface

Application of suitable catalysts in chemical processes is in many instances decisive for making a chemical process economically viable. A suitable catalyst in a reaction will allow the chemical transformations to be more energy efficient, more selective, less waste will be produced and less harsh reaction conditions can be used. Homogeneous transition metal (TM) catalysts are a specific group of catalysts. They are based on transition metals, but will also exist in the same phase as the reactants (usually a liquid solution). Because the catalyst and the reactants are in the same phase (i.e. dissolved in a liquid phase) the catalysts can interact very intimately with the reactants at a molecular level. This generally makes them highly selective and efficient. A large number of reactions are known where homogeneous TM-catalysts show great potential. But the greatest obstacle to a wider application of homogeneous TM-catalysts in more processes has to do with their intrinsically difficult separation from the reaction medium in an active state. Ideally a catalyst can be straight forwardly separated from a reaction mixture and then recycled to be used many times over. The separation and recycle of conventional homogeneous transition metal catalysts applied in continuous industrial processes are all having very specialised separation and recycling strategies with strict limitations on the substrates and products that they can handle.

New innovative approaches towards solving the recycling issue of homogeneous transition metal catalysts are continuously being proposed and explored to expand the available toolbox. One promising and potentially highly generally applicable approach is the use of organic solvent nanofiltration, OSN, in combination with molecular weight enlarged ligands. For this to make sense, it is important that stability and longevity of the ligand, which is to be molecular weight enlarged, is under control and well understood.

Hence, the first objective in this work was to identify what type of ligands are sensitive to what type of conditions and what measures can be put in place to manage any instability issues. Phosphite ligands were identified as being particularly prone to decomposition when applied in long-term continuous processes and so a more extended study about how this instability of phosphite ligand can be managed was carried out. Phosphine ligands and Brønsted acids were identified to be less problematic and so molecular weight enlargement of such ligands and catalysts was directly investigated.

Chapter 2: Theoretical Background

2.1. Introduction to Catalysis

The central theme of this thesis is to improve the utilisation of catalysts by making such entities more recyclable and reusable through application of the concept of molecular weight enlargement in conjunction with membrane nanofiltration. Catalysts have been utilised by humans for millennia, if we count the enzymes in yeast responsible for the anaerobic fermentation of sugars to alcohols and carbon dioxide. The term “catalysis” was coined in 1835 by the Swedish chemist Jöns Jacob Berzelius.^[1] Albeit Berzelius’s idea of catalysis was an “internal force” of an inert body responsible for the decomposition of other bodies and that this allowed the rearrangement of those into new bodies of higher affinity. Today we know that a catalyst lowers the activation energy (E_a) of reactions by stabilising chemical intermediates without itself being consumed in the process. The process where a catalyst is conveying the chemical transformation of a substrate and reactant is called a catalytic cycle. In an ideal catalytic system, a catalyst will never form stable bonds that result in the catalyst losing its specific properties. But all catalytic systems are imperfect by nature as there is always a chance of irreversibly forming unwanted, energetically stable bonds, which result in their deactivation. Unwanted side reactions, poisoning and deactivation of a catalyst can be minimised when knowledge about the most significant deactivation pathways is gained. In general, a catalyst’s longevity can be enhanced by using purer substrate feeds, controlling the environment of the catalyst, or simply designing a more robust catalyst. The number of times a catalyst can convey a catalytic reaction is summed up and presented by the catalyst’s turnover number (TON) which is a measure of the catalyst’s productivity. The activity of a catalyst is measured by the number of catalytic cycles it can perform in a certain period; this is called the turnover frequency (TOF). Today it is estimated that over 90% of all industrial chemicals are produced by the aid of catalysts.^[2] Apart from the economic impact on production, catalysts have also proved useful in waste water treatment, industrial off-gas and car exhaust treatment to reduce the amount of harmful compounds in our environment.

Heterogeneous and Homogeneous Catalysis: There are two general classes of catalysts, heterogeneous and homogeneous. The names refer to the relative phases of the catalyst and to where the reaction occurs. Hetero means different or other, and is a reference to the different phases that the catalyst and reactants exist in. Heterogeneous catalysts are commonly solids and the reactants exist in either the liquid or the gaseous phase, although they will have to adsorb and interact with the heterogeneous catalyst in order to react. The other category of

catalysts has the name “homo” in it, which means “same”. This is a reference to that the catalyst and reactants will exist in the same phase which is usually the liquid. Hence, homogeneous catalysts are commonly thought of as a dissolved molecular species where each entity acts as an independent catalytic site allowing for minimal mass transport limitations and high activity. The term ‘Homogeneous catalyst’ encompasses Lewis and Brønsted acids and bases, metal complexes, metal ions, organometallic complexes, organic molecules and biocatalysts. Although in modern literature it is not unusual to equate homogeneous catalysts with dissolved organometallic complexes because of their overwhelming applicability in both industry and academia. The metal-complex usually constitutes a transition metal and coordinating ligands, which makes up the so-called transition metal complex (TM-complex), this is illustrated in Figure 2-1 below.

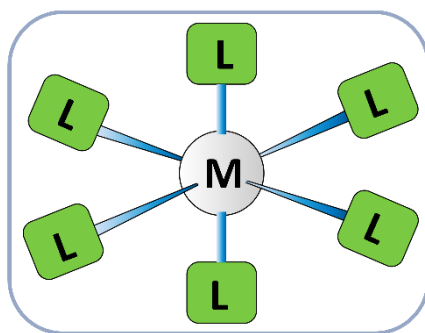


Figure 2-1: Schematic of a generic transition metal complex.
M = central metal atom, L = coordinating ligand

One metal can give many different products from the same substrate under the same reaction conditions by simply changing the ligands coordinating to it.^[3] If the TM-complex contains at least one metal-carbon bond, the complex is strictly speaking an organometallic complex, although this rule is not stringently implemented as there are many complexes that do not contain such a bond, but are still generally referred to as organometallic. In such cases, the ligands that are coordinating to the metal does so not necessarily through a carbon atom. Coordination might be facilitated via a heteroatom (e.g. P, N, O) that is in turn part of a larger organic shrubbery which therefore lends justification to the use of “organo-“ for such TM-complexes. Homogeneous catalysts have great potential for being tailored towards specific purposes through rational catalyst and ligand design derived from in depth mechanistic studies and detailed catalyst characterisation. Furthermore, they can accommodate chiral ligands able to induce enantioselectivity for pro-chiral substrates, opening up many opportunities.^[4] The synthesis and production of fine chemicals is a particular field where homogeneous catalytic systems have and are expected to continuously improve the atom economy^[5,6] and E-factors^[7].

To build an economically viable process from a catalytic system it is important that the product separation and purification can be managed in a suitable manner. The most attractive feature of heterogeneous catalysts is their ease of separation from reaction media, whereby they can simply be filtered off. This is widely recognised by the chemical industry, which is estimated to use heterogeneous catalysts in 60-80% of their catalysed processes.^[8] In particular the oil refining industry is heavily reliant upon heterogeneous catalysts, e.g. modern fluid catalytic cracking units are highly reliant on zeolite type catalysts.^[9,10] Homogeneous catalysts on the contrary require more sophisticated approaches to separate the product from the catalyst such as distillation, extraction, chromatography, crystallisation or other specialised approaches (*vide infra*). The strengths of homogeneous organometallic catalysts undoubtedly lie with their selectivity and activity, while their weakness is their intrinsic non-trivial separation. A few large-scale industrial processes based on homogeneous TM-complex catalysts are in operation. These include Monsanto's acetic acid process,^[11] Shell higher olefin process (SHOP),^[12] DuPont's adiponitrile (AdN) process^[13] and Ruhrchemie/Rhône-Poulenc butanal process^[14] to name a few.

2.2. Hydroformylation

Although homogeneous TM-complexes have been successfully applied as catalysts in several different commercial chemical processes producing bulk chemicals (*vide supra*), further focus will be made here upon the hydroformylation reaction as this was used as a model reaction in three of four chapters in this thesis.

In short: Hydroformylation is a reaction where syngas (CO/H₂) is added across carbon-carbon double bonds in alkenes resulting in aldehyde products. Unless ethene is the alkene substrate, the products formed will be a mixture of linear and branched aldehydes; this is presented in Figure 2-2.

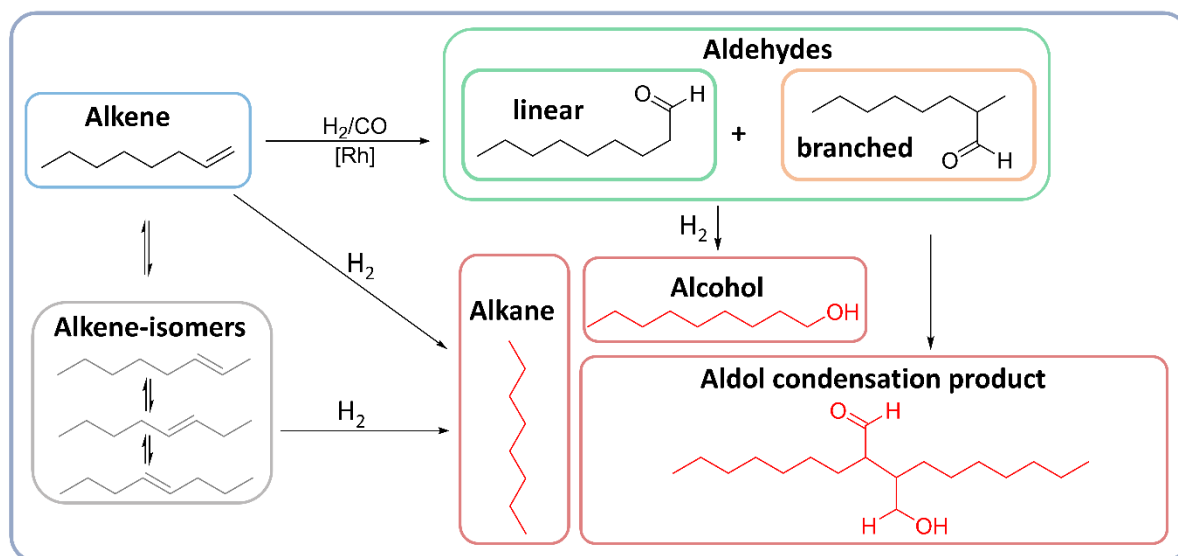


Figure 2-2: General reaction scheme for hydroformylation reaction

To complicate the potential product distribution further; alkenes longer than propene may undergo double bond isomerisation instead of hydroformylation, branched aldehydes can be chiral, and the product aldehydes can undergo reduction to alcohols, oxidation to acids or undergo aldol condensation resulting in various higher boiling residues. Product selectivity is a very important parameter that must be evaluated for any hydroformylation system (regioselectivity, stereoselectivity, isomerisation, hydrogenation, oxidation, condensation).

On industrial scale: An estimated worldwide production volume of 13 million metric tons of oxo products from alkenes in 2016 clearly makes hydroformylation one of the most important homogeneously catalysed reactions in chemical industry.^[15] Most of the production is performed in plants with capacities of several hundred thousand metric tons per year. The aldehydes produced are valuable intermediates for bulk chemical synthesis of alcohols, amines and esters, which are then to be used in the production of e.g. surfactants, detergents, plasticisers, elastomers and monomers. The alkenes being processed to aldehydes are classified according to the number of carbon atoms they contain. Ethene is C_2 , propene is C_3 , butene is C_4 and so forth up to dodecene being C_{12} . Beyond this point the alkenes are generally referred to as longer-chain alkenes or higher alkenes ($>\text{C}_{12}$). Hydroformylation of propene to give *n*-butanal is by far the most economically important.

2.2.1. Historical Developments in Hydroformylation

Hydroformylation was discovered through serendipity by the German industrial chemist Otto Roelen in 1938 when working at the Ruhrchemie GmbH. He was at the time investigating cobalt-catalysed Fischer-Tropsch reactions where H_2/CO is converted into alkanes and alkenes

over heterogeneous iron or cobalt catalysts.^[16] Roelen had tried to increase the yields of the process by recycling ethylene over a heterogeneous cobalt on ThO₂/SiO₂ catalyst. Propanal was identified as a product and this new reaction was named the “oxo-process”.^[17,18] The first industrial hydroformylation process was realised at IG Farben Leuna/Merseburg in Germany in 1942.^[19] Other metals than cobalt have since been explored for their potential application to catalyse this reaction and the generally accepted ordering of the activities of the central metal atom in hydroformylation is presented in Table 1 below.

Table 1: The relative activity of different metals in hydroformylation reaction

Metal	Rh	Co	Ir	Ru	Os	Pt	Pd	Fe	Ni
RA	1000	1	0.01	0.01	0.001	0.0001	0.000001	0	0

For any commercial oxo-process the central metal atom is thus restricted to either rhodium or cobalt while the other metals are so far only of academic interest.

Cobalt based first and second generation hydroformylation processes: The first generation hydroformylation process was based on the unmodified cobalt carbonyl complex [Co(H)(CO)₄]^[20] while a second generation cobalt catalyst was modified by a tributyl phosphine ligand to form a catalyst complex [CoH(CO)₃(PBU₃)]. Both the first- and second-generation catalyst complexes are presented in Figure 2-3 below.

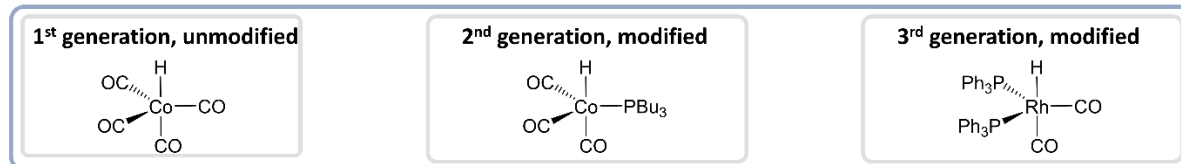


Figure 2-3: The three generations of hydroformylation catalysts.

First generation hydroformylation catalysts (left side) were unmodified cobalt-carbonyl complexes. The second-generation cobalt catalysts (middle) were modified by PBU₃ ligands, the third generation (right side) were Rh based and modified with phosphine ligands.

These Co-based processes are synonymous with harsh reaction conditions; high temperature (150 – 180°C) and pressure (200 – 350 bar) have to be used because of the low reactivity of cobalt.^{[21], [22]} Cobalt catalysts modified with monophosphine ligands are still today used in large industrial oxo-processes by companies such as BASF, Exxon, Sasol and Shell whenever long-chained and internal alkenes are the substrates for the production of high-boiling aldehydes and alcohols.^[15]

Rhodium-based third generation hydroformylation processes: Rhodium catalysts modified with phosphorus ligands constitutes the third generation hydroformylation catalysts and is presented in Figure 2-3 above right side. These are generally more selective, have superior activity and can operate under milder conditions than the cobalt-based processes. Application

of a phosphine ligand-modified rhodium complex $[\text{RhCl}(\text{PPh}_3)_3]$ in catalysis was first reported by Wilkinson and co-workers in the mid-1960s, good activity in both hydrogenation and hydroformylation was reported.^[23] Because of the superior activity of this rhodium system, industry soon took serious actions. The first PPh_3 -modified rhodium-catalysed hydroformylation process for *n*-butanal production came online in 1974 (Celanese), soon after UCC (Union Carbide Corporation) commissioned a plant for ethylene in 1975 and one for propene in 1976.^[24] Two years later in 1978 MCC (Mitsubishi Chemical Corporation) also opened a plant for propene. Because these third-generation processes are operated at considerably lower pressures (10-20 bar) and temperature (85 – 130°C) than the cobalt-based processes, they soon became known as “low-pressure oxo processes” (LPO processes). In order to separate the product and recycle the rhodium catalyst UCCs first approach was a “gas recycle process” to continuously remove the aldehydes by evaporation from the reaction mixture by applying a large gas recycle, the schematics of such a plant is presented in Figure 2-4 below, left side.

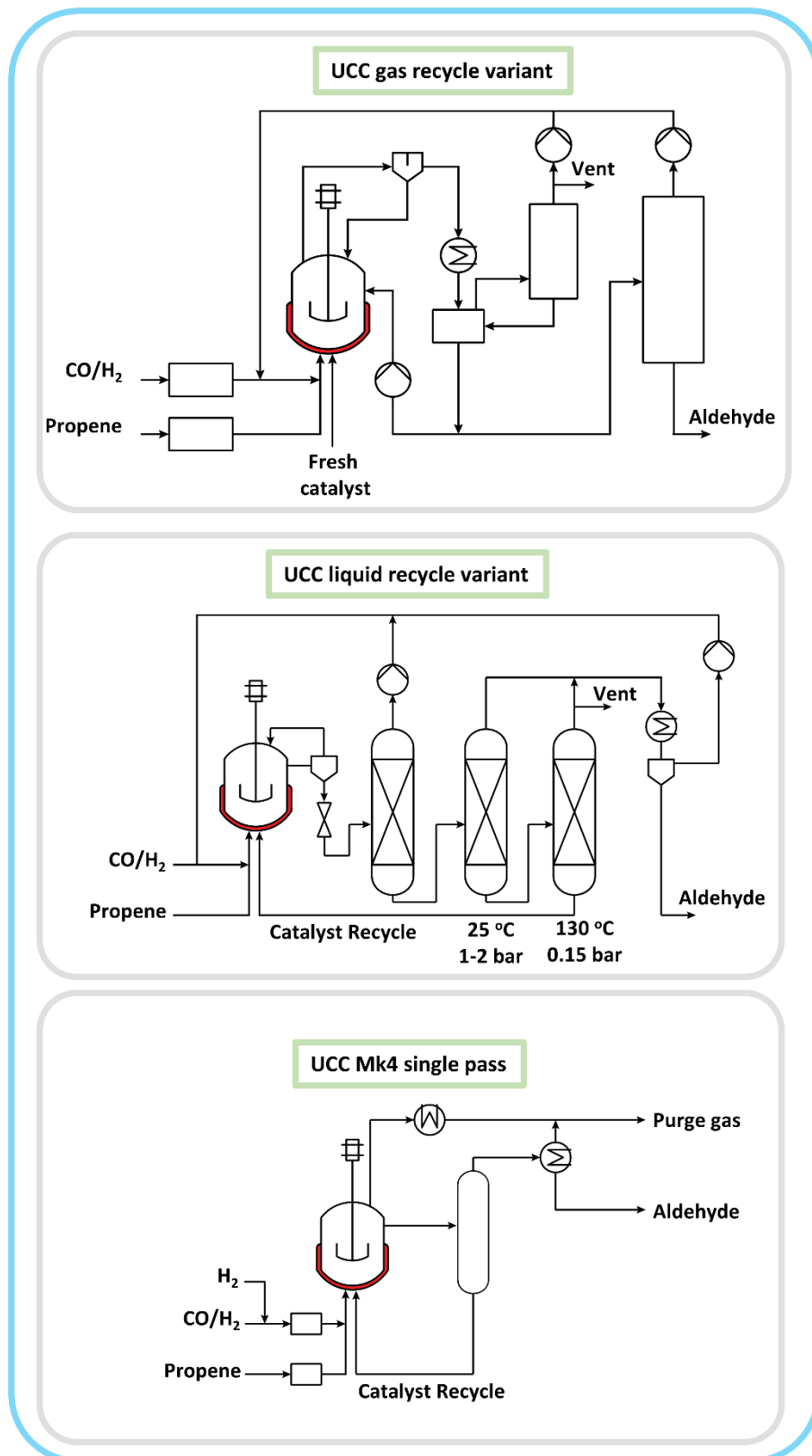


Figure 2-4: Schematic representation of three generations of LPO reactors
 (Left) UCC "gas recycling process", (Middle) UCC "liquid recycle process", (Right) UCC Mk4 single pass. Flow diagram based on one from^[24]

This required a large syngas compressor to generate the required continuous gas stream as well as other rather complicated plant equipment. Later a “liquid recycle process” was developed by UCC and MCC which is today used in most LPO plants, the schematics are presented in Figure 2-4 above, middle. The fundamental concept here was to first remove the product from the reactor in the liquid phase into a separator and a let-down valve for pressure release. The liquid then proceeds to a flash-evaporator where unreacted alkenes are removed, compressed and recycled back to the reactor. The liquid is introduced to the first distillation column where most of the product aldehyde is distilled off. The un-distilled bottom is introduced into a second distillation column where further evaporation under reduced pressure concentrates the catalyst solution, which is then recycled back into the reactor. The vapours from both columns are condensed and collected while off gases are recycled back to the reactor or vented off. This system allowed a reduction in compressor capacity compared to the “gas recycling process” and removal of heavy condensation products is less strenuous for the catalyst. The third generation LPO process by UCC is the so-called Mark IV process which is a “liquid recycle process”. This is a more common version of the LPO processes where the catalyst recycling has been decoupled from the reactor.^[25] A schematic representation of the process is given in Figure 2-4 above. Highly purified propene and syngas is introduced to the reactor containing a highly active and selective bisphosphite-modified rhodium catalyst dissolved in a single phase of butanal aldol condensation products.^[26] The process uses moderate temperature (85 – 95°C) and pressure (15 – 20 bar). The reaction mixture is transferred as a liquid to a separate vessel where low boilers are vaporised off, condensed and collected. The rhodium catalyst stays dissolved in the high boilers and is recycled back to the reactor. The high activity of the rhodium phosphite catalyst allow 98.7% conversion of the propene feed in a single pass. The wide bite angle chelating coordination mode of the ligand allows a product mixture of linear to branched aldehydes in a ratio of 30:1. All the third generation hydroformylation processes are limited to process short chain alkenes because the processes rely on distillation of the product aldehydes from the catalyst. The catalysts TM-complexes and ligands have limits when it comes to thermal stress, and it is generally not advisable to expose homogeneous TM-complex catalysts to more than 150°C for any length of time. The boiling point of linear aldehydes of increasing chain length is presented in Figure 2-5 below.

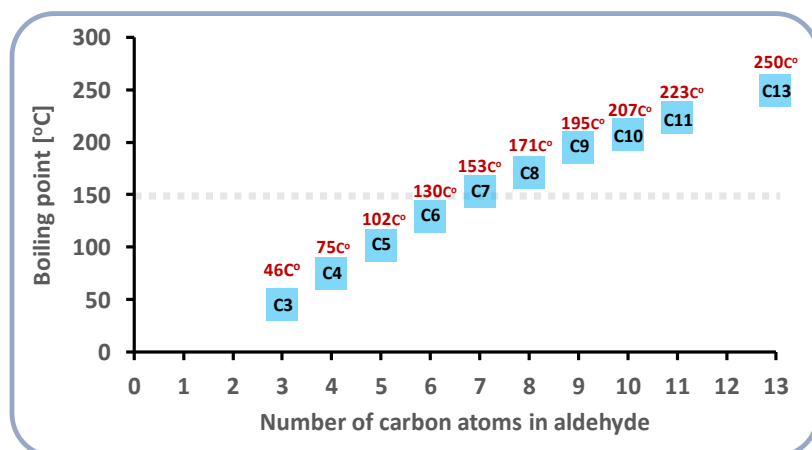


Figure 2-5: The boiling point of linear aldehydes at atmospheric pressure.

The dashed line represents a generalised threshold for what thermal stress homogeneous TM-catalysts are capable of handling.

With high boiling products it is obviously possible to lower their boiling points by reducing the pressure. But for TM-complexes that have been optimised to operate under a syngas pressure this option can be problematic. It is known that inactive and stable Rh-clusters (see Figure 2-6 below) can form from active Rh-phosphine catalyst complexes if there is not sufficient CO and H₂ dissolved into the catalyst solution.^[27,28]

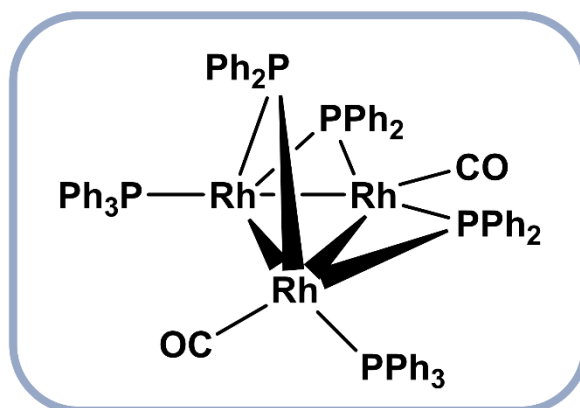


Figure 2-6: A rhodium cluster that may form in the hydroformylation mixture

Rhodium-based fourth generation hydroformylation processes. The only member of the “fourth generation” hydroformylation system is the so called Ruhrchemie/Rhône-Poulenc (RCH/RP) process, which started at the Oberhausen site of the former Ruhrchemie AG (now Oxea) in 1984.^[29] The process is based on aqueous biphasic hydroformylation of short chain alkenes, mostly propene but also some butene is also processed. The catalyst is immobilised in the aqueous phase thanks to the highly water soluble ligand triphenylphosphine trisulfonate (TPPTS), which forms the Rh-complex [HRh(CO)(TPPTS)₃]. The almost exclusive preference of this Rh-complex to be dissolved in the water phase allows a simple decantation of the organic product phase from the aqueous catalyst phase, and no further distillation or columns are

needed to separate the catalyst. The TPPTS/Rh-complex and the schematics of the process are presented in Figure 2-7 below.

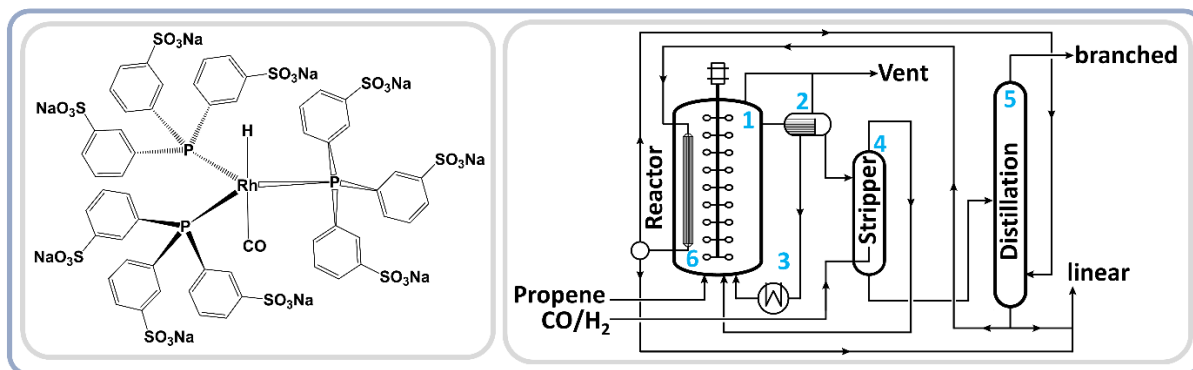


Figure 2-7: The 4th generation hydroformylation process
(Left side) The highly water soluble TPPTS-modified Rh-carbonyl complex $[HRh(CO)(TPPTS)_3]$. (Right side) Schematic representation of the Ruhrchemie/Rhône-Poulenc process; 1. Reactor; 2. Decanter; 3. Heat exchanger; 4. Stripper; 5. Distillation tower; 6. Falling-film evaporator. Flow-scheme is based on one presented in^[29]

The two phases are thoroughly mixed in a continuously stirred tank reactor (1) and phase separation takes place in the decanter (2). The aqueous fraction runs through a heat exchanger (3) before returning to the reactor (1). The organic fraction is run through a stripper (4) supplied with syngas to recycle unreacted alkene to the reactor. The aldehyde products are introduced into a distillation column (5) to separate iso- and n-aldehydes using the heat from the exothermic oxo reaction extracted by a falling-film evaporator (6) incorporated inside the reactor. It had an initial C₄-product production capacity of 100 kt/a, after two additional units coming online the total capacity got to over 500 kt/a.^[15] The RCH/RP process is limited to only process lower alkenes ($\leq C_5$) because of the decreasing solubility of the longer chained alkenes in the aqueous phase with increasing number of carbon atoms, as shown in Figure 2-8 below. Attempts have been made at using various types of phase transfer agents (co-solvents, detergents and surfactants) and amphiphilic water-soluble ligands to increase the productivity of the systems for longer chained alkenes.

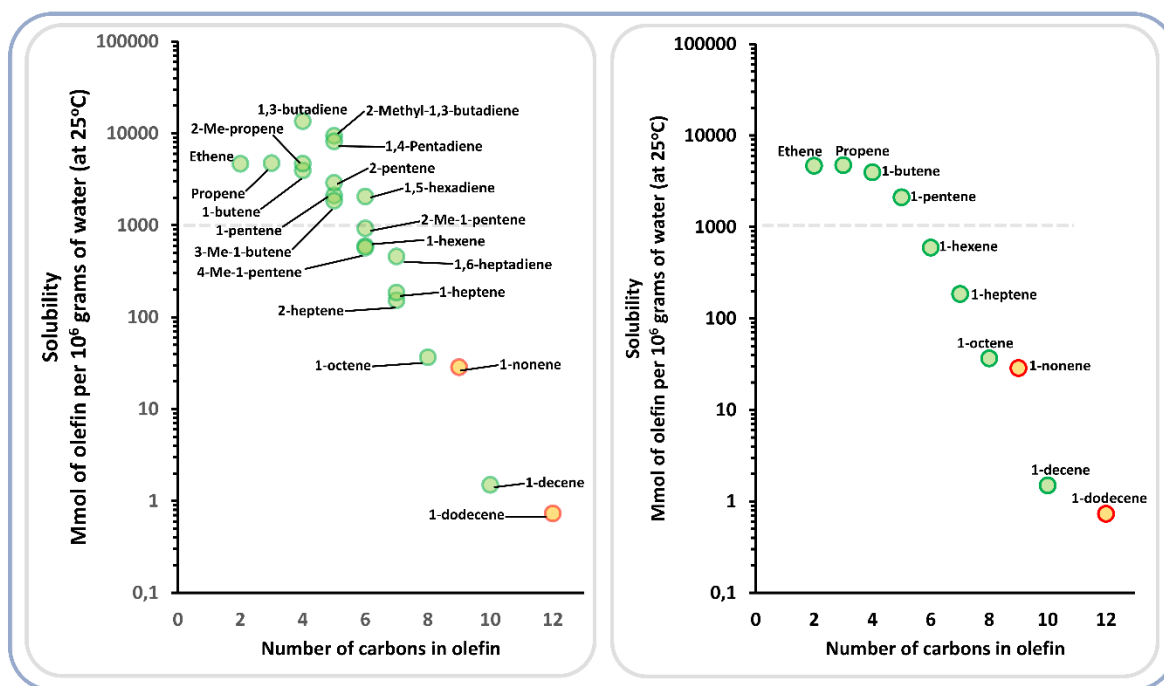


Figure 2-8: The solubility of alkenes in water with increasing carbon chain lengths^[30,31]
 (Left) Collection of alkenes and their water solubility, (Right) Terminal alkenes and their water solubility. The dashed line represents the cut-off between substrates that have enough solubility in water to be hydroformylated with economically sufficient space-time-yield (above) and those that do not meet such criteria (below).

Today, there are hydroformylation processes operating with either cobalt type catalysts as well as those using much more active rhodium type catalysts. A rough comparison between rhodium- and cobalt-based systems is presented in Table 2 below.

Table 2: A crude comparison between Rh- and Co-based oxo-processes.

Conditions	Catalyst	
	Cobalt (unmodified) [HCo(CO) ₄]	Rh (ligand modified) [HRh(CO)L ₃]
Temperature (°C)	130 - 180	85 - 130
Pressure (Bar)	200 - 300	10 - 50
Catalyst concentration (%)	0.1 - 0.5	0.01 - 0.05
LHSV (h ⁻¹)	0.5 - 1.5	0.1 - 0.3
I/b	80/20	>90/10
By-products	high	low
Catalyst recovery and recycle	complicated	simple
Restrictions	none	alkenes <C ₆

Although rhodium has higher selectivity, better atom economy, E-factor, higher yields, less by-products, and operate under lower pressure and temperature during the hydroformylation reaction, applications are limited to lower alkenes for the aqueous phase process. Co-systems are applied on higher alkenes as it allows an easy separation of the catalyst from high-boiling products. Because the recycling processes for Co-systems are based on chemical transformations, some losses are always expected. Such losses are easily compensated by addition of fresh cobalt to the system.^[32] A similar chemical transformation of a Rh-complex

for their recycling in a continuous oxo-process would be uneconomical due to the high price of the precious metal that requires very low levels of catalyst decomposition and leaching.

2.2.2. More About Rh-Catalysed Hydroformylation

The Rh-catalysed hydroformylation of alkenes is here presented in a bit further detail as it was used as a model reaction in three of four chapters in this thesis. An expanded version of the generally accepted Wilkinson dissociative mechanism for rhodium-catalysed hydroformylation from 1968 is presented in Figure 2-9 below.^[33]

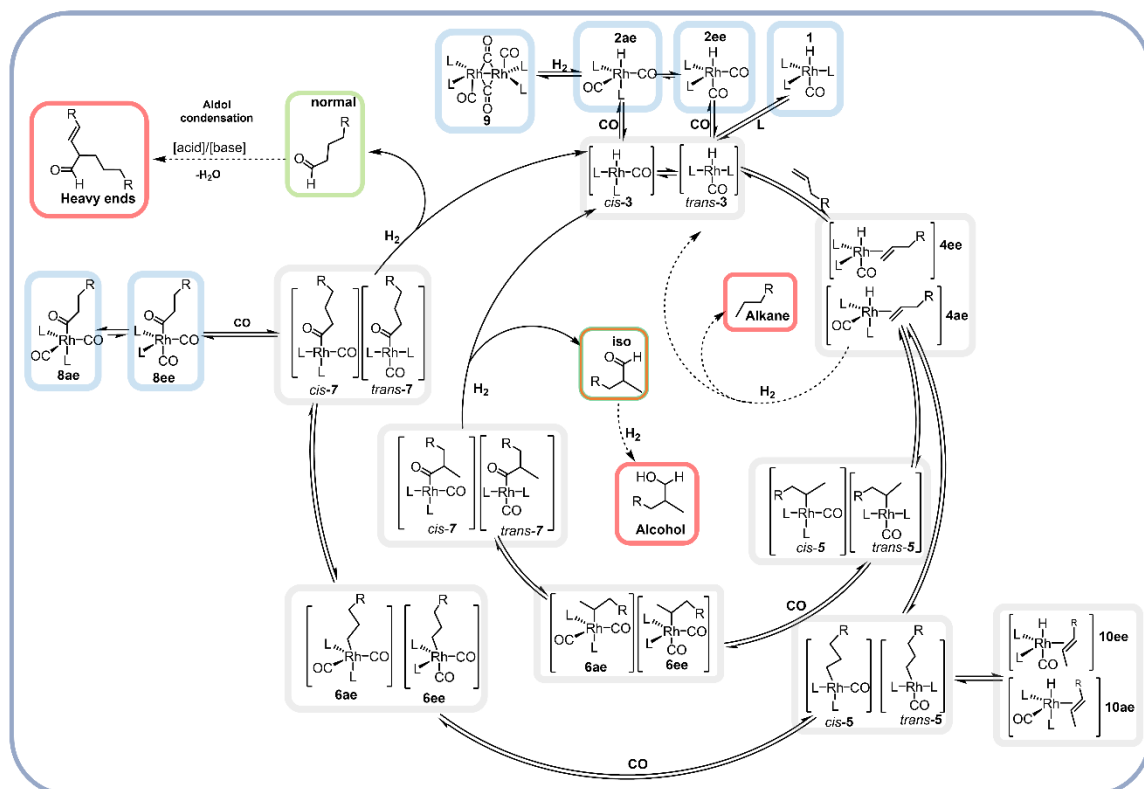


Figure 2-9: The Wilkinson dissociative mechanism for Rh-catalysed hydroformylation of alkenes. Expanded to also include the formation of by-products and the different possible intermediates. Green is highlighting the product aldehydes, red is highlighting by-products, grey means that the species have not been observed and blue means that the species have been observed.^[22,34–38]

For Rh-catalysed hydroformylation systems modified with phosphorus ligands, the active complex is a trigonal bipyramidal rhodium hydride complex, usually containing two phosphorus ligands. Exceptions to this are very bulky monophosphite ligands which exclusively form monoligated rhodium phosphite complexes.^[39] With the common PPh_3 as ligand the usual starting complex is $[\text{RhH}(\text{PPh}_3)_3\text{CO}]$ **1**, upon application of syngas (CO/H_2) the two catalytically active, isomeric complexes **2ee** and **2ae** form. If the phosphine ligands are both in equatorial positions, the complex is referred to as **ee**, when one phosphine ligand is in apical and one in equatorial position the complex is denoted **ae**. NMR studies have shown that the di-equatorial isomer **2ee** is preferred over the equatorial-apical **2ae** in a ratio of 85:15 for a

PPh₃-modified system.^[40] Dissociation of equatorial CO from **2** or equatorial L from **1** lead to the square planar intermediate complexes *cis*-**3** and *trans*-**3**. The rapid equilibrium between **2ee** and **2ae** gives more support for that the mechanism cycles through this square planar intermediate. All the complexes shown in brackets (and highlighted with grey) have to the best of my knowledge so far not been observed. An alkene coordinates to the square planar complexes *cis*-**3** and *trans*-**3** to give the trigonal bipyramidal complexes **4ae** and **4ee** with the hydride in the apical position and the alkene in the equatorial plane. The complex **4** undergo migratory insertion to form square planar alkyl complexes either *cis*-**5** and *trans*-**5**, here regioselectivity of the reaction is decided. In the absence of CO and when the aryl or alkyl groups are lacking β-hydrogens, such square planar *cis*- and *trans*-complexes have been isolated.^[38] These complexes can then either coordinate another CO to form trigonal bipyramidal complexes **6ee** or **6ae**, or they can undergo β-hydride elimination which can lead to isomerisation if longer chained alkenes are the substrates. Thus, at lower CO pressure a higher rate of isomerisation is to be expected. The insertion reaction is usually considered irreversible at sufficiently high pressure of CO (>10 bar) and low temperature (<70°C). Continuing the cycle, the trigonal bipyramidal complexes **6ee** and **6ae** undergo the second migratory insertion to form the square planar complexes *cis*-**7** and *trans*-**7**. These can either associate another CO to form complexes **8ee** and **8ae**, which have been observed spectroscopically to be in favour of the **ae** isomer (due to steric effects), or react with H₂ to form the aldehyde product and regenerate the unsaturated square planar complexes *cis*-**3** and *trans*-**3**.^[22] No straightforward picture with regards to the kinetics of the reaction exist, this is because of the many variables involved and how various equilibria are affected depending on Rh, ligand, and substrate concentrations, type of ligand, temperature, pressure etc. When considering “standard” operational conditions for a PPh₃-modified Rh-catalysed hydroformylation system, the following rate expression has been reported.^[41]

$$v = k[C_3H_6]^{0.6}[PPh_3]^{-0.7}[CO]^{-0.1}[Rh]^1[H_2]^0$$

Important features of this rate expression are the positive order in alkene and Rh concentration, negative order in PPh₃ ligand and CO while there is a zero-order dependence on H₂. At high PPh₃ concentrations the catalyst will predominantly exist in the resting state **1** [(PPh₃)₃Rh(CO)H], ligand dissociation is required to form the active complexes *cis*-/*trans*-**4**, which is suppressed by an increased PPh₃ concentration. At low PPh₃ concentration the principal catalyst resting state are the (PPh₃)₂Rh(CO)₂H **2ae/ee**, CO dissociation to form the *cis*-/*trans*-**3** is suppressed by increased CO concentration. At very low syngas pressure the reaction will

slow down due to mass transfer limitations. For some time, it was believed that the selectivity towards the linear aldehyde was strongly correlated with a high **ee/ae** ratio of complex **4** and great efforts were focused on designing ligands that would increase this ratio through designed steric and electronic properties. Further studies on selectively by changing the basicity of bidentate phosphine ligands has revealed that a more complex picture exist.^[42] It is still safe to say that overall correlations between the two parameters exist, but that a high **ee/ae** ratio is not the soul parameter responsible for deciding the n/i-selectivity of a ligand.

2.3. Phosphorus Ligands

Phosphorus ligands constitute a large and diverse class of ligands. The common denominator is that they all have at least one phosphorus atom that is closely involved in the coordination of the ligand to a central metal atom. A few processes currently operating on commercial scale and rely on phosphorus ligands include the SHOP for the oligomerisation of ethene and production of alkenes of various lengths,^[43] hydrocyanation of 1,3-butadiene for the production of adiponitrile (DuPont),^[44] telomerisation of butadiene for the production of 1-octene (DOW)^[45] or together with water for the production of 1-octanol (Kuraray),^[46,47] asymmetric hydrogenation for production of L-dopa (Monsanto/Bayer) (now defunct as L-dopa is produced biocatalytically),^[48] asymmetric isomerisation - production of L-Menthol (Takasago),^[49] and various C-C coupling reactions.^[50]

2.3.1. Classification of Phosphorus Ligands

Trivalent phosphorus ligands come in different forms and can be classified according to the oxidation state of the phosphorus atom. More common is to see the phosphor bonded directly to carbon atoms or oxygen atoms which then lends the name of a phosphine respectively a phosphite. Other options include bonding the phosphor to an amine or creating ligands that are combinations of the three. The classification of phosphorus ligands is done according to Figure 2-10 below.

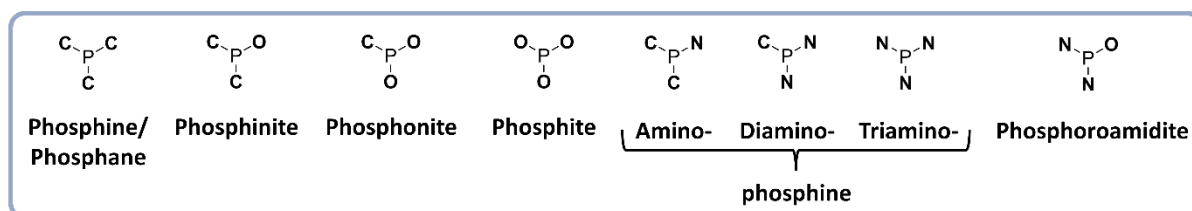


Figure 2-10: Classification of different types of phosphorus ligands

It is possible to further classify phosphorus ligands according to various other features that they might present. The relative σ -donation and π -acceptor properties between a set of phosphorus

ligands containing phosphine, phosphite, amino-phosphine and combinations thereof showed that phosphoroamidites bearing N-pyrrolyl moieties are stronger π -acceptors than phosphites, see Figure 2-11 below.

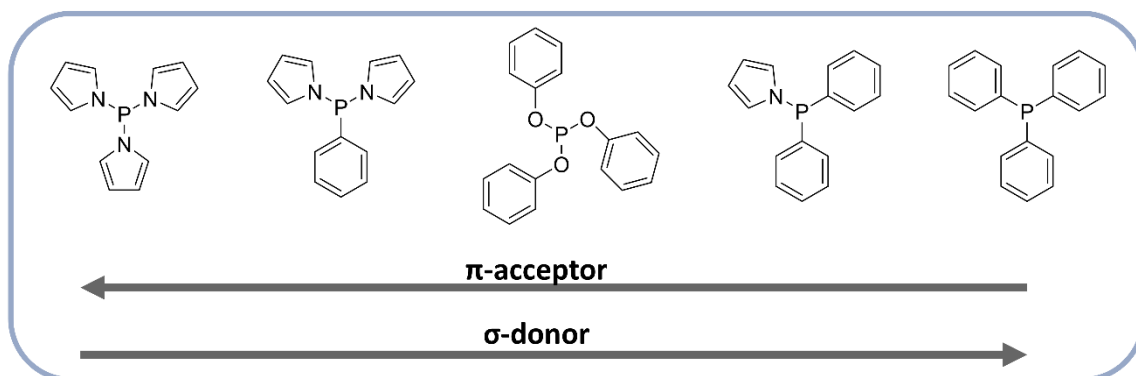


Figure 2-11: The relative σ -donation and π -acceptor properties of different ligands.^[51]

Several steric parameters have also been developed to compare different ligand's steric properties. One of the most famous parameters for monodentate ligands is the Tolman cone angle θ , which represents the apex angle of a cone formed from the vertex (centred at 2.28 Å from the metal) to the van der Waals radii of the outermost atoms of the ligands. The steric properties of bidentate ligands are governed by the nature of the backbone and the allowed conformations that its two coordinating heteroatoms may take relative to each other. Both Tolman angle, bite angle and flexibility range are illustrated in Figure 2-12 below.

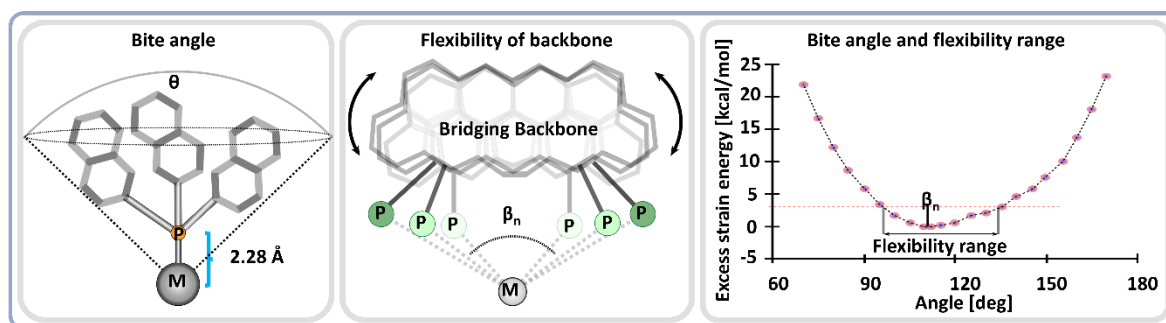


Figure 2-12: Steric ligand properties for mono- and bidentate ligands (Left) The Tolman cone angle (θ) of monodentate ligands, (Middle and right) The bite angle and flexibility range of bidentate ligands.

The concept of natural bite angle (β_n) and flexibility range were introduced by Casey and Whiteker to aid in the evaluation of the steric properties of bidentate ligands.^[52] The natural bite angle of a ligand is the preferred P-M-P angle according to computational calculations based on simple molecular mechanics simulations.^[53] The flexibility range is a parameter used to evaluate the rigidity of the ligand backbone by plotting the energy potential map of the ligand

as a function of the bite angle, and allowing a maximum of 3 kcal mol⁻¹ excess strain energy moving away from its lowest energy conformation.

2.3.2. Introducing TPP, Xantphos and Biphephos:

Three different types of commercially available and widely applicable phosphorus ligands will now be discussed. These are; TPP, Biphephos and the Xantphos-type ligands, which are presented together in Figure 2-13 below.

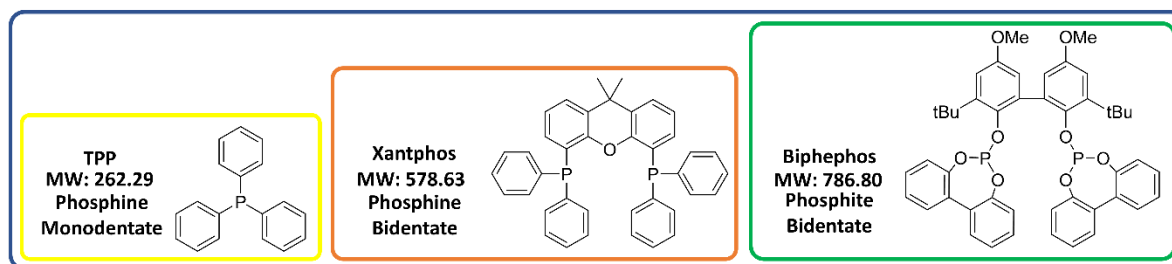


Figure 2-13: Three common phosphorus ligands
(Left): Triphenylphosphine (TPP), (Middle) Biphephos, (Right) Xantphos.

All three ligands have been thoroughly studied for their applications in Rh-catalysed hydroformylation as they have attractive features in terms of price, activity and selectivity. But their application potential also goes beyond hydroformylation as they have proved suitable in various other reactions as well.

General about triphenylphosphine: This is a simple monodentate phosphine ligand constituting a central phosphorus atom connected to three phenyl rings. It has seen applications in both classical organic synthesis as a reducing agent (whereby TPP is itself oxidised), and as a widely applicable ligand in various TM-complex catalysts and catalytic systems. It is a relatively small ligand when compared to other common commercially available phosphorus ligands as is presented in Figure 2-20 on page 24. In pure form it exists as a white solid material and is then non-sensitive towards oxidation. It is soluble in a range of organic solvents and once dissolved it will be readily oxidised by any dissolved O₂ or other oxidising agent (e.g. peroxides) present within the solvent. Although TPP is a very simple ligand, it is commonly included in ligand screenings as it is very cheap, accessible and already has commercial process applications.

Connecting TPP to a support material: There have been several publications on various polymer-supported TPP and their applications, the first reported attempt was made in the 1970s.^[54,55] And since then many more have been reported, a brief overview can be found in the following review.^[56] There are also various commercially available polymer-supported

TPP ligands. A fully soluble support materials that TPP has been grafted to is POSS; Cole-Hamilton et al. grafted TPP moieties to the corners of the POSS cage (Figure 2-14a)^[57], the ligand showed a “positive dendritic effect” as it gave unexpectedly high regioselectivity to the linear aldehyde (l/b = 14:1) in Rh-catalysed hydroformylation of 1-octene. A different approach was shown by Vogt et al. who grafted one POSS cage to each phenyl moiety of the TPP ligand (Figure 2-14b).^[58] The TPP-POSS-3 ligand was tested in Rh-catalysed hydroformylation of 1-octene and provided a TOF at 42% of unmodified TPP, and an l/b = 2.5.

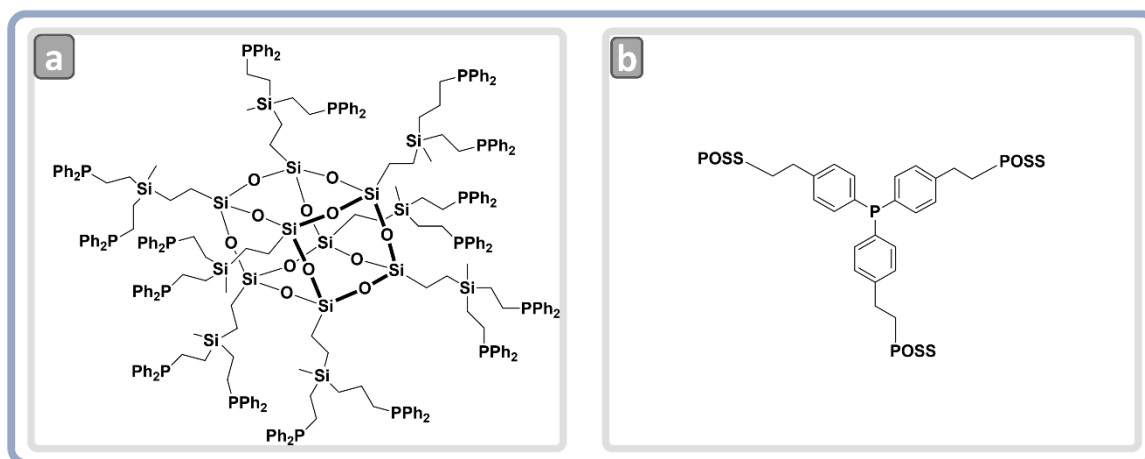


Figure 2-14: Triphenylphosphine grafted to POSS cages

More impressively was its application in a continuous flow nanofiltration membrane reactor, for almost 2 weeks a single charge of the ligand could support steady operation with conversion greater than 90%, a total turnover number (TTN) of 120 000 Rh⁻¹ and in the end 99.99% of the Rh and P had been retained inside the reactor.

General about Xantphos-type ligands: The Xantphos-type ligands is a group of bidentate, wide bite-angle phosphine ligands based on the structure of the rigid xanthene backbone. The first synthetic procedures towards Xantphos-type ligands were published almost simultaneously by two independent groups, van Leeuwen et al.^[59] and Haenel et al.^[60] The ligands of the Xantphos-type ligand family together with their bite angle are presented in Figure 2-15 below.^[61,62]

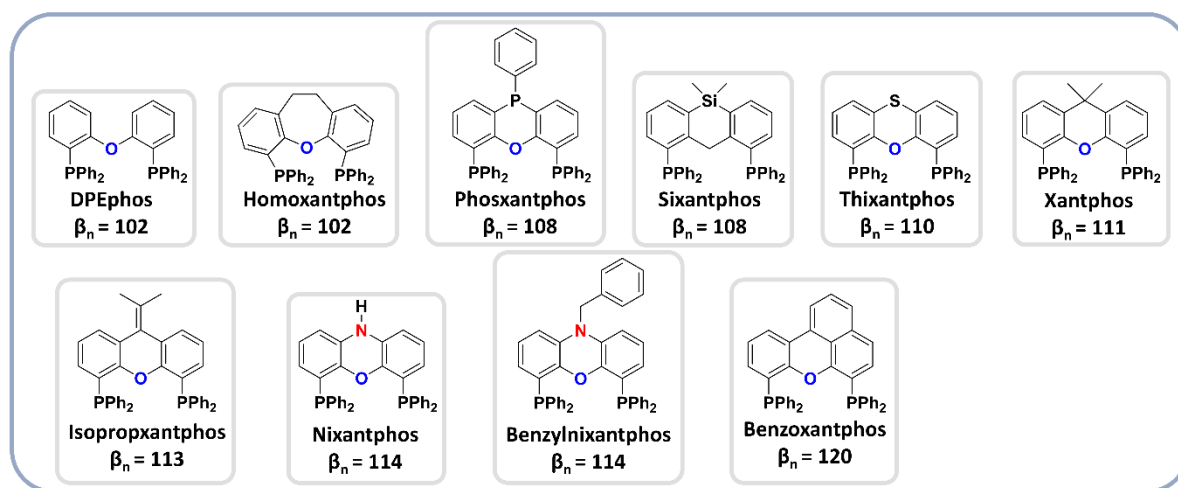


Figure 2-15: The Xantphos-type ligand family

In pure form at room temperature these ligands are solids that can be handled in open air. They dissolve in a range of different organic solvents whereupon exclusion of O_2 becomes necessary. Amongst the ligands of the Xantphos family, Xantphos is the most widely tested and investigated ligand. Over 2900 research publications make use of Xantphos or a very similar analogue as a ligand in TM-metal catalysed reactions.^[63]

Application of Xantphos-type ligands: All of the ligands within the Xantphos family are active and highly selective in Rh-catalysed hydroformylation^[64,65], but Xantphos-type ligands also show good results in other reactions. Examples include hydroaminomethylation,^[66–70] amination of alcohols,^[71] alkoxyacylation^[72], hydrocyanation,^[73,74] C-C coupling^[75–80], C-N coupling^[70,81], C-S coupling^[82], C-O coupling, hydroesterification of alkynes^[83], conversion of 1,4-alkynediols into pyrroles^[84] to name a few. An illustrative overview of a few different reactions where Xantphos was the most effective ligand is presented in Figure 2-16 below, although these examples only represent a fraction.

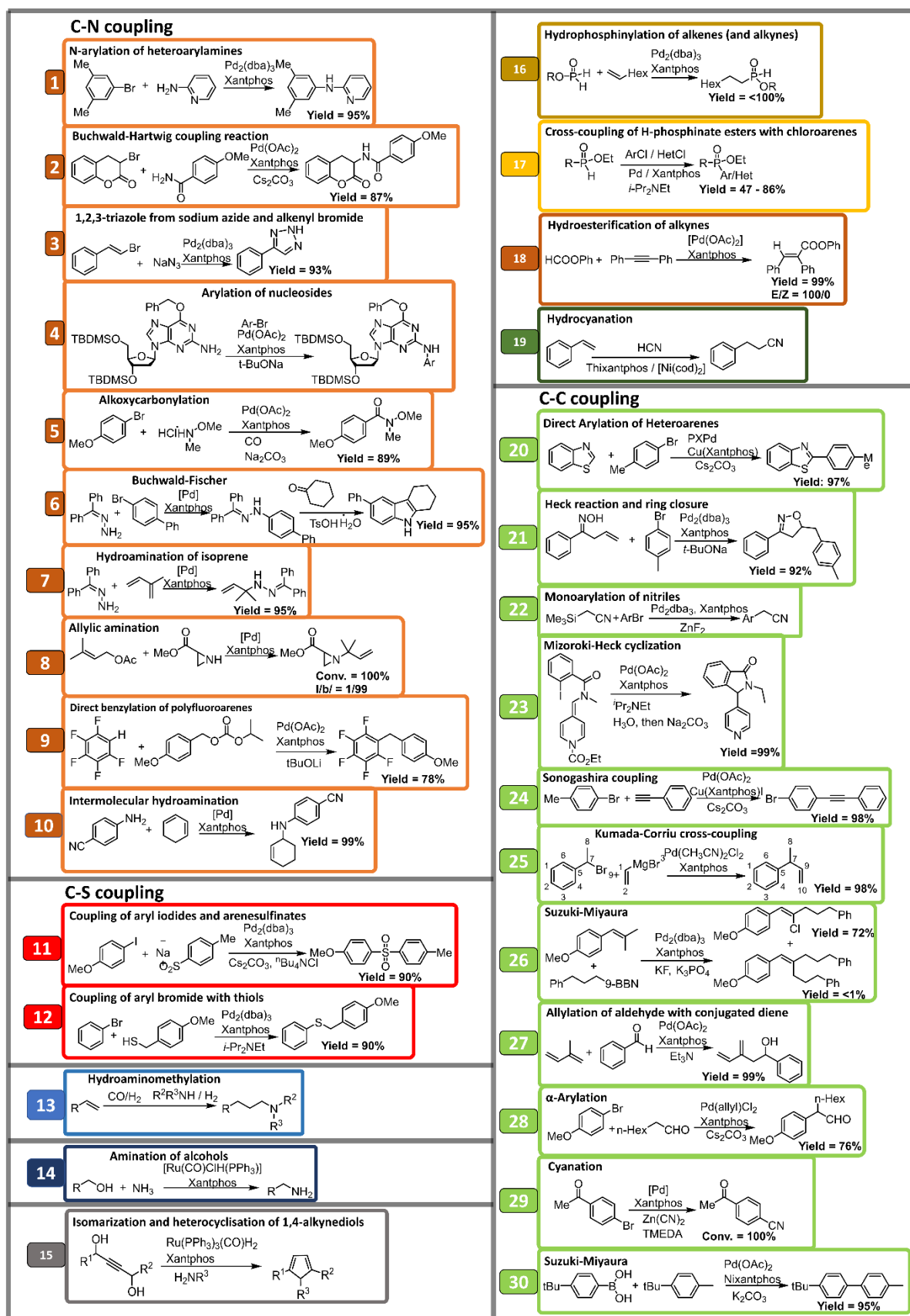


Figure 2-16: A selection of reactions in which Xantphos(type) ligands performs well.

References: 1^[85], 2^[86], 3^[87], 4^[81], 5^[72], 6^[88], 7^[89], 8^[90], 9^[91], 10^[92], 11^[93,94], 12^[82], 13^[68,69], 14^[95], 15^[84], 16^[96], 17^[77], 18^[83], 19^[74], 20^[80], 21^[79], 22^[97], 23^[98], 24^[99], 25^[100], 26^[101], 27^[102], 28^[103], 29^[104], 30^[105]

Many more examples can be found in either of two reviews on Xantphos.^[63,106] Due to the large number of reactions where Xantphos has proven to be a very effective ligand, it is possible to say that Xantphos is a “favoured” type of ligand. In most of the studies that screen different ligands only Xantphos is tested from the Xantphos family. The reason for this restriction in the screening process is likely due to that the Xantphos-type ligands have very small differences between their bite angle and electronic effects, and it can therefore be assumed that relatively similar effect will be measured between different Xantphos-type ligands. Hence it is fair to say that if Xantphos shows good results in one reaction there is then potential for e.g. Nixantphos and Benzylnixantphos to also be suitable ligands in such a system.

Synthesis of Xantphos-type ligands: The synthesis of the Xantphos-type ligands follow the same general pattern in all cases, a backbone is accessed in various ways depending on the ligand. The backbone is then lithiated and finally reacted with PPh₂Cl. Xantphos is based on the backbone 9,9-dimethylxanthene, which is accessed from the reaction between xanthone and AlMe₃ in quantitative yield^[107,108]. Xanthone is accessed by thermolysis of phenyl salicylate of phenol and salicylic acid at 275°C.^[63,109,110] The synthetic scheme towards Xantphos is presented in Figure 2-17 below.

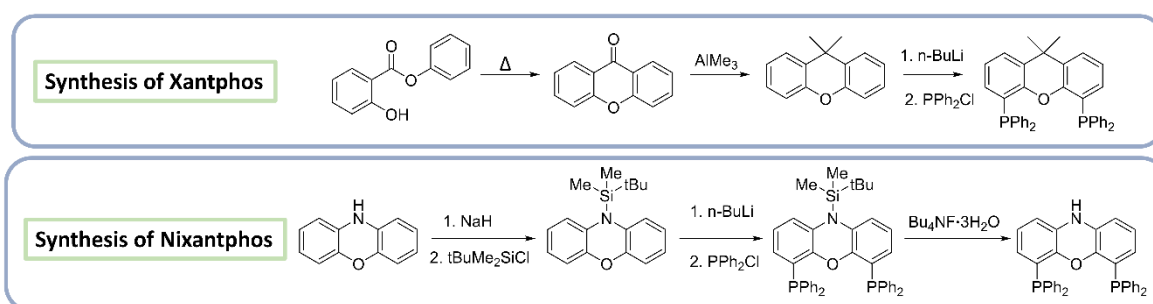


Figure 2-17: Synthetic scheme for Xantphos (top) and Nixantphos (bottom)

For the synthesis of Nixantphos the backbone component is 10-H-phenoxazine. This compound is used in dye synthesis and is therefore widely accessible.^[111–119] Before the lithiation of the 10-H-phenoxazine backbone, the NH group is protected by a bulky trialkylsilyl group.^[61,120] The full synthesis of Nixantphos is presented in Figure 2-17 above. The Phosxantphos, Sixantphos and Thixantphos can be made from convenient starting materials but the ligands themselves are not commercially available. The backbone of Isopropxantphos, Benzoxantphos and Homoxantphos are more challenging to access and these ligands are also not commercially available.

Modified Xantphos-type ligands for immobilisation: There has been a strong interest in finding good approaches towards the immobilisation of Xantphos-type ligands, much of the work was done by Kamer and van Leeuwen and colleagues. They showed that controlled sulfonation of Xantphos gives the water-soluble ligand Sulfoxantphos in high yields, Figure 2-18a below.^[121] The same group later also made a tetra-sulfonated Xantphos-type ligand with surface active pendant sulfonated groups, Figure 2-18b below^[122]. The tetrasulfonated Xantphos ligand requires considerably more synthetic manoeuvring than Sulfoxantphos.

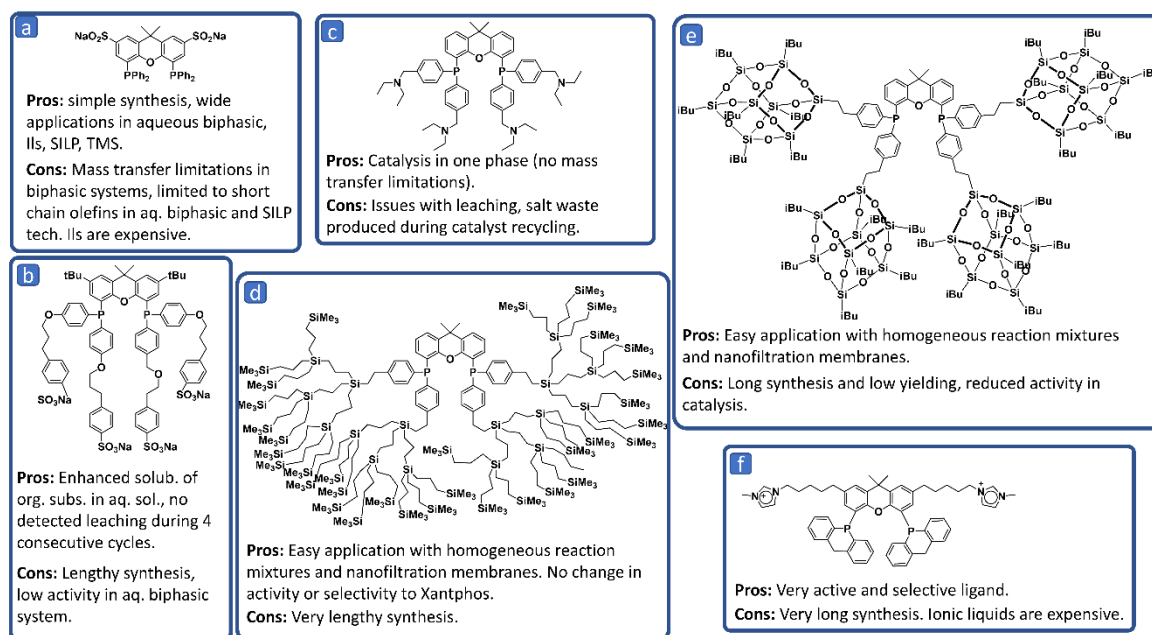


Figure 2-18: Different ways in which Xantphos-type ligands can be immobilised
a): direct di-sulfonation of xantphos^[121]; b): tetrasulfonated surface active xantphos-type^[122]; c): amphiphilic “xantham”^[123]; d): core functionalised dendrimeric xantphos^[124]; e): tetra-POSS-modified Xantphos; f): I functionalised Xantphos-type.

Yet another approach by the same group was the amphiphilic Xantphos-based ligand “Xantham” (Figure 2-18c) that dissolves in the organic phase during catalysis but can be extracted into the aqueous phase by lowering the pH, although the extraction was far from 100%.^[123] A molecular weight enlarged core functionalised dendrimeric Xantphos-based ligand (Figure 2-18d) was also reported by Kamer and van Leeuwen et al., this ligand required a rather tedious synthetic protocol.^[124] The tetra-POSS-modified Xantphos ligand “XantPOSS” (Figure 2-18e) synthesised by Vogt et al. has fewer synthetic steps, but requires temperatures of -196°C in the synthesis and suffers from poor yields. The ligand itself showed a 40% lower TOF as compared to unmodified Xantphos in Rh-catalysed hydroformylation of 1-octene.^[125,126] Xantphos-type ligands designed to be used with ionic liquids (Figure 2-18f) have also been reported by Kamer and van Leeuwen et al. Although the catalytic system was reported to not lose activity during four consecutive reactions with no leaching detected, the synthesis of the ligand is very

lengthy.^[127] There are essentially two different positions on the Xantphos ligand that have been modified so far, either replacing the phenyl groups attached to the phosphor with different suitable substituents, or functionalisation at the 2,7-positions of the backbone. The tetra-POSS-modified “XantPOSS” ligand (e) showed a 37% reduction in activity compared to Xantphos in Rh-catalysed hydroformylation of 1-octene while the core functionalised Xantphos ligand (d) showed no change in both activity and selectivity. Hence, adding bulk close to the active site of the ligand can have a negative impact upon activity, but not necessarily.

Nixantphos: This is the only ligand in the Xantphos family that has a secondary amine embedded in its backbone. The secondary amine allows for easy functionalisation, it is embedded at the rear of the backbone of the ligand, away from the active centre where the two phosphorus atoms are coordinating to a metal. Different support materials have been attached to the amine of the Nixantphos as is shown in Figure 2-19 below.

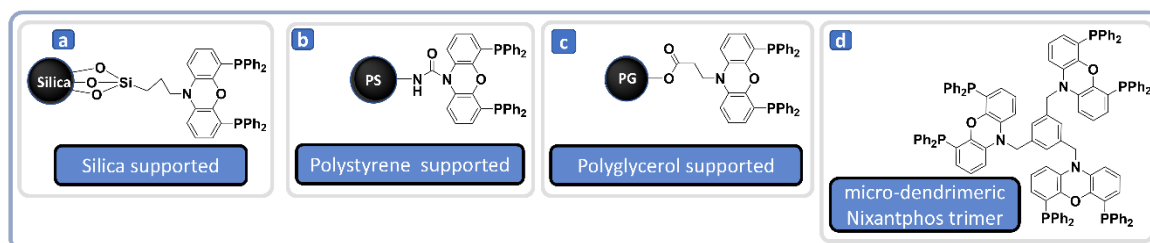


Figure 2-19: Different ways Nixantphos has previously been grafted to support materials. Silica, polystyrene (PS), polyglycerol (PG) and as a part of micro-dendrimers.

Kamer and van Leeuwen et al. investigated attaching the Nixantphos to silica via linkers (a)^[128–130]. Work by Haag et al. showed that Nixantphos can be linked to polystyrene, polyglycerols and made into a trimer (b, c and d).^[131] In all these examples the resulting ligands showed reduced catalytic activity and sometimes also reduced selectivity when applied in the Rh-catalysed hydroformylation reaction. So far, no attempt has been made at attaching a single individual molecular support to each individual Nixantphos ligand in a 1:1 ratio, an approach that could reduce negative mass transfer limitations that a solid supporting material or polymeric support might have.

General about Biphephos: It is a sterically hindered wide bite-angle bidentate bulky phosphite ligand, originally developed by UCC and patented in the mid-1980s.^[132,133] The molecular weight of Biphephos is 786.78 g/mol, which can be viewed as in the mid-range amongst other conventional and commercially available ligands. To put this into perspective, a handful of commercially available ligands and their molecular weight are presented in Figure 2-20 below.

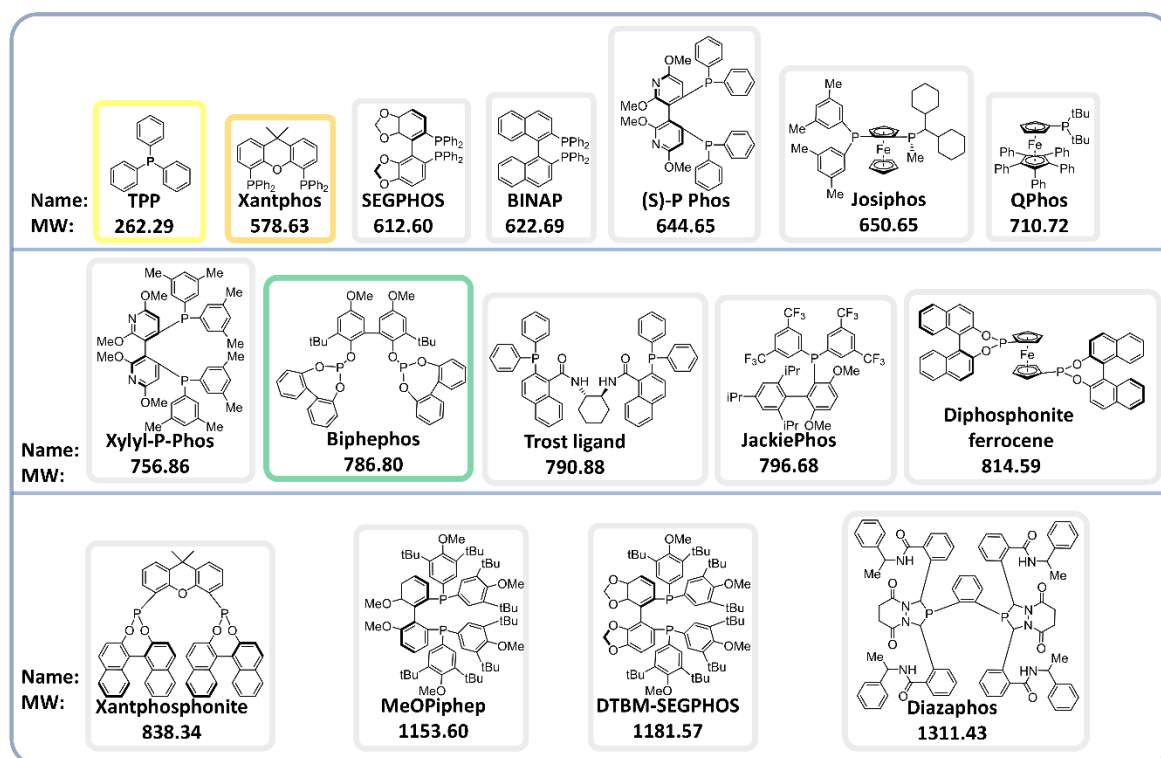


Figure 2-20: A collection of commercially available phosphorus ligands and their molecular weight (MW).

In pure form Biphephos exists as a white solid material. It is soluble in various organic solvents, albeit with somewhat restricted solubilities that are difficult to predict by intuition, but can be better predicted with computational help.^[134]

Application of Biphephos: Biphephos and its likes are reasonably inexpensive ligands and are a preferred type of ligand for application in large scale hydroformylation of alkenes when the terminal aldehyde is the desired product.^[15] The I/b ratio with Biphephos in Rh-catalysed hydroformylation is expected to be around 100 with TOF of around 3000 h⁻¹, depending on alkene substrate and exact conditions.^[35] Furthermore, Biphephos is also very active in isomerising the position of the double bond of the substrate from terminal to internal, and vice versa, which also renders Biphephos suitable for isomerisation-hydroformylation of internal alkenes towards terminal aldehydes.^[135–137]

Synthesis and purification of Biphephos-type ligands: These type of diphosphites are generally easy to synthesise from readily accessible starting materials and reactants. The basic building blocks constitute substituted biphenols that react with phosphorochloridites, usually in the presence of a base (e.g. NEt_3) and in a solvent like THF or toluene. Since the release of the first patent on Biphephos, several generations of improved synthetic procedures have followed.^[138–145] Simultaneously a great deal of attention has also been paid to the purification processes of such phosphite ligands from chlorine contaminants, where every ppm arguably matters.^[146–150] The reason is that phosphites can decompose via several different reactions, many of which are acid-catalysed. More about phosphite deactivation/decomposition can be read in section 2.5.2. on page 32 of this thesis. By reducing the amount of chloride contaminants, the amount of HCl present with the Biphephos during reaction conditions is reduced and thus a slower rate of ligand degradation is ensured.

Connecting Biphephos to a support material: Tunge and Jana reported the polymer-bound JanaPhos ligand, which is a Biphephos-type ligand bound to a polymer (Figure 2-21 below).

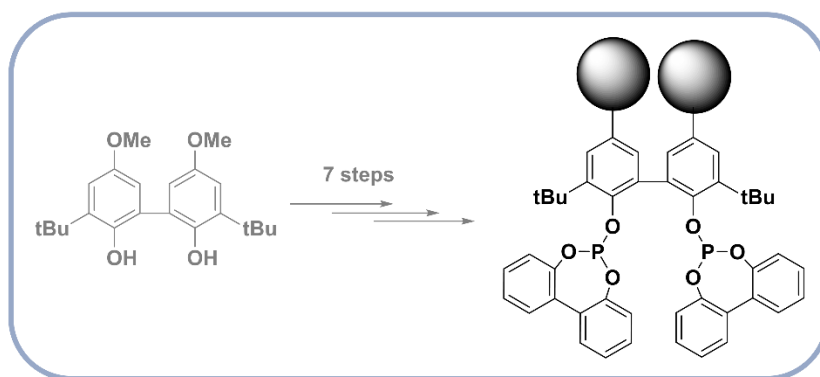


Figure 2-21: The polymer supported version of Biphephos: JanaPhos

The synthesis of JanaPhos requires a rather lengthy synthesis that involves several protection/deprotection steps. The performance in Rh-catalysed hydroformylation of 1-octene was significantly different to unmodified Biphephos ($1/b \approx 100$), JanaPhos gave a $1/b$ ratio = 3.5. It is possible that the hydroformylation experiments of JanaPhos suffered from premature decomposition of the ligand as few active measures were taken to prevent such scenario. Later on Ding et al. used the synthetic scheme of JanaPhos to synthesise a vinyl Biphephos ligand that they then copolymerised with tris(4-vinylphenyl)phosphine monomers^[151]. The resulting material was impregnated with Rh and used in the Rh-catalysed hydroformylation of alkenes showing high activity ($\text{TOF} = 11200 \text{ h}^{-1}$) and good selectivity ($1/b = 50 - 98$)^[152]. The major drawback of this type of catalyst is again the extensive synthetic procedure required to make it.

2.4. Application of Phosphorus Ligands in Continuous Processes:

It is one thing to show that a ligand will support a reaction performed in batch setup, where the longevity and recyclability of the ligand and catalyst are not necessarily considered. It is a different scenario to operate a continuous process where the catalyst system is constantly being fed new substrate and exposed to harsh reaction conditions over a longer period.

2.4.1. Continuous Phosphine-Based Processes

Most of the industrial processes that were mentioned in the beginning of section 0 are based on phosphine ligands. From an academic point of view, there are also a decent number of published works on experiments run in miniplant setups/recycling setups that successfully utilised phosphine ligands of various sorts. A few selected examples from the academic community will highlight this: Cole-Hamilton et al. showed a highly stable continuous hydroformylation system based on a monodentate phosphine ligand in an ionic liquid/scCO₂ biphasic system.^[153] Wasserscheid et al. showed a continuous SILP (supported ionic liquid phase) system based on Sulfoxantphos as ligand operated in gas-phase hydroformylation of propene.^[154] Vogt et al. applied the POSS enlarged TPP ligand in continuous hydroformylation of 1-octene in a ceramic nanofiltration membrane reactor.^[58] Vorholt et al. applied a Ru-Macho catalyst complex in continuous synthesis of formamides in a miniplant setup.^[155] Behr and Heite showcased a continuous process for the telomerisation of 1,3-butadiene and CO₂ to produce lactones based on a Pd/tricyclohexylphosphine catalyst.^[156] Behr et al. also showed a miniplant process for the continuous hydroformylation of 1-octene using a Ru/imidazole-substituted phosphine catalyst in a TMS system.^[157] Schomäcker et al. constructed a miniplant for the continuous rhodium-catalysed hydroformylation of long chained alkenes in aqueous multiphase systems.^[158] Chaudhari et al. made and applied a phosphine-functionalised PDMS/Rh catalyst in continuous hydroformylation of 1-octene using a nanofiltration reactor^[159]. The systems had stable product distributions within the time frames that were presented in the publications without using any catalyst makeup, which serves as good indication for the stability of the catalysts. Hence it can be assumed that phosphine-based catalyst systems are generally not too complicated to operate with regards to the stability of the phosphine ligands. It is commonly argued that oxidation of the phosphine ligands is the most likely threat to catalyst deactivation for above mentioned systems.

2.4.2. Continuous Phosphite-Based Processes:

There are two examples of commercial reaction systems based on phosphite ligands; the DuPont Ni-catalysed hydrocyanation of butadiene to produce adiponitrile, which uses a monodentate phosphite ligand^[160] and the 3rd generation hydroformylation processes based on Rh/Biphephos-type catalysts^[161]. Other good sources on continuous phosphite-based processes can be found in the patent literature from the 1980s and 90s where continuous experiments were used to give evidence about the long-term stability of various newly invented phosphite ligands (including Biphephos) and to show the effectiveness of various stabilising additives.^[132,133,138,161–165] The first academic literature presenting phosphite ligands in continuous processes was showcased by van Leeuwen et al. in the early 1990s who investigated the concept of heterogenized monodentate phosphite ligands^[166,167] Later on a polymer-supported Biphephos-type ligand called JanaPhos was synthesised by Tunge and Jana.^[168] JanaPhos was applied in continuous hydroformylation in a reactor integrated with nanofiltration membrane.^[169,170] Stable operations were reported for 15 h and 50 h respectively, although with l/b ratio = 3.5 and 8 respectively, which is much less than what is expected of unmodified Biphephos (l/b = 100). These publications made no mention of ligand decomposition or measures taken to safeguard against that. Priske from Evonik et al. published a report where they studied a “bulky phosphite ligand”/Rh system being applied in consecutive batch hydroformylation and nanofiltration^[27]. They explored the catalyst deactivation caused by cluster formation due to reduced CO partial pressure. They did not mention anything about decomposition of the phosphite ligand. Vogt et al. also studied a bulky monodentate phosphite ligand applied in Rh-catalysed hydroformylation, but using a continuous jet-loop rig with coupled ceramic membrane separation^[171]. They showed a continuous experiment lasting 50 h (4 residence times) with no signs of instability and deactivation. Dreimann et al. used consecutive batch hydroformylation and nanofiltration to explore the application of a Biphephos/Rh system^[172]. Complete deactivation of Biphephos was initially observed between a first and a second hydroformylation experiment when reactor and OSN setup were independent units that required the reaction mixture to be manually transferred between them using “standard Schlenk technique”. Better stability was achieved between two consecutive hydroformylations when the reactor and OSN unit were integrated. Dreimann et al. then applied Biphephos in continuous hydroformylation/OSN operation showing the stability of the system breaking down after 18 h^[173]. A very different concept called SILP (supported ionic liquid phase) has shown good result in continuous gas-phase hydroformylation of propene using a

Biphephos-type ligand.^[174] Using “technical C4 cuts” resulted in highly instable systems that quickly lost activity and/or selectivity. Good stability for over 850 h was achieved only after application of purer substrate feed and a non-volatile acid scavenger (Tinuvin 770), the authors stressed that the purer substrate feed was significantly dryer and that this was very important. Behr et al. applied Biphephos in a DMF/decane TMS system that was batchwise hydroformylated and subsequently decanted of product and replenished with fresh alkene substrate^[175]. Excellent stability of the system was maintained in terms of l/b ratio = 100 throughout 30 cycles, albeit with a reduced activity in each consecutive run due to leaching of the catalyst into the product phase. This Biphephos TMS system was then implemented in a miniplant to allow for continuous operation experiments^[176]. The continuous system became unstable after 20 h online as the l/b ratio dropped from 100 to 2.7, indicating ligand decomposition. Stable operation was achieved by applying a ligand make-up. Dreimann et al. were faced with the same reality of an unstable Biphephos ligand in their integrated TMS-OSN miniplant experiment, where again a make-up of Biphephos was the solution to establish stable operation.^[177,178] Overall, none of the more recent publications on phosphite-based continuous processes focused much attention on what parameters were influencing the stability of the ligand. Since the above-mentioned sources all have very different focus in their stories and different goals for their publications, a summary and analysis of these systems, their setups, lessons to be learned from them and possible limitations of these and some others is presented in Table 3 below. Those systems, which were significantly more stable, have been highlighted in green. The definition of being significantly more stable is that it was clearly stated that the l/b ratio was consistently high without a continuous ligand makeup. And/or the state of the phosphite ligand was monitored by ³¹P-NMR.

Table 3: Publications on phosphite ligands applied in continuous reaction processes.

Ligand	Take away	Substrate	Stabiliser	Other measures	Stable [h]	Ref.
Triphenyl-phosphite	Decomposition of "open" phosphites will not fully halt even with application of stabilising tertiary amines.	1-butene	Tertiary amines	1-butene feed vessel pressurised with O ₂ free N ₂ . Syngas fed through an oxygen guard unit.	-	[179]
Mono-dentate phosphite	Stable system when [amine] in reaction mix was high enough, less volatile n-Oct ₃ N most suitable.	1-butene	Et ₃ N, n-Pr ₃ N, n-Oct ₃ N		300	
Mono-dentate phosphite	Less bulky phosphite is more sensitive to hydrolysis. Rapid decomposition resulted in phosphonic acid precipitate and plugging the reactor. All phosphite decomposed in <0.8 days.	1-butene, 2-butene	No stabiliser	0.5 wt.% 2,6-di-tert-butyl-4-methylphenol as antioxidant. Reactor was	19	[162]

Mono-dentate phosphites	Bulky phosphites are less sensitive to decomposition. Amine-Aberlyst-A21 scavenge phosphonic acid decomposition products, no negative effect on reaction system.	1-butene, 2-butene	amine-Aberlyst A-21	purged with N ₂ to remove O ₂ before start.	528	
Biphephos derivative	Stable system for 124 days with constant activity and selectivity (I/b $\approx$ 30). Single charge of Rh and Biphephos.	propene, 1-butene, 2-butene	1,2-epoxy-dodecane	2,2-biphenol as antioxidant. Reactor purged with N ₂ to remove O ₂ before start.	3000	[161]
Biphephos derivative	Decomposition not mentioned. Stable activity and selectivity (I/b $\approx$ 33) for >5 days. Rh:L = 1:8.5	1-butene	No stabiliser	Reactor purged with N ₂ after adding reaction mixture.	130	[133]
Biphephos derivative	Decomposition not mentioned. Stable activity and selectivity (I/b = 54.4-76.9) for >5.4 days. Rh:L = 1:8	propene, 2-butene	No stabiliser	Reactor purged with N ₂ after adding reaction mixture.	130	[138]
Biphephos derivative	Decomposition not mentioned. Stable activity and selectivity (I/b $\approx$ 33) for >5 days. Rh:L = 1:8.5	1-butene	No stabiliser	Reactor purged with N ₂ after adding reaction mixture.	130	[132]
Different mono-dentate phosphites	Monodentate phosphite applied in continuous hydroformylation experiments lasting between 3 - 14 days. Some phosphites showed good stability, others were less stable.	1-butene	No stabiliser	Purged with N ₂ after adding reaction mixture. Used 2,6-di-tert-butyl-4-methylphenol as antioxidant.	74 - 336	[163]
Mono-dentate phosphites	Stabiliser free control reaction had 50% phosphite decomposed, Co stabilised had no phosphite decomposition. Hydroformylation activity was reduced in presence of Co additives.	propene	Co ₂ (CO) ₈	System purged with N ₂ after adding reaction mixture.	288	[164]
Mono-dentate phosphites	Epoxide containing reaction had most hydrolysis. Additive free control reaction less effected. Ru containing reaction had least decomposition.	propene	control / Ru ₃ (CO) ₁₂ / dodecane epoxide	System purged with N ₂ after adding reaction mixture.	288	[164]
Biphephos derivative	Series of batch reactions (120°C), intermittent product separation by distillation (120°C), adding fresh alkene substrate. Additive free control system went from 80.5% alkene conversion to 14.25% after 2 cycles. Tinuvin stabilised system gave 29.4% conversion after 14 cycles. No information about I/b ratio.	1-octene	Tinuvin 770	No details about special care taken.	14 cycles	[165]
Silica grafted polymer bound phosphite	The authors claim the system was stable and there was no deactivation.	1-octene	No stabiliser	No details about special care taken.	140 - 500	[167]
Biphephos derivative	Recycled the catalyst 5 times in a Suzuki-Miyaura reaction and consistently reached 83% yield. Substrate was a boronic acid, MeOH/H ₂ O used to crash out the catalyst for recycling.	phenylboronic acid	No stabiliser	Filtered catalyst under air for recycling. No loss of catalytic activity.	5 times	[168]
Biphephos derivative	JanaPhos applied continuous hydroformylation of 1-octene. I/b ratio =	1-octene	No stabiliser		15	

	3.5. No attention to phosphite decomposition.			No details about special care taken.		[169]
"Bulky phosphite ligand"	Each experiment contained 4 reactions and 3 filtrations. Dodecene hydroformylated at 150°C, octene hydroformylated at 120°C. No stabilisers added, no attention to potential phosphite decomposition. Interesting rejection over time graphs.	1-dodecene, 1-octene	No stabiliser	No details about special care taken.	3 filtrations and 4 reactions	[27]
Biphephos derivative JanaPhos	Hydroformylation in toluene/1-octene. Steady operation of the nanofiltration reactor for 50 h. Steady I/b = 8 throughout. Very low selectivity towards isomers and octane.	1-octene	No stabiliser	No details about special care taken.	50	[170]
Biphephos	2 reactions & 1 filtration. 1st reaction gave 60% yield of I-aldehyde. 2nd reaction yielded 21% of I-aldehyde and complete loss of I/b ration. Mention catalyst deactivation.	1-dodecene	No stabiliser	Reactor evacuated & filled with argon X 3, before filling with reaction mixture.	1 filtration & 2 reactions	[172]
Biphephos	Integrated reaction and filtration. Continuous experiment lasted 40 h, typical selectivity of Biphephos broke down after 19 h likely due to ligand decomposition.	1-dodecene	No stabiliser	No details about special care taken.	40 (19)	[173]
Biphephos derivative	Initially bad performance in continuous operation, suggested issue of hydrolysis. Changed substrate source to purer and dry substrate gas feed and applied acid scavenger, stable for >850 h. Author is suggesting decomposition peaks 5 -8 ppm are oxidised ligand species.	C4 raffinate	Tinuvin 770	Applied Tinuvin as acid scavenger. Used dry C4 raffinate ([H ₂ O] > 16 ppm).	850	[174]
Biphephos	DMF/dodecane TMS system. 30 recycling cycles, always I/b = 99, each recycle lost a few % of Rh and P into nonpolar phase. Last recycling experiment was left to react longer resulting in high I-aldehyde yield. No decomposition of the catalyst. Albeit no ³¹ P NMR of the final reaction solution was made.	1-dodecene	No stabiliser	Standard Schlenk technique to load reactor, no further purging before starting reaction.	30 cycles.	[175]
Biphephos	Initially stable for 20 h, then selectivity broke down. Stated that loss of selectivity happens when Rh:L is below 1:2. No evidence given to if the P is decomposed or leached out. Biphephos makeup for system stability.	1-dodecene	No stabiliser	No details about special care taken. Used a Biphephos make-up stream to keep system stable.	75	[176]
Biphephos	Continuous reaction used Rh and Biphephos makeup for stability. Despite this, there were times with higher levels of branched aldehyde products. No discussion about ligand decomposition.	1-dodecene	No stabiliser	Before batch filtration the system was flushed with N ₂ for 10 min to remove O ₂ .	200	[177]
Biphephos	Integrated mini-plant with distillation of product phase for recycle of unreacted alkene and isomerised alkene. Reaction	1-dodecene	No stabiliser	No details about special care taken.	150	[180]

	used a Rh/L makeup . No discussion about catalyst degradation.			Used ligand make-up for system stability.		
Biphephos	High I/b ratio for the first 40 h, slowly decreasing. Compensated with increased cat. makeup , relatively stable over the total 90 h, although I/b was unstable. Rh and P rate of leaching calculated to be 1.4%/h. No information about Rh/L makeup and mass balance.	1-dodecene	No stabiliser	No details about special care taken.	90	[181]
				Used ligand make-up for system stability.		

In many of the above sources the phosphite ligands were handled using air free techniques making sure oxygen (O_2) was excluded from the reaction system. The argument being in some cases that air could potentially cause oxidation of the catalyst^[173,174] Many of the early (patent) sources described very specifically that the reactors were always purged with O_2 -free N_2 after they had been filled with reaction mixture and prior to the start of a reaction. This step in the preparation methodology can be justified with different arguments. First, the solubility of O_2 in many common organic solvents can be greater than 10 times the solubility of O_2 in water^[182]. Second, it is not a trivial task to efficiently remove all dissolved O_2 gas from large volumes of liquid (>100 ml). Third, even if a satisfactory level of O_2 has been successfully removed from a liquid, it is then not trivial to maintain this state of the liquid until it has been properly introduced into the reactor system, using standard Schlenk technique or not. Comparing the various substrates that the different studies used, we can categorise them as either gas (propene and butenes) or liquids (1-octene and 1-dodecene) at ambient temperature and pressure. The propene and butene are delivered as liquids under pressure in canisters. It is therefore not too difficult to maintain a high purity and low concentration of oxygen within the alkene as it is being transferred from the original canister to another container/reactor vessel. Unnecessary exposure and contact with air can thus easily be avoided. The liquid long chain alkene substrates will on the other hand have a high probability of having dissolved O_2 inside the liquid as they are usually bought as non-inert products. Furthermore, because they are rather long chained and nonpolar, they will dissolve a relatively high concentration of O_2 . The oxygen will then over time of storage result in autoxidation of the alkenes, resulting in the formation of non-volatile dissolved peroxides. Two issues are therefore present for these liquid substrates; they must be purified from any dissolved peroxides and O_2 prior to use as a substrate.

2.5. Ligand Stability, Deactivation and Decomposition

The stability of a catalytic system will be largely influenced by the stability of its constituent parts, being the ligands and the TM-complex (which itself is made up of a central metal atom and ligands). The stability of a TM-complex will be influenced by factors such as the propensity for the central metal atom to come together and form unwanted clusters, more often than not an issue with Pd-catalysed systems^[183]. But that potential will depend on many different factors apart from the type of metal, and it can be highly dependent upon the conditions hence difficult to generalise about. The stability of the ligand can on the other hand to some extent be generalised about according to what type of ligand it is; phosphine or phosphite. The two types of ligands have different structures which gives them different potential for reactivity and deactivation. The most direct way to study the state of a phosphorus ligand is with the use of ³¹P-NMR^[184,185].

2.5.1. Decomposition of phosphine ligands

Phosphine ligands have a high electron density at their phosphor-atom which is provided through the electron rich R-substituents. Phosphines are therefore thermodynamically prone to form phosphine oxides when in contact with oxygen or another oxidising agent. Nevertheless, some phosphines show impressive kinetic resistance towards oxidation due to their chemical structure. In a study on phosphine ligand oxidation, a collection of different monodentate phosphine ligands were dissolved in toluene, fully exposed to air and heated to 100°C for 3 days. Most of the phosphine ligands were completely oxidised by the end of the experiment while certain dialkylbiaryl phosphines only showed a few percent of oxidation^[186].

2.5.2. Decomposition of Phosphite Ligands

A phosphite is defined by its generic structure where the phosphorus atom covalently bonds to three oxygen atoms, which are further connected to carbon atoms that are then part of rest groups, see Figure 2-22 below.

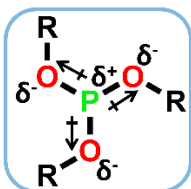


Figure 2-22: Structure of generic phosphite ligand.

The oxygen-phosphor bonds are polarised due to the large difference in electronegativity between phosphor and oxygen.

Because the phosphor is bonded to electron withdrawing oxygen atoms, the electron density of the phosphor is reduced. This polarisation of the phosphor-oxygen bond renders the phosphor

significantly less sensitive towards direct oxidation from O₂, but can still be oxidized by reaction with peroxides. Many of the phosphite decomposition reactions have been extensively studied by the polymer community as they are used as stabilisers in polymer-blends acting as secondary antioxidants.^[187–189] An overview of the most important phosphite decomposition reactions is presented in Figure 2-23 below, note that most of them are being catalysed by acids.

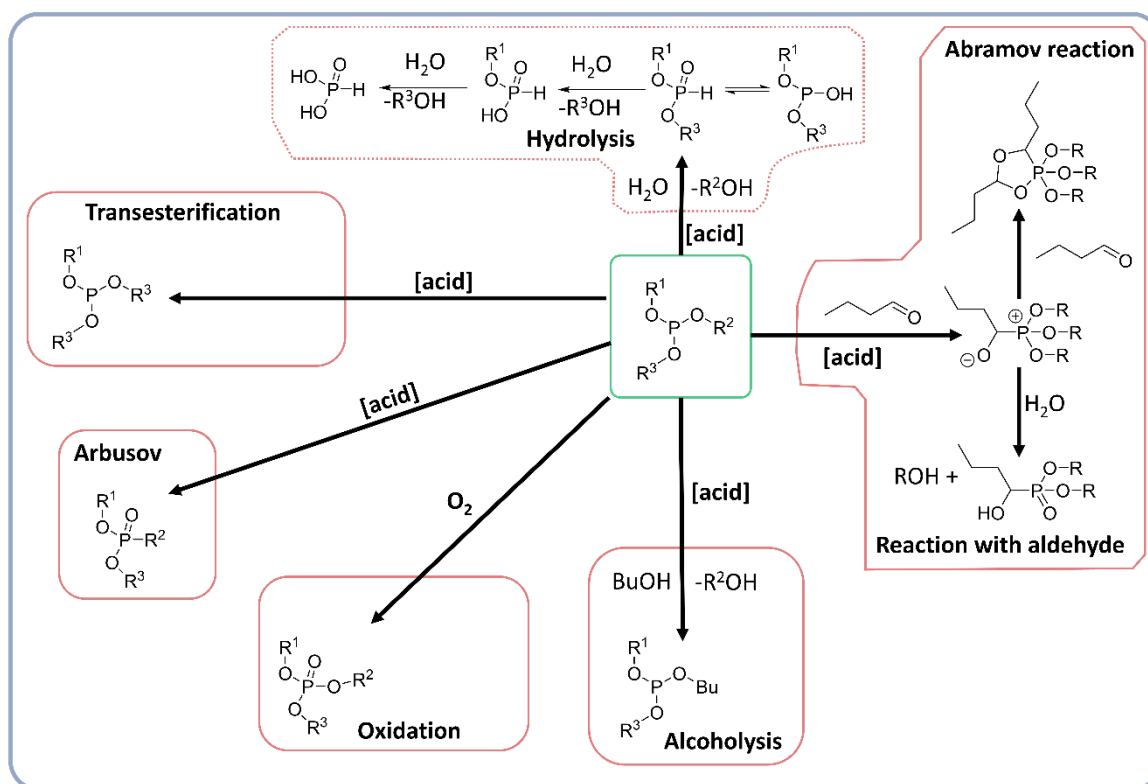


Figure 2-23: Decomposition pathways of phosphites.
All these decomposition reactions are catalysed by strong and weak acids.

The decomposition reactions that phosphites can undergo include hydrolysis, alcoholysis, trans-esterification and Arbusov rearrangement.^[28] Additionally, when phosphites are applied as ligands in hydroformylation their susceptibility to perform nucleophilic attack on aldehydes (Abramov reaction) must also be considered.^[163] In this context of catalysis it can be highlighted that the terminology of decomposition and not necessarily deactivation is being made use of, as it is known that many of the resulting decomposition products are not necessarily deactivated in terms of their ligating properties. And so, when they continue to contribute to the overall activity of a reaction system, they will do so by also reducing the systems overall selectivity. By far, the three most important decomposition reactions of phosphite ligands applied in hydroformylation systems are oxidation, hydrolysis and reaction with aldehydes. The hydrolysis reaction is catalysed by weak and strong acids and strong bases. Water acts as a nucleophile and attacks phosphorus, which causes the cleavage of the P-O bond

and the formation of phosphorus acid diester species.^[190,191] This species can undergo further hydrolysis to phosphorus acid and finally phosphonic acid respectively.^{[192],[193]} The decomposition becomes autocatalytic if the formed acids are not being actively removed from the system. The decomposition products do not necessarily lose their ability to ligate to catalytically active metals. The pentavalent phosphorus species formed from the hydrolysis are also known as pentavalent heteroatom-substituted phosphine oxide (HASPO). A HASPO can rearrange and form trivalent phosphorus compounds which have ligating capabilities, see Figure 2-24 below. The two types of species exist in a tautomeric equilibrium with each other.

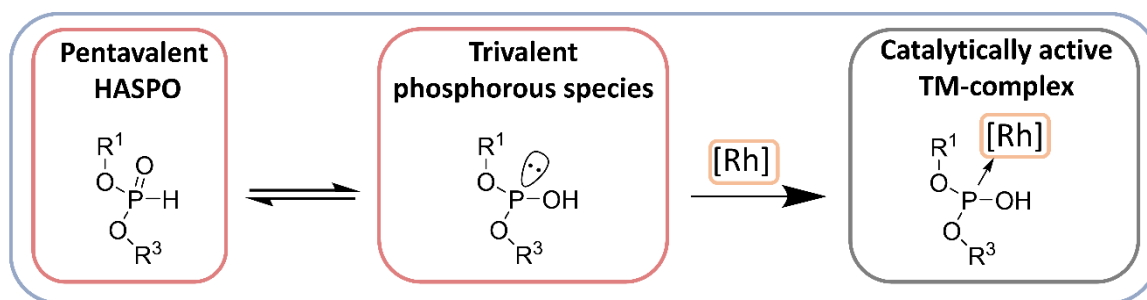


Figure 2-24: A phosphonic acid diester in equilibrium with a trivalent species
The trivalent species can coordinate to a metal, e.g. rhodium.

Trivalent HASPOs have been studied as ligands in various catalytic systems,^[194–202] including Rh-catalysed hydroformylation.^[203,204] They form Rh-complexes that are highly active in hydroformylation, but without any selectivity. Thus, the expectations of the catalyst system based on the initially applied phosphite ligand will become increasingly tainted when HASPOs accumulate in the reaction mixture. To complicate things even further, one must recognise that HASPOs will also react (reversibly at elevated temperatures) with aldehydes (or other carbonyl group containing compounds) by nucleophilic addition (Pudovik reaction)^[205] The resulting species from the addition of HASPOs to an aldehyde are α -hydroxy phosphonates, which are also acidic in nature and thus also contribute towards the autocatalytic decomposition of remaining phosphite species. As mentioned earlier, phosphites themselves can also react with aldehydes in a so-called Abramov reaction, another reaction that is acid-catalysed. The result from this reaction are phosphonates, in patent literature it is reported that such species are readily hydrolysed to their corresponding hydroxy alkyl phosphonic acids.^[162] Hence, once again an acidic species is generated from the decomposition reaction, which will further add to the autocatalytic decomposition of remaining phosphites. Typically, these undesirable hydroxy alkyl phosphonic acids are relatively insoluble in a typical hydroformylation reaction medium. Thus, if there is enough build-up of such acidic species there is an increasing risk that precipitation will happen. In a continuous liquid recycling system this can have dire

consequences if recycling lines become plugged. Patent literature suggests a weak base (e.g. sodium bicarbonate) can be used to extract the precipitate/acid.^[133]

Since high performance phosphite ligands can be expensive, and their decomposition result in autocatalytic cascade decomposition of remaining ligands, it is not a viable solution to merely replace decomposed ligands with a make-up as this would quickly result in the accumulation of acidic decomposition products within the reaction system. Instead, it is of the highest importance that the initial rate of any phosphite decomposition happening at all is minimised. There are two types of approaches available; the first is to apply appropriate ligand design (pre-measure) and the second option is to adjust the environment that the phosphite ligands are being exposed to (post-measure). Considering the first approach of ligand design, a “rule-of-thumb” is that bulkier phosphites are more robust.^[15,206] Alkane phosphites can undergo the Arbuzov decomposition reaction (Figure 2-23 page 33) while aryl phosphites do not, hence one major reason for why the majority of phosphite ligands are aryl-based.^[207] The second line of defence is to control the environment which a phosphite is exposed to, this can be influenced by e.g. temperature, solvent, pH and additives. The general idea with additives is that they should act to scavenge any formed acids within the system. A collection of suggested additives from various sources is presented in Table 4 below. Notice that the columns have been arranged in order of the temperature that the study used for the evaluation of the additive. This is because higher temperature studies are more representative of a scenario where the phosphite is applied as a ligand in Rh-catalysed hydroformylation.

Table 4: Additives capable of stabilising phosphites against hydrolysis.

^[a] “Hydroformylation” means that an alkene substrate, Rh and syngas was present ($\text{CO}:\text{H}_2 = 1:1$, 20 bar) during the experiment and that aldehydes were formed as a product.

Source	Additive	Phosphite	t [h]	T [°C]	Conditions ^[a]	Effect
Hydroformylation patent ^[165]	Tinuvin 770	Biphephos derivative	28	120	Batch hydroformylation	14 cycles, start conversion 86%, end conv. <30%
Hydroformylation patent ^[161]	cyclohexene oxide	Biphephos	24	110	Batch hydroformylation	3 % hydrolysed
Hydroformylation patent ^[208]	n-Oct ₃ N	Monophosphite	20	101	Continuous hydroformylation	Steady concentration of phosphite
Hydroformylation patent ^[161]	1,2-epoxydodecane	Biphephos	2976	100	Continuous hydroformylation	Stable system for 124 days
Hydroformylation patent ^[209]	Co ₂ (CO) ₈	Monophosphite	288	100	Batch hydroformylation	0 % hydrolysed
Hydroformylation paper ^[210]	AcONa	P(OPh) ₃	10	90	Batch hydroformylation	"catalyst life" >10 hr
	KOH	P(OPh) ₃	10	90	Batch hydroformylation	"catalyst life" >10 hr
	NBu ₃	P(OPh) ₃	10	90	Batch hydroformylation	"catalyst life" >10 hr

	N(n-Oct) ₃	P(OPh) ₃	10	90	Batch hydroformylation	"catalyst life" >10 hr
Hydroformylation patent ^[208]	Et ₃ N	Monophosphite	20	77	Continuous hydroformylation	Slow drop in activity, Et ₃ N is volatile
Hydroformylation patent ^[208]	n-Pr ₃ N	Monophosphite	20	77	Continuous hydroformylation	Steady activity, amine less volatile
Hydroformylation patent ^[163]	Amberlyst-A21	Monophosphites	528	70	Continuous hydroformylation	Stable system for 22 days
Polymer patent ^[211]	ZnO ₂	Phosphite	480	60	polymer blend, 90% r.h.	1.5% hydrolysed
Polymer patent ^[212]	J = TMP derivative	Phosphite	72	50	polymer blend, 75% r.h.	19.6% hydrolysed after 72h
	Q = TMP derivative	Phosphite	72	50	polymer blend, 75% r.h.	21.7% hydrolysed after 72h
Polymer patent ^[213]	Diisopropanolamine	P(OPh) ₃	72	25	polymer blend, 50% r.h.	1.9 % hydrolysed
	Aniline	P(OPh) ₃	72	25	polymer blend, 50% r.h.	1.1 % hydrolysed
	Triisopropanolamine	P(OPh) ₃	72	25	polymer blend, 50% r.h.	1.5 % hydrolysed
	Ethylenediamine-tetra-isopropanol	P(OPh) ₃	72	25	polymer blend, 50% r.h.	0.69 % hydrolysed
	Metaphenylene diamine	P(OPh) ₃	72	25	polymer blend, 50% r.h.	0.92 % hydrolysed
Hydrolysis paper ^[214]	K ₂ CO ₃	cyclic phosphite	72	25	water/THF mixture	no hydrolysis
	Et ₃ N	cyclic phosphite	72	25	water/THF mixture	1% hydrolysed
	Molecular sieves	cyclic phosphite	72	25	water/THF mixture	1% hydrolysed

Amongst the better performing amines presented above is a subclass that can be identified, namely those based upon the general structure of 2,2,6,6-tetramethylpiperidine (TMP), Figure 2-25 below. These TMP-based derivatives are also known as hindered amine light stabilisers (HALS) in the polymer community due to their ability to protect polymers from photo-oxidation (radical scavenger).^[215–217]

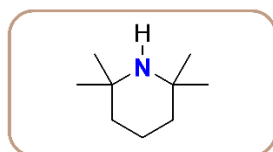


Figure 2-25: Structure of 2,2,6,6-tetramethylpiperidine (TMP)

But these amines were also discovered to be very effective at protecting phosphites blended into the polymer formulation against hydrolysis.^[218] A completely different class of phosphite stabilisers are the epoxides. Their mechanism of stabilisation is to react with any phosphonic acid(esters) present and form cyclic inert compounds and thereby stop the autocatalytic degradation. Many different commercially available epoxides exist, and so far, only a handful

have been tested and reported upon for the application as a phosphite stabiliser. The best performing epoxide reported so far is cyclohexene oxide.^[161] Apart from the typical Brønsted acids, it has also been reported that Rh clusters of the type $\text{Rh}_6(\text{CO})_{16}$ (Figure 2-26) can contribute to the decomposition of phosphite ligands.

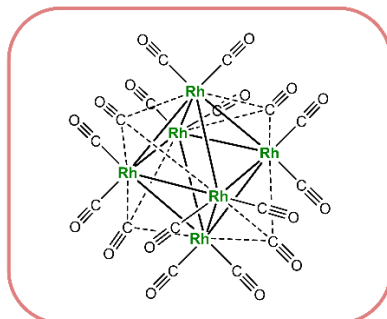


Figure 2-26: Hexadecacarbonylhexarhodium or $\text{Rh}_6(\text{CO})_{16}$

Suggested measures to control this type of decomposition pathway involves addition of Group VIII metal carbonyl compounds (other than Rh) to the reaction mixture (such as e.g. $\text{Co}_2(\text{CO})_8$).^[209] A remarkable difference in stability of the mono-phosphites investigated therein was observed. After 12 days of continuous Rh-catalysed hydroformylation of propene (100°C, 11 bar CO/H_2) no phosphite decomposition was observed when $\text{Co}_2(\text{CO})_8$ was present, while an additive free control reaction resulted in 47 % of the total phosphite ligand content decomposing. Overall, there are only a handful of studies on phosphite stabilisation by additives that are specifically aimed at hydroformylation reaction conditions. And so, there is not much information about what other effects various additives have upon the catalytic system.

2.6. Brønsted-Type Acid Catalysts

Since this thesis is about expanding the applications of POSS as an MWE-unit also for Brønsted acids, a short introduction to such acids is presented here. The POSS-modified Brønsted acid which was studied in this thesis will also be introduced, followed by the acid-catalysed ketalisation reaction between glycerol and butanone, which was used as a model reaction in order to explore the catalytic potential of the POSS-modified Brønsted acid. Brønsted acids are those compounds that will react with a base to form conjugated acid/base pairs due to the exchange of a proton, i.e. a Brønsted acid must have a proton that will readily dissociate. Some examples of homogeneous Brønsted acids include the common mineral acids and organic acids, such as HCl , H_2SO_4 , H_3PO_4 , lactic acid, acetic acid, formic acid, citric acid and p-toluenesulfonic acid (PTSA) to mention a few. Some industrially important acid-catalysed reactions include (i) Brønsted acid catalysed vapour phase hydration of ethene to form ethanol^[219,220] (ii) Brønsted acid catalysed isomerisation of n-hexane to iso-hexane.^[221] Overall,

the petroleum industry employs large amounts of different (solid) acid catalysts to facilitate the various cracking, isomerisation and alkylation reactions applied for upgrading oil. Solid Brønsted acids include zeolites^[222–224], heteropolyacids (HPAs)^[225], sulphated metal oxides^[226,227], solid phosphate catalysts^[228–236], acidic clay catalysts^[237–239], sulfonated (organic) solids^[240–243].

Sulfonated octa-phenyl-POSS (H-S-POSS): Although this compound has never been applied as an acid catalyst in a reaction up to this moment, it has been reported in literature for various other applications. Since one chapter of this thesis is dedicated to exploring the application of this compound as an acid catalyst, a short introduction about the compound is given here. The sulfonation of octaphenyl-POSS can be achieved by direct sulfonation of the octaphenyl-POSS (OP-POSS) using chlorosulfonic acid to produce the chlorosulfonated octaphenyl-POSS ($T_8(C_6H_5SO_3Cl)_8$), this was patented by Laine et al. from the university of Michigan in 2005.^[244] Also fuming sulfuric acid has been reported as a possible way forward.^[245] The H-S-POSS molecule is presented in Figure 2-27 below.

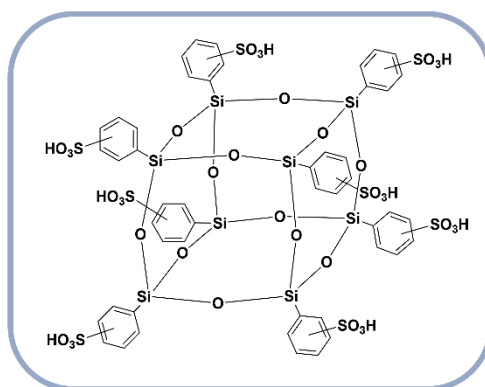


Figure 2-27: Structure of a fully sulfonated H-S-POSS.

According to literature the sulfonation will happen mainly at the meta position but there will always be a small distribution.^[246] The H-S-POSS has previously been explored for application as part of a highly porous, electrically conducting polymer nanocomposite materials with a large specific capacitance showing potential for production of high performance capacitors.^[245] Another application was as additive to polybenzimidazole membranes, where the H-S-POSS facilitated the transfer of protons across the membrane and thus allowed the membrane for application in high temperature H_2 /air membrane fuel cells.^[247] But the catalytic potential of H-S-POSS has never been explored. It is possible to liken the H-S-POSS molecule with a molecular weight enlarged (MWE) version of the classical organic acid p-toluenesulfonic acid (PTSA) which is presented in Figure 2-28 below.

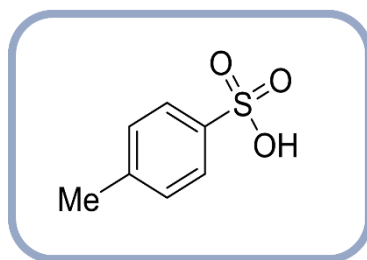


Figure 2-28: Structure of *p*-toluenesulfonic acid.

PTSA is a solid in pure form at room temperature, it can dissolve in water, alcohols and other polar organic solvents and is classified as a strong acid. It is highly popular and widely used in homogeneous acid catalysis, but it is limited by the accompanied separation and recycling issues.

2.6.1. Ketalisation of Glycerol with Butanone

This reaction was used as a model reaction when the H-S-POSS compound was studied as a catalyst in this thesis. The ketalisation of glycerol with butanone is an equilibrium condensation reaction that is catalysed by Brønsted acids and gives cyclic ketals. The product ketal can be used as fuel additive in diesel fuels to improve their combustion properties and engine performance^[248,249]. The ketalisation reaction mechanism is presented in Figure 2-29 below.

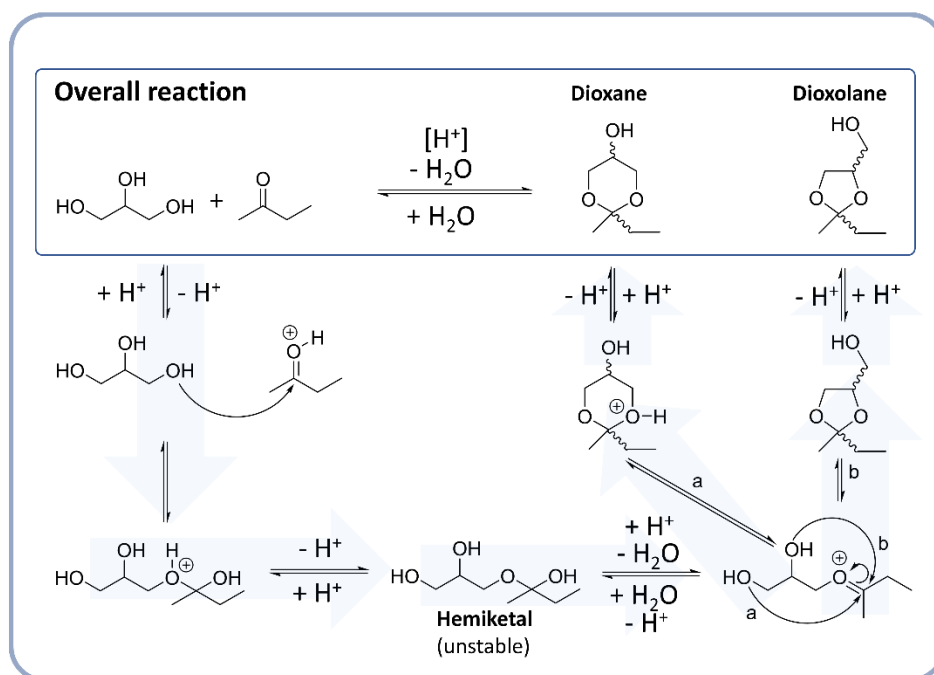


Figure 2-29: The acid-catalysed ketalisation of butanone with glycerol.

The upper box only concerns the overall reaction while the lower section explains the reaction mechanism.

The acid protonates the 2-butanone in the first reaction step. Glycerol can then perform a nucleophilic attack on the protonated butanone, which then leads to the unstable hemiketal. This is then undergoing an S_N1 nucleophilic substitution reaction by which one of the two

possible products will be formed (not considering the various stereoisomers that are possible). Which of the two potential products will be formed depends upon which of the two different potential path the reaction will take from the unstable hemiketal. What differs between the two routes is whether the β or γ -hydroxyl group will be the one performing the nucleophilic attack upon the oxocarbenium ion (path a or path b). The two possible products will be either the 1,3-dioxane (six-membered ring, path a) or the 1,3-dioxolane (five-membered-ring, pathway b). In the presence of an acid catalyst the two products will undergo isomerisation from one to the other.^[250] For cyclic ketals it is the five-membered ring that is the most stable while the six-membered ring is slightly less stable. One explanation for this is that there is an axial repulsion between one of the alkyl groups in the 2-position of the 1,3-dioxane ring and the axial hydrogen atoms in the 4- and 6-positions, illustrated in Figure 2-30 below.^[250]

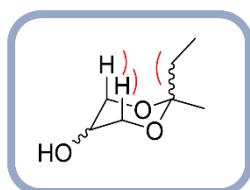


Figure 2-30: The six-membered ring structure of the 1,3-dioxane ketal. Internal repulsion between the hydrogen atoms in 4- and 6-position and one of the alkyl groups in 2-position makes the six-membered ring less stable.

Hence, the five-membered ring 1,3-dioxolane will be thermodynamically favoured over the six-membered ring 1,3-dioxane. And because the selectivity of this reaction is controlled thermodynamically the 1,3-dioxolane will be the main product. If the reaction is conducted neat without any externally added co-solvents the reaction mixture will start off biphasic as the glycerol and butanone are non-miscible. The ketal products act as mixing agents, which help the two phases mix with each other. After reaching a sufficiently high yield of the ketals, the two liquid phases merge into a single homogeneous phase. In a reaction system where acetone was used instead of butanone, the two phases merged after a conversion of 26% had been reached starting from equimolar ratios of reactants.^[251] It is possible to use an external co-solvent (e.g. ethanol, isopropanol) from the beginning of the reaction, which will enable the two reactants to be fully mixed already from the start of the reaction.

Glycerol: Glycerol is a virtually nontoxic alcohol to both human and environment. It is a by-product in the production of biodiesel by transesterification of fats and oils with e.g. methanol, from soap production by saponification of glycerides (oils and fats) and from hydrolysis or splitting of fats and oils with water to produce fatty acids. The rapid expansion of the biodiesel industry has resulted in increasingly larger excess volumes of glycerol by-products being

produced, which has caused the price of glycol to steadily drop.^[252] Traditionally, glycerol has found a large variety of uses in society, in pharmaceuticals, cosmetics and food industries, but at the moment it is not enough. Increased attention has been given to the use of glycerol in the production of oxygen-rich biofuel additives,^[253] e.g. di- and tritert-butyl glycerol (DTBG and TTBG),^[254,255] or glycerol acetals and ketals.^[256–258] These additives have been shown to significantly enhance various properties of biodiesels, such as their freeze point, cold flow properties, combustion and engine performance.^[256,258,259]

Butanone: Butanone is mainly produced via dehydrogenation of *sec*-butyl alcohol (SBA), which was beforehand readily produced by hydration of *n*-butenes.^[260] An alternative “green” route to butanone is from butane-2,3-diol, which in turn can be made by fermentation of sugars, cellulose or hemicellulose.^[261–263]

2.7. Separation and Recycling of Homogeneous Catalysts

Homogeneous catalysts using TM-complexes have been able to perform many different reactions with very high selectivity and activity and unlocking new pathways for the organic chemist to synthesise increasingly complicated molecules with less resources. The homogeneous TM-catalysts have added many new “tools” to the toolbox of the organic chemist. To create a full production process, the reaction is only one part of a story, the other part is how to separate and isolate the product from the reaction mixture. The most important separation techniques and concepts for homogeneous catalysts are briefly introduced below in Figure 2-31. Some of them are already extensively used in industry while others are at a stage of being reviewed, developed and researched.

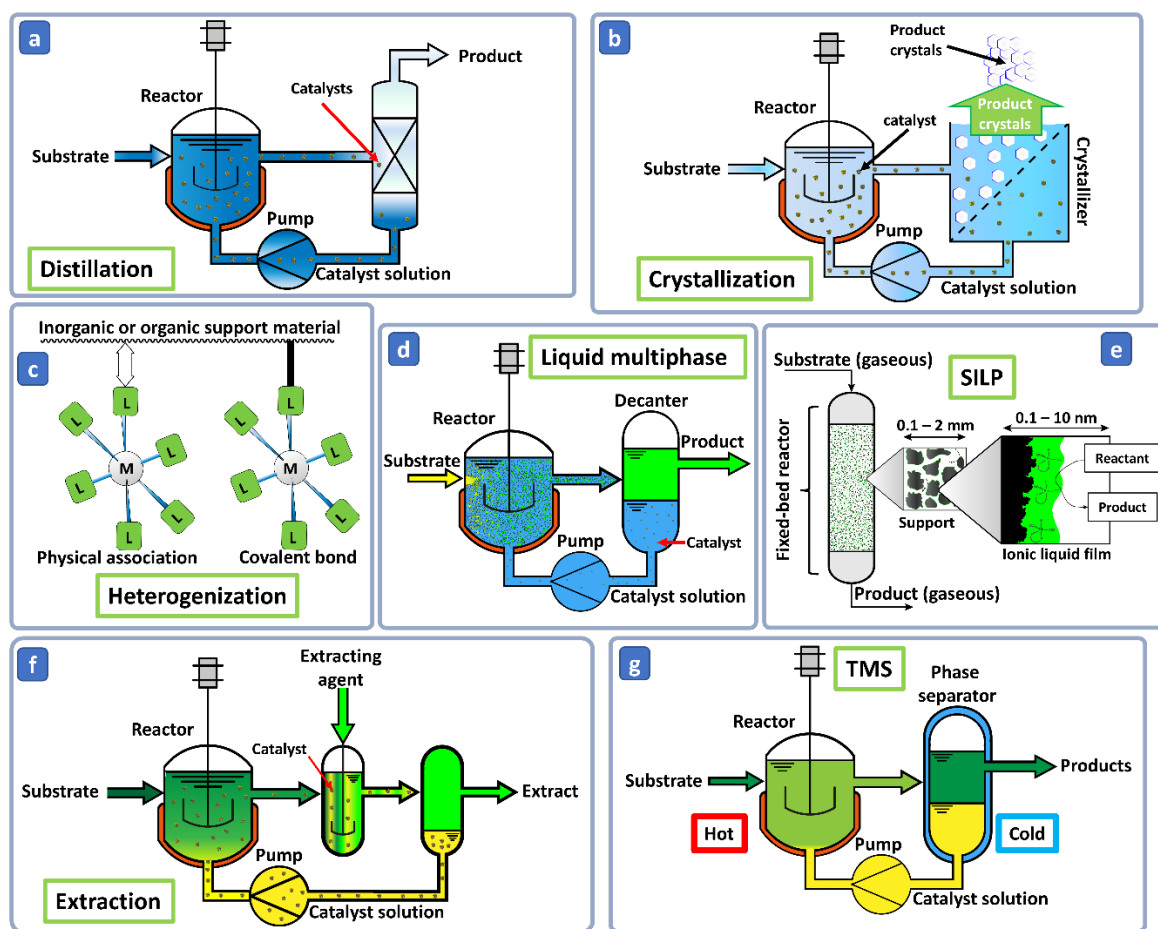


Figure 2-31: Different separation technologies available for homogeneous catalysts.

a: distillation/rectification; b: crystallisation/precipitation; c: Heterogenization; d: Liquid multiphase system; e: supported ionic liquid phase (SILP); f: Extraction; g: Thermomorphic multicomponent solvent system (TMS).

2.7.1. Distillation/Rectification

Distillation is a method of separating components of a liquid based on their different vapour pressures, or volatilities. It is the most important separation technique in the chemical industry for liquids. The more volatile species of a mixture will be enriched in the vapour phase while the less volatile species will be concentrated in the liquid phase. In Figure 2-31a above is presented the continuous recycling of the catalyst from a reaction mixture. The product is volatilised and collected at the top of the column while the catalyst remains in the liquid at the bottom of the column and is reintroduced to the reactor. Most homogeneous catalysts have very strict limitation on how much thermal stress they can handle before they start decomposing at unsustainable rates. Hence there are strict limitations on what substrates and products can be distilled while recycling ligands and TM-complexes.

2.7.2. Crystallisation/Precipitation

The process by which a solid phase is formed from a solution is called crystallisation. If the crystals are very small in size and were formed very quickly, the term precipitation is commonly used instead. Crystallisation can be used as a recycling method for homogeneous TM-catalysts if either the product or the catalyst can selectively form crystals out of the reaction mixture solution. The formation of crystals happens as a response to that the solution has reached supersaturation with regards to the solute that is to form the crystals. Supersaturation of the solute in a solution happens due to a change in the properties of the solution (cooling, concentration change due to solvent evaporation or a change in the solvent composition). The system then tries to reach thermodynamic equilibrium by nucleation and the growth of nuclei.^[264] The process of crystallisation is performed in a vessel called a crystalliser which is designed to provide residence time for the process streams to reach equilibrium. In Figure 2-31b above is presented the product separation by crystallisation and catalyst recovery in the liquid stream.

2.7.3. Catalyst Heterogenization

This is where the homogeneous catalyst is immobilised onto a solid support material.^[265] The immobilisation can be established by either grafting the TM-complex to the support via covalent bonds, or relying on physical association to the support material via physisorption, encapsulation, immobilisation in polymer matrix or hydrogen bonding, this has been illustrated in Figure 2-31c above.^[266] There are commercial products of heterogenized TM-complexes available, FibreCat® and SMOPEX® are two brand names. Different monodentate phosphorus ligands and metals are on offer.^[267] The support material in FibreCat® is an insoluble polymer, allowing for simple catalyst separation.^[268] The heterogenization of a TM-complex will most likely result in extra synthetic steps being incorporated into the preparation of the catalyst, which is adding cost. Many examples from the literature highlight that heterogenized TM-complexes may suffer from a lower catalytic activity, have problems with leaching, deactivation and can have reduced selectivity.^[183,269,270]

2.7.4. Liquid Multiphase System

Another way is to create a system where the catalyst and product are dissolved in different liquid phases that are non-miscible. This can be achieved when the catalyst is designed to have functional groups that make it selectively soluble in one liquid phase and not the other, while the products from the reaction that it is catalysing will dissolve in, or form, the other phase. With strong stirring of the reaction mixture the surface area between the two liquid phases will

increase, which benefits the mass transfer of substrates, reactants and products across the two phases. The reaction mixture is then separated into two phases in a decanter to allow the product phase to be collected and the catalyst phase to be recycled back into the reactor. The concept of liquid-liquid biphasic system is illustrated in Figure 2-31d above. This concept has been successfully implemented in industrial processes, e.g. Ruhrchemie/Rhône-Poulenc process^[29] or the Shell higher olefin process (SHOP)^[43] (*vide supra*).

2.7.5. Supported Ionic Liquid Phase (SILP)

Supported ionic liquid phase (SILP) has the TM-complex catalyst dissolved into a stationary liquid phase on a solid support.^[271–275] The stationary liquid phase is an ionic liquid (IL), which must be stable at reaction conditions. Many ILs have very low vapour pressure and high thermal stability which prevents them from evaporating and decomposing during continuous flow reactions. SILP technology is best suited for gas phase reactions as these will have no issues with catalyst leaching or the ionic liquid being washed out.^[276] This requires that substrate and products are relatively volatile as they must enter and leave the reactor in the gas-phase without causing an accumulation of liquid inside the reactor at the reaction temperature of the system. The concept of SILP is illustrated in Figure 2-31e above.

Liquid-phase SILP systems are possible but will require careful tuning of the relative polarities of all the involved species (IL, solvent, reactant, product, catalyst) in order to prevent leaching of the IL and catalyst. From a hydroformylation point of view SILP technology is best suited for processing the relatively volatile short chained alkenes.

2.7.6. Extraction

During the reaction one single phase will be present, but during the workup an extraction liquid is added, which results in the formation of two liquid phases. The product will then be extracted into the added extractant, which results in the formation of two phases that can then be separated. Ideally the extraction liquid will dissolve very little into the reaction mixture, the catalyst will have a very low affinity for the extractant which should have a low boiling point for easy removal after the extraction. In Figure 2-31f above is presented the catalyst extraction from a reaction mixture. An example of an industrial process using homogeneously catalysed reaction followed by product extraction is the “Kuraray process”.^[277] This is a palladium-catalysed telomerisation of butadiene and water, giving octadienols. The process is based on Pd/TPPMS using a solvent mixture of sulfolane and water. The product feed from the reactor is extracted with hexane, which selectively removes the nonpolar octadienols and any unreacted butadiene. Another example of post extraction is the hydroformylation of long-

chained alkenes (C₆-C₁₄) using the Rh/TPPTS as the catalyst and N-methylpyrrolidone (NMP) as solvent run by Union Carbide.^[278] After the reaction water is added, giving two liquid phases. Water/NMP make up one phase in which the Rh/TPPTS catalyst will almost exclusively be present while the nonpolar C₇-C₁₅ aldehydes make up a second phase that can easily be separated. Supercritical carbon dioxide (scCO₂) together with ionic liquids (IL) have been applied to create liquid-liquid biphasic systems for Rh-catalysed hydroformylation of long chained alkenes using TPPTS ligands that immobilise the catalyst complex into the IL phase. The beauty of this system is that scCO₂ is a bit soluble in the IL, while the IL is insoluble in the scCO₂. Furthermore, scCO₂ is fully miscible with the permanent gases and a good solvent for alkenes and aldehydes. Therefore the scCO₂ is able to facilitate the transport of substrate and reacting gases to the catalyst in the IL, whilst extracting the product without any IL and therefore minimises the amount of catalyst leaching.^[279,280]

2.7.7. Thermomorphic Multicomponent Solvent System (TMS)

Instead of adding another liquid component to the reaction mixture to create two phases at the end of the reaction, it is possible to create a system that contains all components from the beginning, is homogeneous at reaction conditions, but will separate into two liquid phases upon a change in the conditions of the system (e.g. T, p). Such a system is known as a thermomorphic multicomponent solvent system (TMS system). A process flow diagram for a TMS system has been illustrated in Figure 2-31g above. A number of different reaction systems have been explored in different TMS systems,^[281-289] but to the best of my knowledge so far there are no commercial process relying upon this concept.

2.7.8. Scavenging

The last conventional option would be to not consider the direct recycle of the TM-catalyst and ligand, but instead focus on merely collecting the metals, and with the option to send them for reprocessing into new catalyst precursors/TM-complexes. Two types of scavengers are available, non-selective (absorbing both catalyst and product) and selective (targeting only the specific solute – e.g. the catalyst). Examples of non-selective scavengers include activated charcoal/carbon, silica, alumina and celite/Keisegel. Selective scavengers come in many different forms depending on what the target is, in broad terms these scavengers include ion-exchange resins, functionalised polymers, functionalised silica. Scavengers have found many applications in the pharmaceutical industry in the productions of APIs due to strict limits on metal content in such products.^[290-292]

2.8. Organic Solvent Nanofiltration

Organic solvent nanofiltration (OSN) can be used to separate homogeneous catalysts from a reaction mixture. It is a separation process that is energy efficient and allows the separation/recycling to take place at non elevated temperatures. It has therefore been recognised as a potential approach towards solving the separation and recycling issue that homogeneous TM-catalysts and ligands are generally facing before they can be applied in large scale commercial processes to produce high boiling point chemicals. For ceramic nanofiltration membrane the separation of solutes follows the principle of size exclusion. This means that larger solutes (e.g. TM-complex and associated ligand) should be rejected by the ceramic membrane while smaller molecules (products and solvent) will permeate the membrane as a consequence of the relative size difference between the species and pores of the membrane, this is illustrated in Figure 2-32 below.

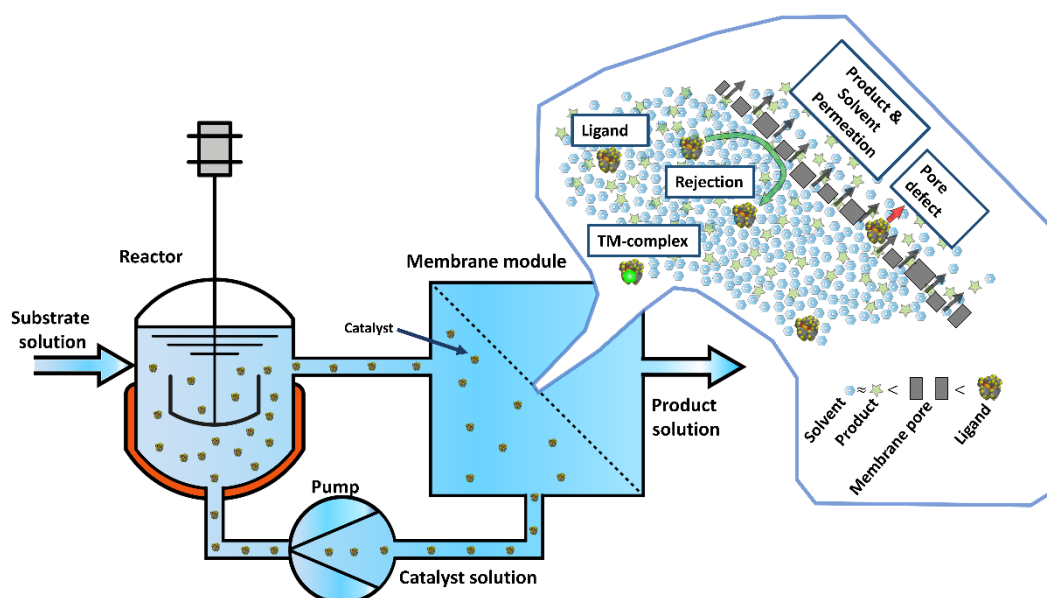


Figure 2-32: Reactor coupled to an organic solvent nanofiltration membrane unit.

But the rejection of solutes is also governed by solution-diffusion mechanism which are based upon the relative interactions between solute-solvent-membrane, and the structural flexibility of those elements. Therefore, the separation of solutes by polymeric nanofiltration membranes is better described by solution-diffusion mechanisms rather than a strict focus on the relative size between solutes and membrane pores. A liquid feed is separated into two portions, the one that permeates the membrane is called the permeate and the portion that is rejected by the membrane is called the retentate. The driving force for the separation of molecular species by OSN is the cross-membrane pressure (reverse osmosis). The membrane performance is typically characterised by two different parameters: flux and rejection. Flux is simply the liquid

volume passing through the membrane per unit area and per unit time. Normally flux is expressed with the units $\text{L m}^{-2} \text{h}^{-1}$, and by normalising the flux with the applied pressure we get the permeance of the membrane, usually expressed in terms of $\text{L m}^{-2} \text{h}^{-1} \text{bar}^{-1}$. Retention of a solute is calculated as a function of the solute concentration $c_{s,r}$ in the retentate and the solute concentration $c_{s,p}$ in the permeate, see Figure 2-33 below.

$$Rej_s = 100 \left(1 - \frac{c_{s,p}}{c_{s,r}} \right)$$

Figure 2-33: Formula for the rejection of a solute.

The concentration of ligands and metals in the permeate or retentate can be practically measured by ICP. It is important to recognise that ICP can only measure the concentration of an element, e.g. P or Rh, and will not know if that P or Rh came from an active TM-complex, intact ligand, decomposed ligands, or metal clusters. Hence to extrapolate knowledge about the P and Rh concentration in the permeate measured by ICP into a statement about the membrane rejection of a specific ligand or TM-complex must require some complementing analytics (e.g. NMR) to safeguard the state of the solutes. The rejection profile of a nanofiltration membrane as a function of solute molecular weight will follow the shape of a broad S-curve. The rejection of solutes with increasingly larger molecular size is only slowly rising towards 100%. An ideal scenario would be where the membrane exhibits a sharp separation curve from one molecular size to the next, meaning that the membrane has the highest possible separation selectivity. These two scenarios have been illustrated in Figure 2-34 below.

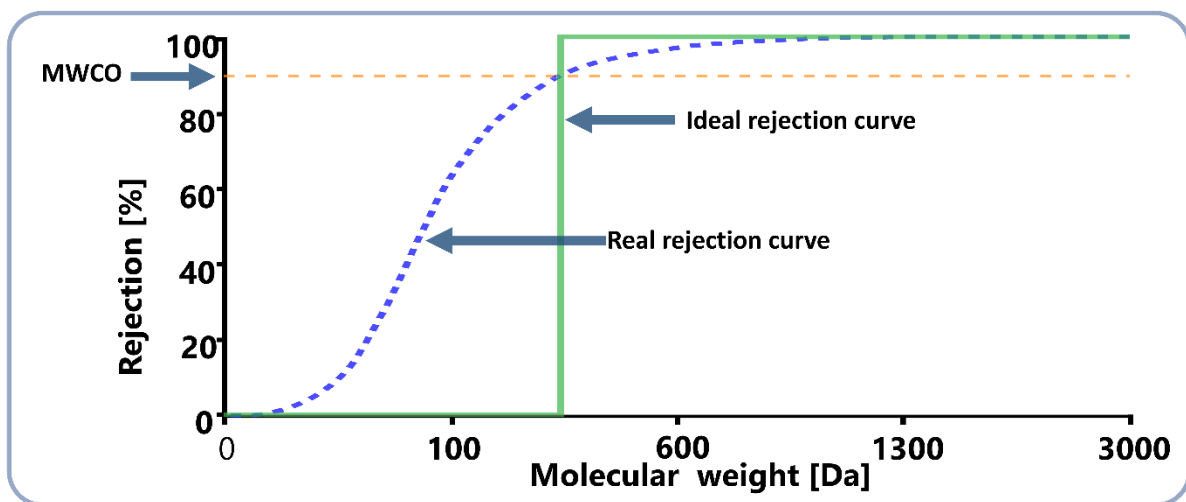


Figure 2-34: The ideal and real membrane rejection profiles.
Based on a figure from ref ^[293]

The hypothetical scenario of a membrane having a sharp separation curve is not a realistic scenario as all membranes will have pores of varying sizes (pore size distribution) and will inevitably also include defects. The classification of membranes ability to reject solutes of different sizes is done by quoting their nominal “molecular weight cut-off” (MWCO). This is defined as the smallest solute molecular weight for which the membrane will have 90% rejection. But the MWCO can never give definite answer to how well a new solute will be rejected by the membrane as it is not only the molecular weight of a solute that will determine its rejection by a specific membrane. Other factors such as the shape of the solute, what functional groups the solute/membrane contain, the solvent applied, presence of other solutes, concentration, temperature and cross membrane pressure will all have an influence upon the rejection. To determine the MWCO of a membrane various solutes are commonly used, the more popular ones are oligomeric forms of polyisobutylene (PIB),^[294–296] poly(ethylene glycol) (PEG),^[297–301] or polystyrene (PS).^[301–303] There is no agreed standard procedure or conditions which has to be followed when such MWCO experiments are performed, which is also certainly the case when any other solutes are investigated for their rejections. It is therefore very difficult to decide on a membrane for an application merely based on literature and/or manufacturer specifications. Instead screening of many membranes and different conditions might be necessary. Several large companies have filed numerous patents that relate to the application of OSN for the post reaction separation of products and active TM-complexes which show that this is an area of great interest.^[54,304–308] There are two fundamentally different types of membranes, polymeric (organic) and ceramic (inorganic) membranes, each type comes with certain advantages and disadvantages. Regardless of the membrane type, they must maintain stability under the operational conditions. Ideally the membrane is completely mechanically, chemically and thermally stable and allows for simple cleaning without being damaged.

2.8.1. Polymeric Membranes:

These are produced from an array of various monomers. Depending on what monomers are used in the membrane manufacturing, the characteristics and properties of the membrane can be influenced which gives possibilities for tuning the membrane properties according to the desired application. Most of the polymeric membranes are produced by a dip-coating procedure where the polymeric membrane is applied upon a nonwoven support material that provides mechanical stability. Producing the membranes on rolls allows for more autonomous, continuous and easily scalable manufacturing that allows cheaper production. Commercially

available polymeric membranes are supplied by a few different manufacturers^[293]. Most of the commercially available polymeric nanofiltration membrane products have different limits to their applications in terms of operational conditions. So far temperature is limited to 70°C at the highest but most of the membranes are limited to only 35 – 60°C. This means that filtrate coming from a high temperature reaction must first pass through a heat exchanger/cooler before it can contact the polymeric membrane.

2.8.2. Ceramic Membranes:

These are more thermally, mechanically and chemically robust than any polymeric membranes. The ceramic membranes are made from inorganic metal oxides, constructed into layers of different porosity. The layers are designed so that the pore size is gradually decreasing from relatively rough support layer until reaching a very finely porous active layer. Typically, the membranes are manufactured as tubular components with the active layer present on the inside of the tube. The tubular membrane is then sealed at each end by a glassified surface in combination with an o-ring at each end of the tube. The o-rings are squeezed tight around the membrane when fitted into the membrane compartment. The hierarchical structure of the membrane layer, the outline of a tubular membrane and the schematics of a ceramic membrane compartment are presented in Figure 2-35 below.

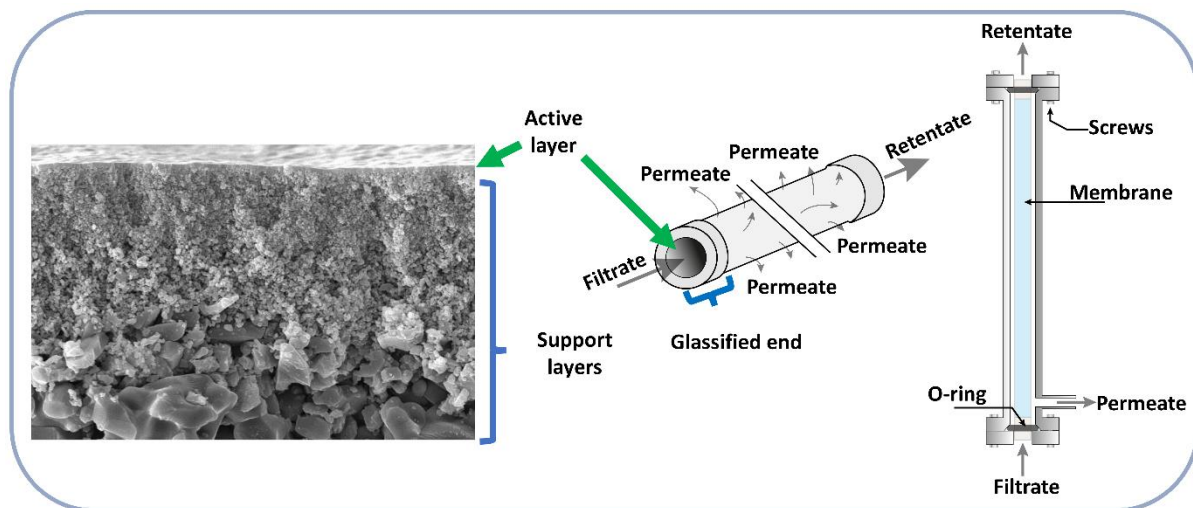


Figure 2-35: Presentation of ceramic membrane structure and application.
(Left side): Cross-section of TiO_2 membrane, inopor^[309]. (Middle): Schematic view of a tubular ceramic membrane. (Right side): Schematic drawing of a ceramic membrane compartment.

The most common materials found in ceramic membranes are Si-, Al-, Ti- or Zr-oxides, and mixtures of these oxides.^[310] The active layer is normally prepared using sol-gel chemistry, which involves condensation reactions of metal alkoxides or salts to form a sol. The production is done in batches and it is known that reproducibility between different batches is difficult to

maintain as retention and flux of solvents can greatly vary.^[311] Ceramic membranes have a very polar and hydrophilic surface because of the metal oxides or silicon-oxide that they are made from, where the outermost layer constitutes hydroxides that can form very strong hydrogen bonds. The hydrophilicity of the membrane surface can have a large influence upon the membrane performance with regards to solvent flux, solute permeability and rejection.^[312] This becomes more evident for tighter/denser pore membranes which generally show larger deviations away from viscous flow membrane transport mechanism, as the interaction between the membrane-solvent and membrane-solute becomes increasingly influential.^[311] The hydrophilic nature of ceramic membranes gives them a natural high-water flux but severely reduced flux for nonpolar organic solvents.^[311] There are a number of reports on negative rejection of various solutes dissolved in organic solvents by ceramic membranes.^[313–319] Some earlier reports on negative rejection concerned phenol with cellulose acetate membranes.^[320–323] The cause of the negative rejection was early on attributed to strong solute-membrane interactions.^[324,325] Thus it is very important to take these competing solute-solvent-membrane interactive forces into consideration when planning out a nanofiltration application. It has been shown that when the affinity between membrane and solute is higher than between solute and solvent, a lower rejection is to be expected.^[317] Hence, a higher rejection of a solute by a ceramic nanofiltration membrane can be expected when a more polar solvent is used which will have a stronger interaction with the membrane than the interaction between the membrane and the solute. The competition between solutes and solvents being permeated through a membrane can be explained by the relative strength in membrane-solute vs. membrane-solvent interactions, as has been illustrated in Figure 2-36 below.

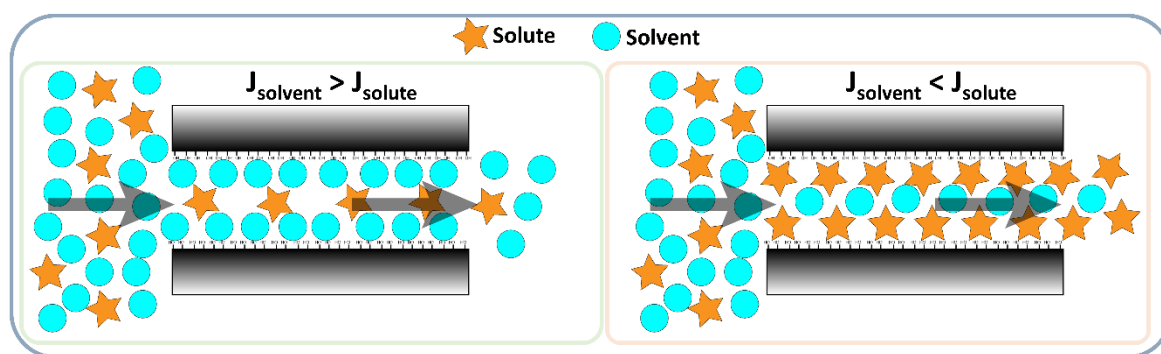


Figure 2-36: The relative strength of the interaction membrane-solute vs. membrane-solvent. Left side: membrane-solvent affinity is higher than the membrane-solute affinity. Right side: membrane-solvent affinity is lower than the membrane-solute affinity. (Adapted from^[318]).

This idea that the relative interaction strength does matter can be further visualised with the help of Hansen solubility parameters (HSP) of solvents.^[311] HSP is a useful tool to predict how

well two different materials will interact with each other and has been used multiple times in studies on both polymeric (PDMS).^[313,315,326,327] and ceramic^[301,311,328] OSN membranes. HSP is made up of three different Hansen parameters; dispersive (δ_d), dipolar (δ_p) and hydrogen bonding (δ_h), each generally measured in MPa^{0.5}. Using group contribution calculations,^[329] the HSP of solutes and polymeric membranes can be estimated. Alternatively, a triplot diagram of the HSP values for various solvents permeated across a membrane can be used for estimating the HSP of the membrane. This is done by using the HSP of the solvents and scaling this according to their relative flux across the membrane. Such an estimation was done for an inopor® 0.9 nm TiO₂ membrane which is presented in Figure 2-37 below.^[312]

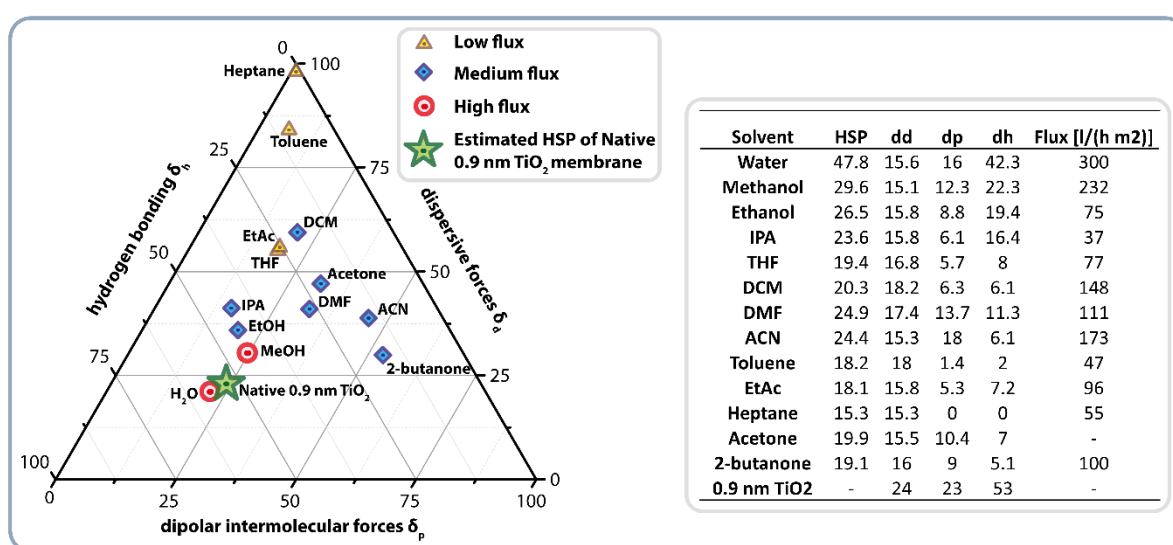


Figure 2-37: HSP diagram and table for solvents and ceramic nanofiltration membrane.

(left) HSP of different solvents together with their flux (high, medium, low) and the membrane by graphical method.^[312] Solvent flux data taken from^[311]

Using HSP will have its limitations as the HSP of a solute must be estimated based on group contribution calculations which will not guarantee an accurate HSP value. Commercially available ceramic nanofiltration membranes with tight pore-sizes can (in this moment of writing) only be acquired from two different producers; inopor (Germany) and cerahelix (USA).

2.8.3. Membrane Setups:

There are three different nanofiltration membrane setups that can be employed when studying the retention of TM-complexes in organic solvent. The simplest setup is a dialysis approach, also known as a “tea-bag” or “cat-in-a-cup”,^[330] see Figure 2-38 (left side) below. It is a concentration gradient driven process. Because of its simplicity it has become a popular initial testing bed for the laboratory scale applications.^[331–335] The next filtration setup is a so called “dead-end” approach, see Figure 2-38 (middle), which is also suitable for laboratory scale work

as it is relatively simple to use. Dead-end nanofiltration is a pressure driven process which gives a more realistic “real world” scenario.^[169,336–347] But this technique has issues with concentration polarisation at the surface of the membrane and so it is not useful in industrial processes. The third approach to nanofiltration is to use a cross flow setup whereby the filtrate is moving along the surface of the membrane at turbulent flow which will minimise the risk of concentration polarisation and membrane fouling. The concept is illustrated in Figure 2-38 (right side). Although the cross-flow setup will ensure the best membrane performance it is far from always used in laboratory work as it requires much more elaborate equipment. There are a few examples from laboratory work where a cross-flow system has been used to study the rejection of various TM-complexes^[58,338,348,349]. Although it is more commonly applied in mini- and pilot plant-setups^[171,178,304–307] as well as membrane characterisation test rigs.^[302,315,318,350,351]

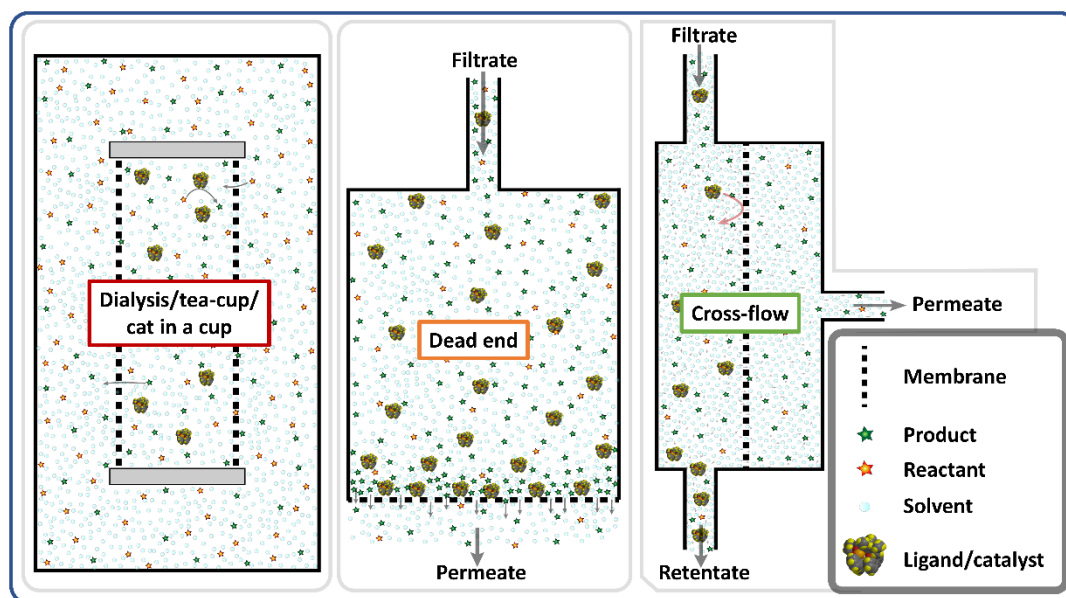


Figure 2-38: The three different membrane setups
(Left side): Dialysis/tea-cup/cat in a cup setup, (Middle): Dead end filtration setup and (Right side): Cross-flow setup.

There are three different kinds of transport mechanism models available to describe the transport through an OSN membrane.^[310] The first model treats the membrane as a “black-box” and is based on irreversible thermodynamics, and it does not account for any membrane properties. The other two models are the pore flow and solution-diffusion^[352–354] models which takes membrane characteristics into consideration. These models describe the transport as a function of structure and physiochemical properties. There are also models which combine features from both pore-flow and solution-diffusion models, i.e. solution-diffusion with

imperfections model. Depending on the membrane properties such as if it is a porous or dense membrane, polar/nonpolar surface some models become more suitable than others.

2.9. Molecular Weight Enlargement (MWE)

Although many ligands and therefore associated TM-complexes have larger molecular weight than the nominal MWCO of various commercially available OSN membranes (polymeric and ceramic), “enough/satisfying/sufficient” rejection is not at all guaranteed. For TM-complexes a rejection as close to 100% as possible is preferred, although it is possible to apply membranes in series/cascade to lower the amount of TM-complex leaching out in the product stream, the number of such cascading membranes required will be reduced when the rejection of each membrane goes up. Hence, to make TM-complexes more amenable to filtration it is possible to “molecular weight enlarged” them by grafting them to a large and soluble molecule.

2.9.1. Different MWE-Units

Many different soluble supports have been explored for the use as MWE-units of TM-complexes and ligands; a summary of them is presented in Figure 2-39 below.

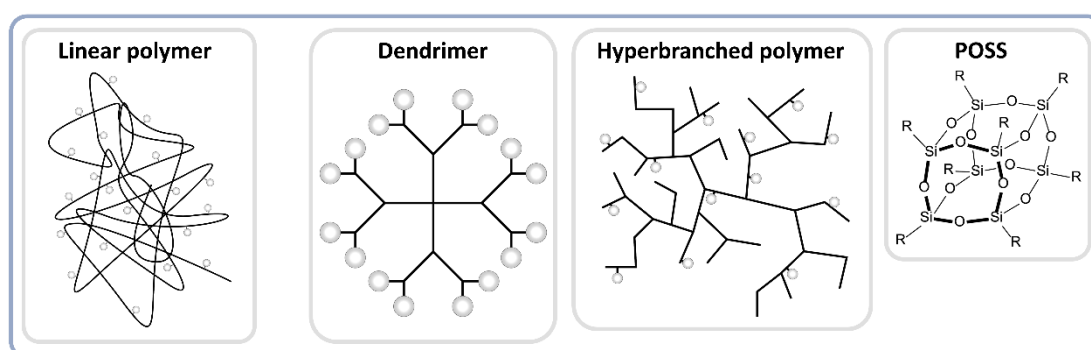


Figure 2-39: Different molecular weight enlargement units for homogeneous TM-complex catalysts.

Each MWE-unit comes with certain pros and cons.^[310] Polymers are relatively cheap as they can be synthesised in one step. They have the catalysts anchored throughout the polymer which may affect catalyst activity as some active sites will be less accessible than others.^[355,356] Dendrimers are well defined, high MW molecules and are mostly in a globular shape.^[357] They have a lower intrinsic viscosity and their active sites are usually in their periphery and thus more accessible than catalysts anchored to polymers.^[358] But dendrimers are generally expensive to produce as they rely on labour-intensive multistep synthesis procedures.^[359] Hyperbranched polymers are a cheaper alternative to dendrimers, they are synthesised in one step, have their functionalities distributed throughout, they are randomly branched and thus less well defined and come with a polydispersity.^[360–362] They offer a price per active site comparable with supports such as polystyrene and silica.^[363] The periphery functionalised

nature of dendrimers effectively results in that they have extremely high ligand and metal concentration in a very closely defined volume of space.^[125] This can be an advantage when catalyst stability is enhanced by a high excess of ligand. But a high local concentration can also make dendrimers less ideal for reaction systems that deactivate through bimetallic mechanism. Overall, also the polymer-based supports have a relatively high localised concentration of ligands and metals but less than dendrimers. POSS cages are rigid three-dimensional cage-structures that are chemically and physically stable and have shown good potential as MWE-units applied in OSN.

2.9.2. Polyhedral Oligosilsesquioxanes (POSS)

POSS are a class of compounds that are based upon the repeating unit $\text{RSiO}_{3/2}$.^[364] The properties are derived from its hybrid combination of the chemically inert and thermally stable Si-O-Si fragments, in combination with the potentially more reactive and modifiable organic R-Si groups. Polyhedral oligosilsesquioxane refers to species based upon the formula $(\text{RSiO}_{3/2})_8$ and are also known as simply POSS (trademarked by Hybrid Plastics^[365]). These are highly rigid, symmetrical three-dimensional Si-O based cage structures with pendant R groups situated at each of its corners. A POSS cage can also be described by the form of T_8R_8 where the “T” represents a silicon atom bearing three oxygen atoms which are subsequently connected to another silicon. Another common name for these compounds is $\text{T}_8\text{-R-POSS}$. As example the POSS molecule seen in Figure 2-40 below can be expressed as $\text{T}_8\text{R}_7\text{X}$ or $\text{T}_8\text{-(iBu)}_7\text{-X-POSS}$

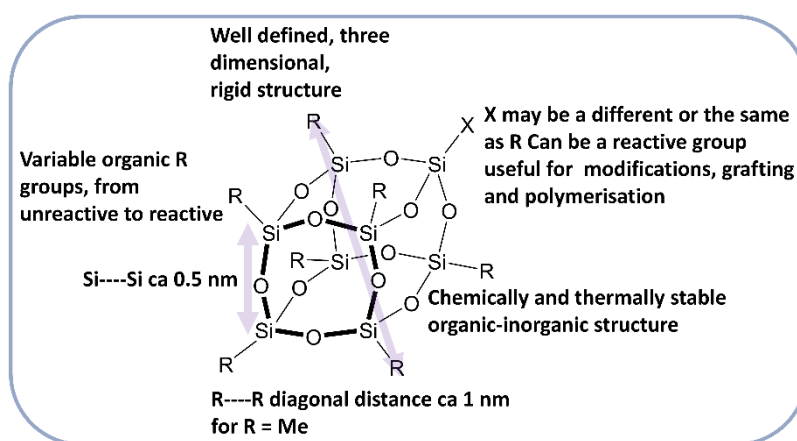


Figure 2-40: The general structure and features of a cubic T_8R_8 polyhedral oligomeric silsesquioxane (POSS)

Apart from the fully condensed T_8R_8 type POSS molecules, also a POSS-trisilanol version is readily accessible. The trisilanol POSS or $\text{T}_7(\text{R})_7(\text{OH})_3$ moiety can be prepared in a LiOH-catalysed condensation reaction using an appropriate trimethoxysilane and an exact amount of

water. The synthesis of $T_7(\text{iBu})_7(\text{OH})_3$ from isobutyl(trimethoxy)silane is presented in Figure 2-41 below.

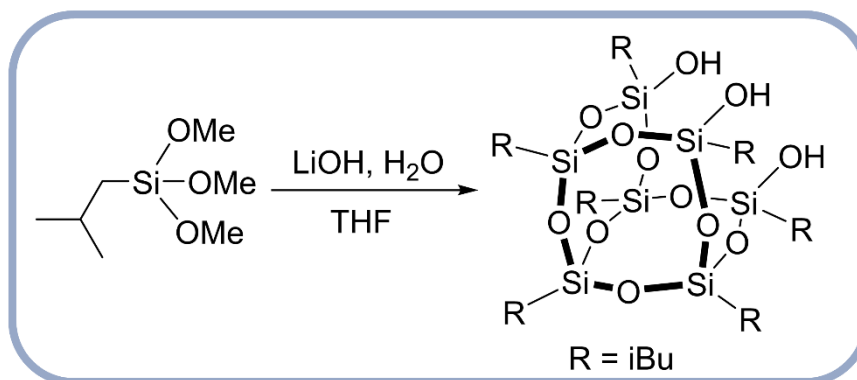


Figure 2-41: The general synthetic procedure for preparation of trisilanol POSS

This partially condensed trisilanol species was first reported in 1965.^[366] Depending on the trimethoxysilane used for the condensation reaction, different functionalised POSS molecules are accessible providing flexibility to tune physical and chemical properties of the moiety.^[364] The ^{13}C NMR chemical shift measurements show that the T_8 POSS has electron withdrawing properties like that of the trifluoromethyl group (CF_3).^[367] POSS has also found potential as an MWE-unit for homogeneous TM-complexes/ligands, a selection of ligands/complexes that has been MWE with POSS are presented in Figure 2-42 below.

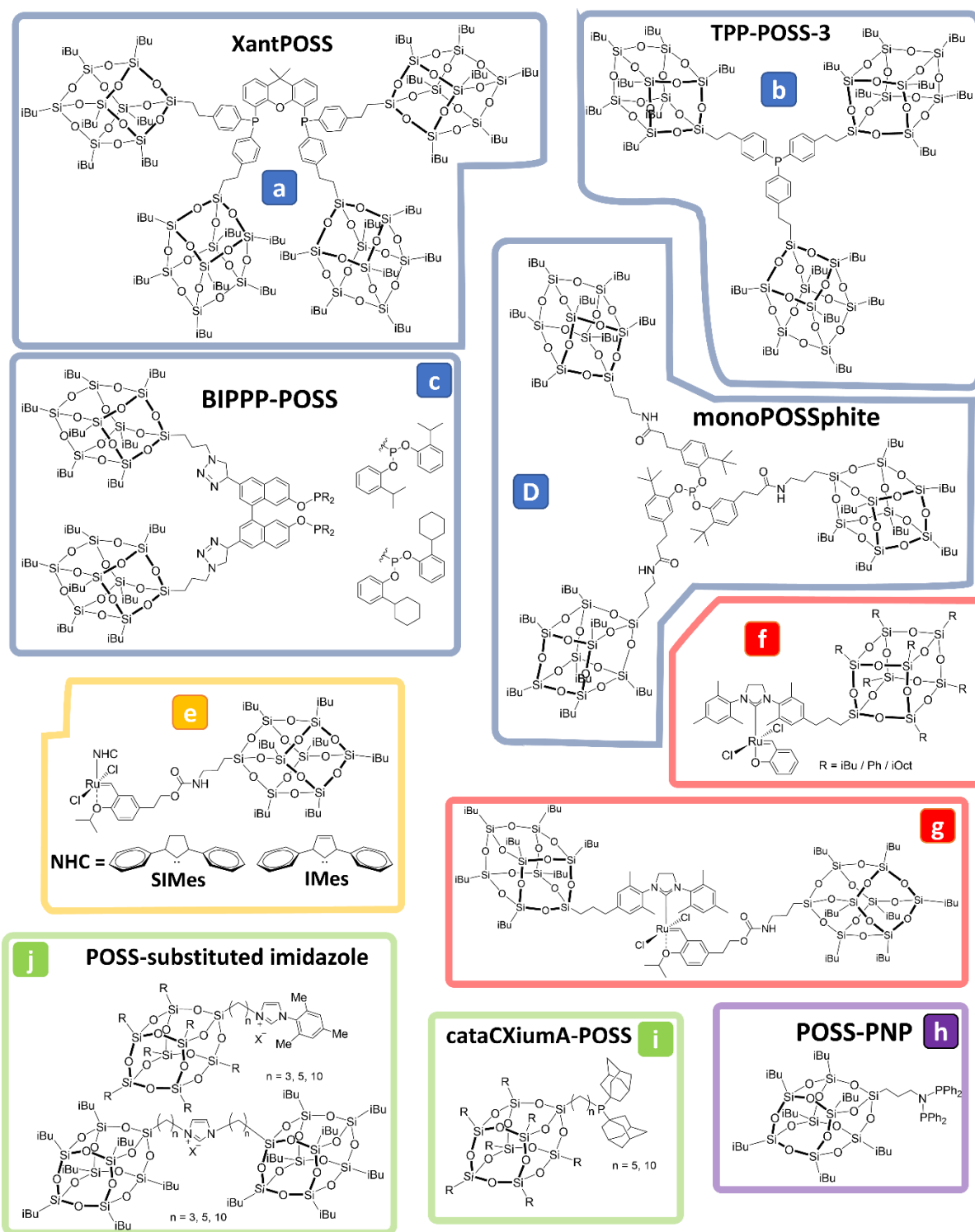


Figure 2-42: Ligands that have so far been molecular weight enlarged with POSS.

The ligands are found in the following ref.: Ligand *a*^[125,126], *b*^[58,126], *c*^[126], *d*^[126], *e*^[368], *f*^[334], *g*^[334], *h*^[369], *i*^[370], *j*^[370].

The XantPOSS ligand (a) above showed a 38% lower activity but similar selectivity to its unmodified Xantphos ligand derivative in batch autoclave Rh-catalysed hydroformylation of 1-octene.^[126] No data on retention by OSN membrane of this ligand is available. Ligand (b) showed excellent retention by a ceramic OSN membrane from inopor (active layer = TiO₂,

MWCO = 450 Da).^[58] Rejections of both Rh and P were above 99.9% as measured by ICP-OES which was achieved during continuous Rh-catalysed hydroformylation of 1-octene, operated in a loop reactor with integrated membrane unit. No rejection data is available for ligand (c) although it managed to retain activity in batch isomerisation of 2-methyl-3-butenenitrile while ligands having POSS moieties crafted close to the active site lost all their activity. The monodentate POSSphite ligand (d) was highly active in batch autoclave Rh-catalysed hydroformylation when it was applied in a continuous flow membrane reactor the system was quickly deactivated. Ligand (e) was rejected by polymeric OSN membranes (Starmem 228) to “100%” using toluene as solvent.^[368] Ligand (f) and (g) gave no exact number of their retention by a ceramic OSN membrane used in tea-bag setup. But the work did highlight the need for MWE enlarging both the N-heterocyclic carbene as well as the benzyldiene moiety to improve the longevity of the metathesis catalyst under catalytic conditions.^[334] Ligand (h) was never investigated for its rejection by OSN membrane, the authors focused instead on the solubility enhancing properties that the (iBu)₇POSS tag provides to the ligand in nonpolar solvents.^[369] The cataCXiumA-POSS ligand (i) and the two POSS substituted imidazole ligands (j) come from a patent by Evonik.^[370] Very little information about their potential in catalysis was presented and no information about rejection by a membrane is available.

2.10. Critical Evaluation

For a wider application of homogenous catalysis in industrial processes the intrinsic problem of catalyst separation from the reaction mixture and recycling them in an active state with minimised losses of catalyst/metal/ligands must be addressed. Conventional separation techniques have strict limitations on what is possible to achieve and can be highly application specific. E.g. a combination between delicate, high boiling products and efficient recycling of the active TM-metal catalyst are far from always compatible features. Ideally a separation and recycling process uses less harsh conditions with less by-products and waste, lower capital and operational costs and access to larger and new substrate scopes (with more delicate functional groups). Especially the application of nanofiltration holds a high potential to make this happen. To enhance rejection the concept of MWE of the ligands/catalyst complexes has been suggested. POSS has proved to be an especially attractive MWE-unit being cheap, easy to work with, variable ways of installing, large, thermally and chemically stable, and can provide excellent solubility of the ligand/TM-complex in common organic solvents. But all ligand modifications will come with additional costs. Ultimately, that extra cost of POSS modifying a ligand must be significantly justified by enhanced efficiency/productivity of the new systems

it is part of. There are different aspects of a new separation system accessible by a POSS-modified ligand that can justify the added cost of the required ligand modifications. May it be that the new recycling system via OSN allows for:

- More energy efficient separation/recycling step leading to reduction in energy costs.
- Less harsh conditions of separation/recycling step leading to
 - Increased longevity of the catalyst and thus reduced catalyst/ligand/metal costs.
 - Reduced by-product formation (reduced purification costs, higher value in a purer product)
- Efficient purification of the product with minimal leaching of the metal leading to reduced purification costs and/or reduced product losses during purification.
- Simple process system with minimum number of process units (reduced operational cost, reduced capital cost).
- Possibility to process previously inaccessible substrates that generate delicate high boiling products while also allowing for catalyst recycling (establish processes for new valuable products).
- Increased space time yield (more compact and productive system, reduced capital cost, operational cost).

It becomes easier to make such justifications when the ligand modification cost is kept to a minimum. This is more likely to be the case when a modification is relying on the least number of synthetic steps, applying simple and safe synthetic protocols (smallest possible need for very low or high temperature and pressure) and using readily available/non-exotic/non-toxic reagents, solvents and reactants. And finally, the modified catalyst/ligand must not show significant reduction in activity, selectivity or potential weaknesses in stability when tested in the intended reaction system.

Chapter 3: Gap Analysis

The initial main goal of the presented thesis was to further the use of polyhedral oligomeric silsesquioxane (POSS) as a molecular weight enlargement (MWE) unit of homogeneous catalysts and ligands in order to increase their recyclability by nanofiltration membranes. Three main areas of homogeneous catalysts and ligands were targeted for this expansion of application of POSS and include:

1. Phosphine ligands
2. Phosphite ligands
3. Brønsted acid catalysts.

The status of application of POSS as an MWE in either field was largely different from the status of any of the others, and so to further any of the three fields required the current status within each field had to be identified.

1. Status of using POSS as an MWE-unit for phosphine ligands.

There have already been a few different POSS-modified phosphine ligands reported in the academic literature and in patents, see Figure 2-42 on page 56 for an overview. The majority of those ligands were reported in the thesis of Janssen^[126], which include TPP-POSS-3, XantPOSS, and a DPEPOSS. All of them had the POSS cages installed in the para position of the phenyl-phosphines, hence relatively close to where the ligands coordinate to a central metal atom. All those ligands showed reduced TOF but unaltered selectivity in the Rh-catalysed hydroformylation of 1-octene compared to their unmodified derivatives. From this there are three main questions that can be extracted:

- What degree of rejection can be expected from solutes that have been modified with one and two POSS units instead of three?
- How is the activity and selectivity influenced by changing the number of POSS cages grafted to the ligand?
- Is it possible to attach a POSS cage further away from the active site of the ligand, in the rear of the back-bone of a bidentate ligand like Xantphos.

2. Status of using POSS as an MWE-unit for phosphite ligands.

Only a couple of POSS-modified phosphite ligands have so far been reported, all of which in the thesis of Janssen and include the so called monoPOSSphite and the two derivatives of a POSS enlarged binaphthol ligand named BIPPP-POSS, all presented in Figure 2-42. The

monoPOSSphite ligand had a 65% reduced TOF in batch Rh-catalysed hydroformylation of 1-octene. It gave a highly unstable reaction system when it was applied in continuous hydroformylation in a loop reactor. The system quickly lost activity during several attempts, but “only” 1% of the P had leached into the permeate after 4.2 reactor volumes passing, hence leaching was not the cause. It was briefly mentioned in the discussion that other authors have reported poor stability of phosphite ligand under hydroformylation conditions. The BIPPP-POSS ligands were applied in Rh-catalysed hydroformylation of styrene in autoclave reactions and showed a 66% and 48% reduction in TOF as compared to their non-POSS-modified derivatives. None of the ligands was tested in the continuous nanofiltration membrane setup. A BIPP-POSS ligand was also tested for Ni-catalysed isomerisation of 2M3BN, showing good and stable activity for more than 25 h. Clearly, the stability of these POSS-modified phosphite ligands was not well understood. Performing MWE of a phosphite ligand with the goal of establishing a continuously operated process based on nanofiltration is little more than futile if a good understanding of the ligand’s stability is not first established. Therefore, the most urgent question that needs to be answered in order to advance the further application of POSS as a MWE-unit of phosphite ligands is:

- What factors influence the (long-term) stability of phosphite ligands applied in catalytic reactions?

3. Status of using POSS as an MWE-unit for Brønsted acids

There are currently no reported POSS containing Brønsted acids that have been tested for their catalytic properties, or their potential to be recycled. But, it is established that sulfonated octaphenyl-POSS can be easily synthesised and has already been used in several applications other than as a catalyst. The questions that are most relevant to be answered are therefore:

- What is the catalytic activity of H-S-POSS relative to PTSA, a soluble acid derivative and relative to Amberlyst, a sulfonated polystyrene catalyst?
- Can H-S-POSS be efficiently recycled?

Chapter 4: TPP-POSS-1 -2 and -3 – Synthesis, Catalysis, and Rejection by Membranes

4.1. Abstract

Three different POSS-modified triphenylphosphine (TPP) ligands with either one (TPP-POSS-1), two (TPP-POSS-2) or three (TPP-POSS-3) POSS cages were synthesised. Each POSS cage was grafted by an ethyl-linker in para position of the phenyl rings bonded to the phosphorus atom. The ^{31}P -NMR chemical shift moved downfield with each additional POSS cage added. The ligand's catalytic properties were explored in batch autoclave Rh-catalysed hydroformylation of 1-octene. The selectivity remained unchanged for all TPP-POSS ligands as compared to unmodified TPP. The TOF of unmodified TPP was the highest; TPP-POSS-1 showed a 37% reduced TOF, TPP-POSS-2 had a 73% reduced TOF while TPP-POSS-3 had a 61% reduced TOF relative to TPP. A second set of experiments with a larger reaction mixture volume (all other things the same) showed reduced TOF for all ligands relative to the first set of experiments that used a smaller reaction volume. This reduction in TOF was interpreted as the result of insufficient gas/liquid mixing with the larger volume reaction mixture, but still utilizing the exact same autoclave, over head stirrer set to the same rpm. The unmodified TPP had its TOF reduced by 71%, TPP-POSS-1 TOF was reduced by 64%, TPP-POSS-2 TOF reduced by 61% and TPP-POSS-3 TOF reduced by 49%. More (iBu)₇POSS cages seems to make the ligand less sensitive to a compromised gas/liquid interface mixing, the rational being that the i-Bu-groups of the POSS cages are highly nonpolar and can therefore increase the solubility of CO in the reaction mixture. All three TPP-POSS ligands allowed stable operation in a continuous flow Rh-catalysed hydroformylation of 1-octene in a ceramic OSN membrane loop reactor. An increased yield of isomerisation products was observed for all TPP-POSS ligands during the continuous flow experiments as compared to the results from the batch autoclave experiments. Their rejection by the ceramic nanofiltration membrane followed the order of their increasing sizes; TPP-POSS-1 was rejected to 94%, TPP-POSS-2 rejected to 97% and TPP-POSS-3 rejected to 99%.

4.2. Introduction

This chapter is part of the work towards further the use of POSS as MWE-unit for phosphine ligands. In this chapter three different POSS-modified TPP ligands were synthesised, each having either one, two or three POSS cages attached. These ligands were applied in Rh-catalysed hydroformylation of 1-octene to investigate what effect the number of POSS cages attached to the TPP ligand has upon activity and selectivity. The ligands were then applied in a continuous flow ceramic membrane loop reactor in order to investigate what rejection can be expected from having one, two or three POSS cages attached to a ligand.

4.3. Results and Discussion

Three different POSS-modified triphenylphosphine ligands were synthesised; TPP-POSS-1, TPP-POSS-2 and TPP-POSS-3; they are presented in Figure 4-1 below together with the unmodified TPP. The first two TPP-POSS ligands are new, while the TPP-POSS-3 was already published by Vogt et al. some years ago.^[58]

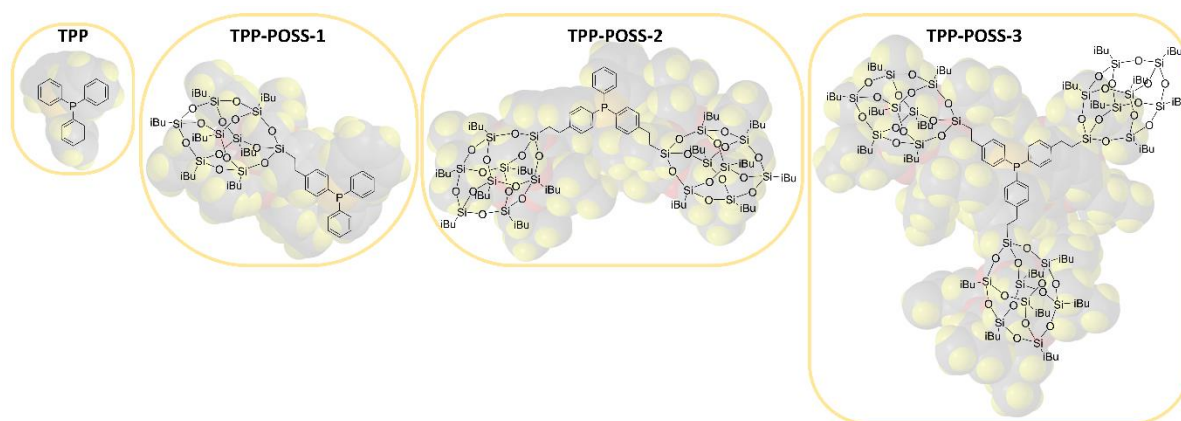


Figure 4-1: The unmodified TPP ligand and the three TPP-POSS ligands.

Their nomenclature (1, 2 and 3) reflects the number of POSS cages that the ligands are bearing, more POSS cages means more bulk. After synthesis, the ligands were applied in Rh-catalysed hydroformylation of 1-octene in batch autoclave reactions to evaluate and compare their catalytic properties in terms of activity and selectivity using TPP as the reference. After this, the ligands were applied in continuous hydroformylation in a ceramic membrane loop reactor where also their rejection by the 450 Da MWCO TiO₂ ceramic nanofiltration membrane was measured. The effect that the number of POSS cages have upon activity and selectivity in Rh-catalysed hydroformylation of 1-octene as well as the rejection by a ceramic nanofiltration membrane were explored.

4.3.1. Synthesis of POSS-Modified TPP Ligands

The general protocol for the synthesis is based upon that published by Vogt et al.^[58] The overall protocol constitutes two parts, where in the first part a Pt catalysed hydrosilylation of 4-bromostyrene is conducted, and the resulting intermediate products is subsequently reacted with (iBu)₇POSS-trisilanol in a corner-capping reaction to give the POSS synthon 4-bromophenyl-ethyl-(iBu)₇POSS, as is shown in Figure 4-2 below.

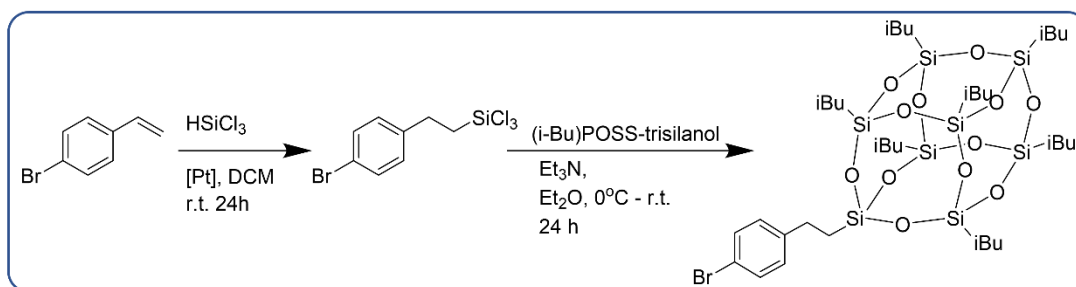


Figure 4-2: The preparation of the Br-aryl-ethyl-(iBu)₇POSS synthon.
Done according to the synthetic procedure described in the publication of Vogt et al.^[58]

The second part of the protocol involves the selective lithiation of this aforementioned POSS synthon via a lithium-halogen exchange reaction using n-butyllithium at low temperature. The intermediate Li-Ar-Et-POSS compound was then reacted with the appropriate phenyl-phosphine-chloride to give the desired TPP-POSS product, TPP-POSS-1, TPP-POSS-2 or TPP-POSS-3 as is illustrated in Figure 4-3 below.

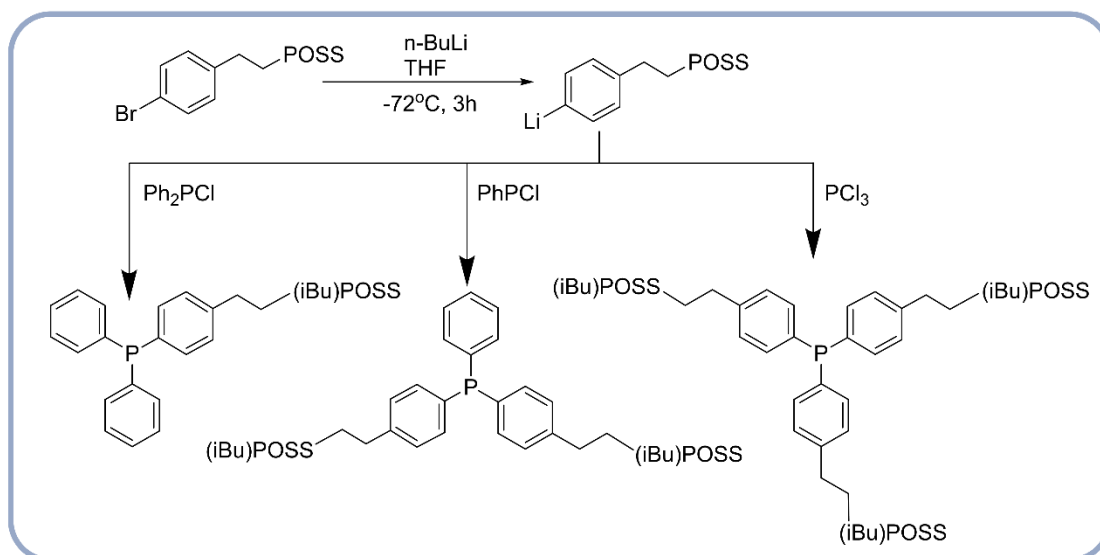


Figure 4-3: Synthetic overview for the three TPP-POSS ligands.

The product phosphines were then isolated by first evaporating the THF followed by aqueous workup. Further purification was done by re-dissolving the crude product in a small quantity

of toluene and subsequent crashing-out by the addition of MeOH, one of the major by-products that could be efficiently removed this way were butyl-phosphine species (^{31}P -NMR $\sim -18\text{ppm}$). The improved purity after the toluene/MeOH solvation/crash out is presented in Figure 4-4 below.

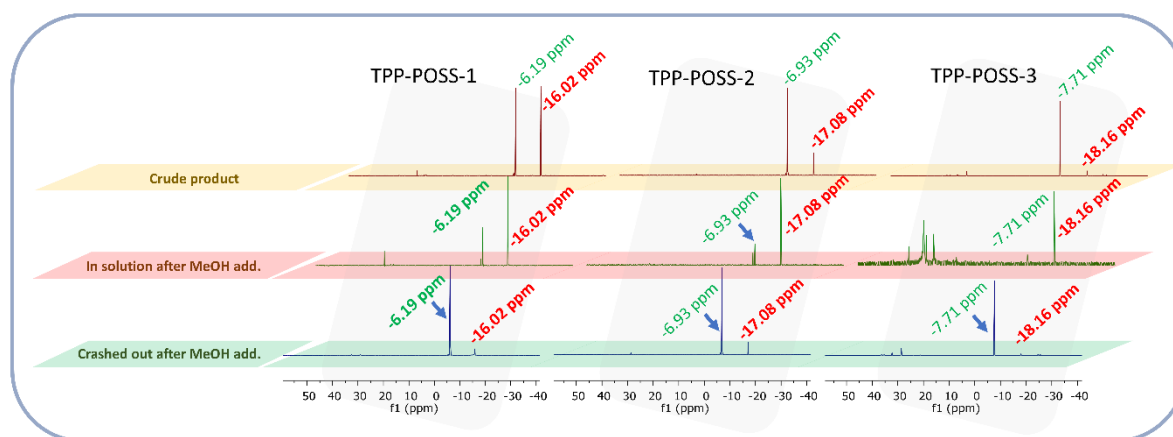


Figure 4-4: ^{31}P -NMR from the purification of the crude TPP-POSS ligands. Solvent was CDCl_3 , Bruker 400MHz. The phosphine species present at -16 to -23ppm are believed to be butyl-phosphine species.

This method of purifying $(\text{iBu})_7\text{POSS}$ containing compounds is possible due to the very nonpolar iBu-groups of the POSS cages that limits the compound's solubility in highly polar solvent mixtures, such as MeOH in toluene. Overall, this purification method proved to be very efficient, fast and with relatively small losses of the products in the process. The phosphines were characterised by ^1H -, ^{13}C -, ^{29}Si - and ^{31}P - NMR. The ^{31}P -NMR chemical shifts have been plotted against the number of ethyl-linked POSS cages in Figure 4-5 below.

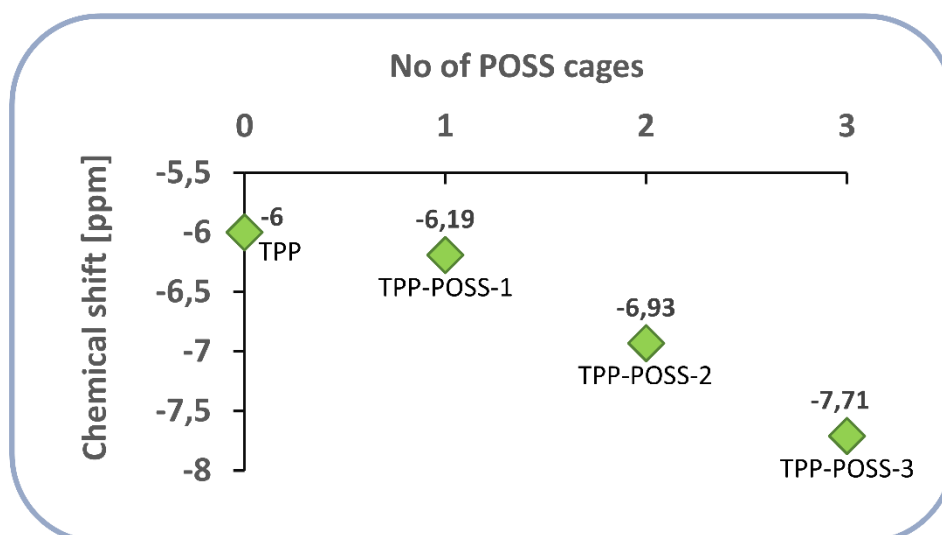


Figure 4-5: Chemical shift of TPP-POSS ligands as well as TPP in ^{31}P -NMR.

As can be seen, the chemical shift changes to a slightly more negative value for each additional POSS cage that the ligand contains. Clearly, the grafting of the ligand so close to the phosphorus atom has a measurable effect upon the electronic properties surrounding the phosphorus atom. The grafting of each consecutive ethyl-linked POSS cage in this series of TPP-POSS ligands resulted in a slightly more electron rich phosphine. A similar change in chemical shift due to POSS linkage was also observed by Janssen et al. when they synthesised XantPOSS (Figure 2-42) (^{31}P NMR δ -20.54ppm) which can be compared with that of Xantphos (^{31}P NMR δ -17.5ppm). XantPOSS was almost 40% less active than Xantphos in the Rh-catalysed hydroformylation.

MALDI-MS was used to also characterise TPP-POSS-1, but the other two ligands (TPP-POSS-2 and TPP-POSS-3) were too heavy to fly in the MALDI instrument that was used. The MALDI-MS spectrum for TPP-POSS-1 is presented in Figure 4-6 below.

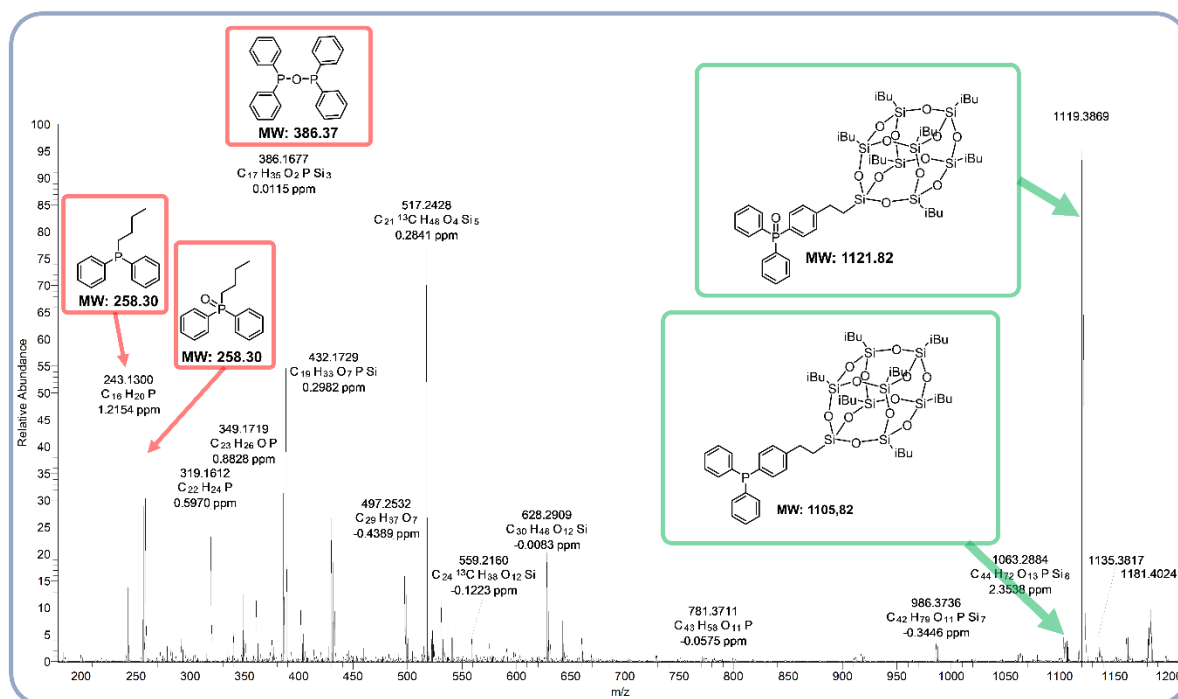


Figure 4-6: The MALDI-MS spectra for TPP-POSS-1.

Peaks in the spectrum have been annotated with compounds that are reasonable to be the source of said peak. The major peak at the higher MW can be assigned to the desired product. Peaks at a lower m/z are most likely from the matrix and fragmentation product. Although three possible side products were also identified. It is worth stressing that MALDI-MS is a qualitative and not a quantitative technique and so the relative intensity of the various peaks in the spectrum does not reflect the actual relative quantity present in the sample that was analysed.

4.3.2. Rh-Catalysed Hydroformylation of 1-octene in Batch Autoclave Reactions

The catalytic properties of the synthesised TPP-POSS ligands were evaluated by comparing them against the unmodified triphenylphosphine ligand in Rh-catalysed hydroformylation of 1-octene in batch autoclave reactions. The reactors that were used are described in the supporting information, section E.4. . An initial set of batch reactions were performed, where the reaction progress was monitored by the gas volume uptake that the mass flow controller logged. No liquid sampling over time was performed, but the final reaction mixture composition was analysed by GC-FID. The results from these reactions are presented in Figure 4-7 below.

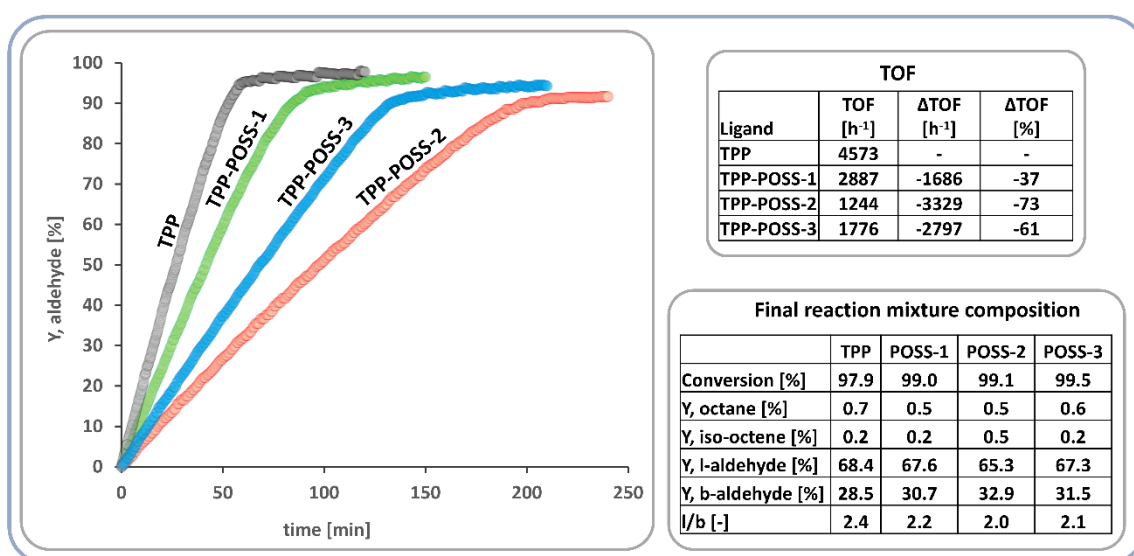


Figure 4-7: Comparing TPP, TPP-POSS-1,2 and 3 in Rh-catalysed hydroformylation of 1-octene, small scale. Performed in batch autoclave reactor. Progress of reaction was based on the gas consumption logged by a MFC. TOF was measured at 20% yield of l-aldehyde. The final reaction mixture composition was determined by GC-FID using the method of internal standard (IS = dodecane). Conditions: Rh(acac)(CO)₂ (0.0116 mmol, 3 mg); Ligand (0.058 mmol); 1-octene (46 mmol, 7.3 ml); Rh:L:1-octene = 1:5:4000; Internal standard = n-dodecane (3.5 mmol, 0.8 ml); solvent = toluene (17 ml); 80°C; 20 bar; CO:H₂ = 1:1; N=700 rpm.

All the POSS-modified TPP ligands were less active than TPP, among the TPP-POSS ligands TPP-POSS-1 was the most active, then TPP-POSS-3 and last TPP-POSS-2. Also, the l/b ratio of the TPP-POSS ligands was lower than that of TPP. The TOF of TPP and TPP-POSS-3 was 45 and 30% higher than what has previously been reported for those ligands by Janssen et al.^[58] The l/b ratio is also different, where Janssen reported l/b = 2.5 for TPP-POSS-3. It is known that Rh/TPP-catalysed hydroformylation systems will become more active and have a lower l/b ratio with a lower Rh/P ratio. Hence, it is possible that the autoclave experiments presented above suffered from partial oxidation of its phosphorus ligands which effectively resulted in unintentional off-sets from the intended Rh/P ratio. To confirm the results from the above set

of experiments, larger scale experiments were performed, so that sampling over time was possible. The reaction progress from these autoclave experiments is presented in Figure 4-8 below.

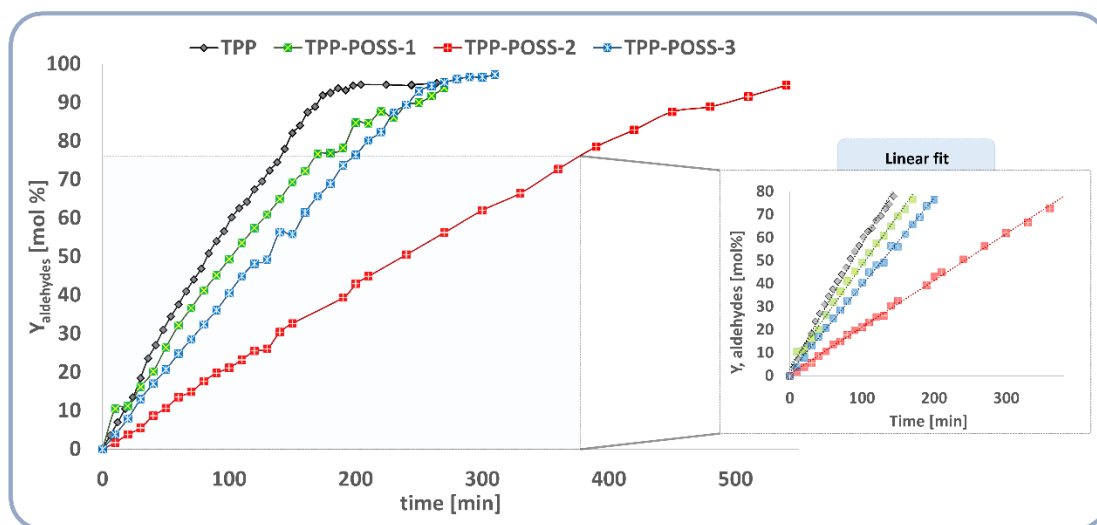


Figure 4-8: Comparing TPP, TPP-POSS-1,2 and 3 in Rh-catalysed hydroformylation of 1-octene, large scale. Performed in batch autoclave reactors and sampled over time. Samples analysed with GC-FID, method of internal standard (IS = dodecane). Linear fit of values between 0 – 80% Y_{aldehyde} . Conditions: $\text{Rh}(\text{acac})(\text{CO})_2$ (0.029 mmol, 7.5 mg); Ligand (0.145 mmol); 1-octene (116 mmol, 18.25 ml); $\text{Rh}:\text{L}:\text{1-octene} = 1:5:4000$; Internal standard = n-dodecane (8.7 mmol, 2 ml); solvent = toluene (43 ml); 80°C; 20 bar; $\text{CO}:\text{H}_2 = 1:1$; $N=700$ rpm.

The same relative order of activity between the ligands is observed, albeit all ligands show significantly reduced activity to previous reaction setup. The final reaction mixture composition is presented in Table 5 below, together with the TOF which was derived from linear functions fitted to the data points up until reaching <80% yield of aldehydes.

Table 5: Final reaction mixture composition from the Rh-catalysed hydroformylation of 1-octene, large scale.

Parameter	Unit	TPP	TPP-POSS-1	TPP-POSS-2	TPP-POSS-3
Conversion	[%]	98.2	98.3	98.4	98.7
Y, octane	[%]	0.5	0.4	1.1	0.1
Y, iso-octene	[%]	2.7	4.0	2.9	1.4
Y, l-nonanal	[%]	68.5	66.8	68.1	70.0
Y, b-aldehyde	[%]	26.4	27.1	26.4	27.1
Y, aldehyde	[%]	95.0	93.8	94.5	97.2
l/b ratio	[-]	2.6	2.5	2.6	2.6
TOF	$[\text{h}^{-1}]$	1310	1050	490	910
ΔTOF	$[\text{h}^{-1}]$	-	-260	-820	-400
ΔTOF	[%]	-	-20	-63	-31

Conditions: $\text{Rh}(\text{acac})(\text{CO})_2$ (0.029 mmol, 7.5 mg); Ligand (0.145 mmol); 1-octene (116 mmol, 18.25 ml); $\text{Rh}:\text{L}:\text{1-octene} = 1:5:4000$; Internal standard = n-dodecane (8.7 mmol, 2 ml); solvent = toluene (43 ml); 80°C; 20 bar; $\text{CO}:\text{H}_2 = 1:1$; $N=700$ rpm.

In this set of experiments, all ligands gave very similar yields of aldehydes, l/b ratio and by-products. Whilst TPP was again the most active ligand with a TOF = 1310 h^{-1} , TPP-POSS-1 and TPP-POSS-3 were not far behind at 1050 h^{-1} and 910 h^{-1} . TPP-POSS-2 was thus

significantly slower with a TOF = 490 h⁻¹. The overall reduction in activity from the first set of experiments to this set of experiments is likely due to insufficient gas-liquid mixing within the autoclave due to the larger liquid volume, where all other things remained the same (autoclave, overhead stirrer, rpm, pressure, temperature, concentration). The larger liquid volume immerses the head of the stirrer so much that it has difficulty in creating enough turbulence of the liquid inside the pot. Nevertheless, the order of activity between the ligands remained the same, but relative differences in TOF between TPP and any of the three TPP-POSS ligands is in this later set of experiment slightly reduced, this has been summarised in Figure 4-9 below.

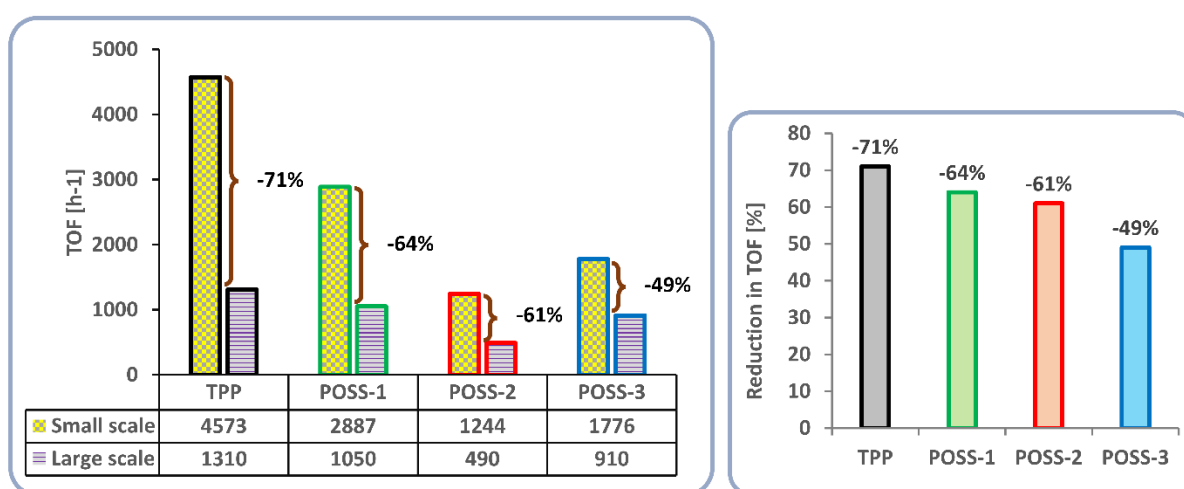


Figure 4-9: The percentage decrease in TOF going from small scale to large scale.

Increasing the number of POSS-cages seems to be able to mitigate the reduced gas-liquid mixing going from small-scale setup to the larger-scale setups. The rationale here is that carbon monoxide is more soluble in less polar solvent,^[371] and the (iBu)₇POSS provides a highly nonpolar environment that stimulates better CO solubility. The amount of isomerisation increased from the more active small-scale experiments to the less active large-scale experiments. Reducing the concentration of dissolved CO is associated with an increase in isomerisation as there is a stage in the catalytic cycle where either CO will be inserted leading to hydroformylation products or a β -hydrogen elimination leading to isomerisation of the double bond (see Figure 2-9 on page 13). Further investigations are required to confirm these initial observations.

Regarding the relative order of activity amongst the TPP-POSS ligands, it is difficult to explain why the TPP-POSS-2 ligand was much less active than both TPP-POSS-1 and TPP-POSS-3. The three ligands have an almost linear relationship in terms of their ³¹P-NMR chemical shift,

suggesting an incremental increase in electron density at the phosphorus with each additional ethyl-linked POSS cage. Each POSS cage also adds an increase in bulk to the ligand. Hence, the reason for the relative order is likely to be more complicated than a simple argument about increased electron density or increased bulk. It is possible that the geometry of the TPP-POSS ligands will influence how they preferentially coordinate to the Rhodium complex, which subsequently can then influence the likelihood of a carbonyl ligand dissociating from the trigonal bipyramidal complex (rate determining step). However, since the selectivity is very similar between the four different ligands, it can be assumed that they all have very similar distributions between them forming ee or ae type trigonal bipyramidal complexes. Overall, all ligands showed comparable selectivity to TPP when they were applied in Rh-catalysed hydroformylation of 1-octene. However, the grafting of POSS via the C₂-alkyl linker so close to the active site of the phosphine ligand clearly had a significant impact upon its activity.

4.3.3. Continuous Rh-Catalysed Hydroformylation in a Ceramic Membrane Loop Reactor

The TPP-POSS ligands were then applied in continuous Rh-catalysed hydroformylation of 1-octene using a loop reactor fitted with an integrated ceramic membrane module for continuous permeation of product mixture from the reactor. The reactor setup is described in the supporting information, section E.5. No experiment was conducted with TPP, as this ligand is clearly too small to be rejected to any meaningful degree by the membrane. Each of the three TPP-POSS ligands was applied in continuous experiments that lasted for 24 h. Samples were taken from the permeate stream at regular intervals and analysed by GC-FID. The result from these continuous flow experiments is presented in Figure 4-10 below.

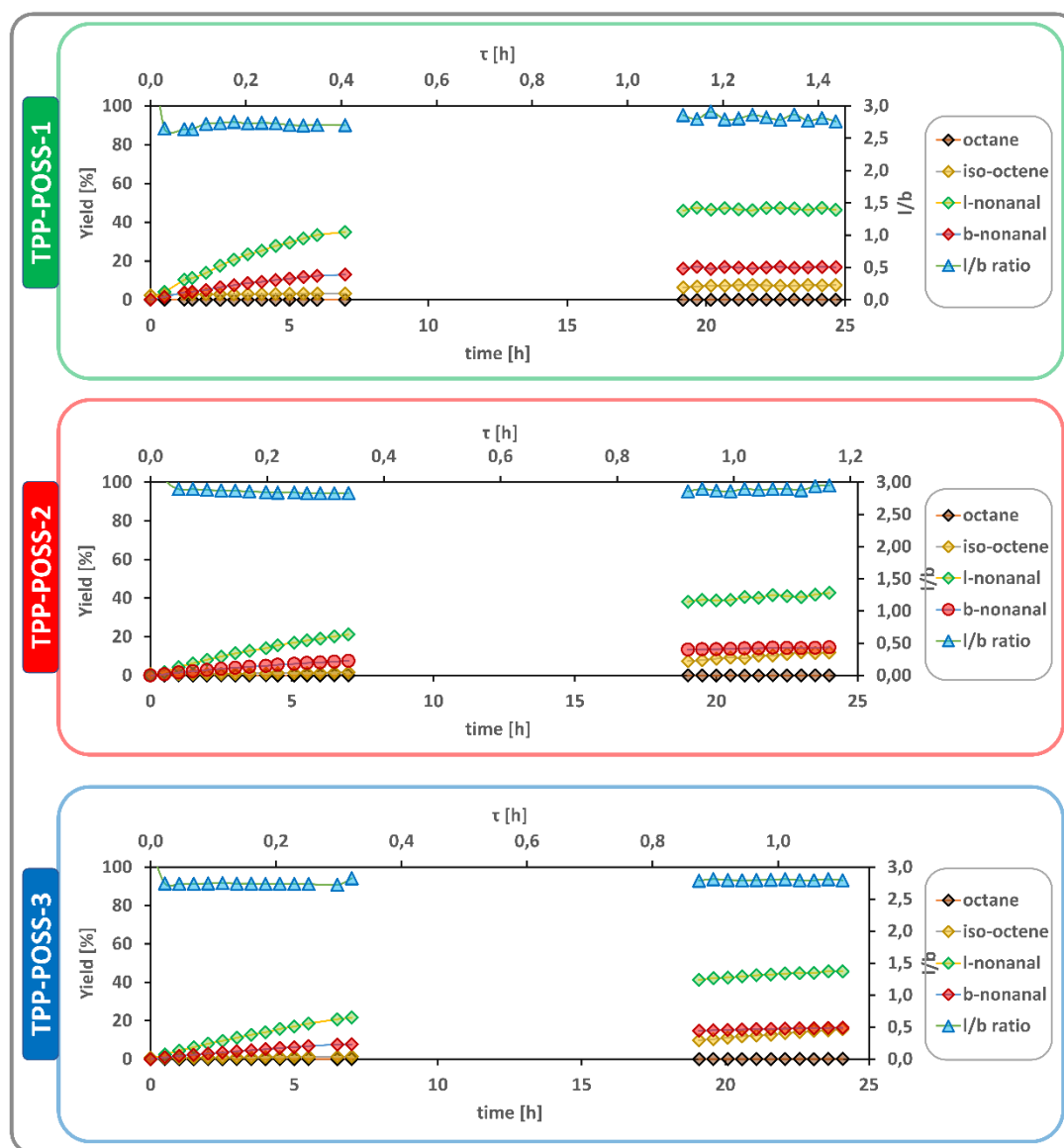


Figure 4-10: The continuous Rh-catalysed hydroformylation of 1-octene using ligands TPP-POSS-1, 2 and 3. Conditions: 80 °C, 20 bar syngas ($\text{CO}:\text{H}_2 = 1:1$); 1.92 M 1-octene in toluene; $M:L = 1:5$; $\text{Rh}(\text{acac})(\text{CO})_2$ (15 mg, 0.058 mmol), TPP-POSS-X (0.290 mmol). Membrane: inopor TiO_2 , 450 Da MWCO.

All ligands showed stable activity and selectivity towards the linear aldehyde with very little hydrogenation products observed. Larger quantities of isomerisation products were observed during the second half of each experiment, between 7 – 16 mol% as compared to the batch reaction mixture compositions. The rejection of the ligands by the ceramic nanofiltration membrane was measured by means of ICP-OES. The results from these measurements and calculations are presented in Figure 4-11 below.

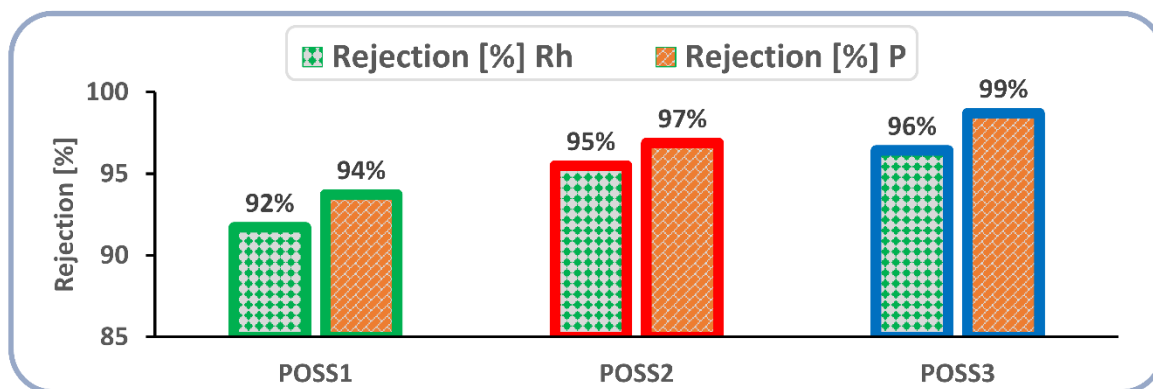


Figure 4-11: The rejection of the three TPP-POSS ligands and Rh by the ceramic nanofiltration membrane. From the continuous flow Rh-catalysed hydroformylation of 1-octene experiment. Rejection was determined by ICP-OES measurements.

There is a clear trend in increasing rejection by the membrane with an increased number of POSS cages attached to the ligand. All ligands had surprisingly low rejections, even the TPP-POSS-3 was only rejected to 99% in P and 96% in Rh. This was far below those values that were reported in the initial publication of TPP-POSS-3 where the rejection of Rhodium was at 99.96%.^[58] It is known that ceramic membranes produced in different batches can give very different rejections of the same type of solute under the same conditions. Reproducibility of ceramic membranes is an issue due to varying amount of defects in the active layer. Hence, it is possible that the membrane that was used in these experiments had a comparatively much less tight pore size distribution or more pore defects than the membrane that was used in the initial work on TPP-POSS-3 by Vogt et al.^[58]

4.4. Conclusions and Outlook

Three different POSS-modified TPP ligands that contained one, two or three ethyl-linked POSS cages were synthesised. The three ligands were applied in the Rh-catalysed hydroformylation of 1-octene in batch autoclaves and compared to each other as well as to the unmodified TPP ligand in terms of activity and selectivity. All three POSS ligand gave less active systems than TPP but with very similar selectivity. TPP-POSS-1 was the most active of the three TPP-POSS ligands, with TPP-POSS-3 the second most active and TPP-POSS-2 significantly less active. The rationale behind this order of activity is difficult to guess without further investigations. The three ligands were then applied in continuous flow Rh-catalysed hydroformylation of 1-octene in a ceramic OSN membrane loop reactor. All three TPP-POSS ligands provided stable reaction systems during the 24 h experiments. The ligands were rejected in the order of the number of POSS cages they contained, where TPP-POSS-1 was rejected at 94%, TPP-POSS-2 at 97% and TPP-POSS-3 at 99%.

Suggestions for future developments related to this chapter: Here will be presented potential future directions of research that is closely related to the material presented within this chapter.

More polar solvents: It can be worth exploring if the use of slightly more polar solvents in combination with the ceramic membrane can help to increase the rejection of these nonpolar (iBu)₇POSS-modified ligands. The rational being that more polar solvents will have a stronger interaction with the ceramic membrane and reduce the potential for TPP-POSS ligand to ceramic membrane interactions, which are necessary for transporting such large solutes through the pores of this type of membrane. The relevant concepts for this argument are presented in section 2.8.2. on ceramic membranes, and illustrated in Figure 5-1.

Increased CO solubility by the presence of (iBu)₇POSS: The initial results on how (iBu)₇POSS can support an increased solubility of CO in the reaction medium can be investigated further. It is also worth investigating if the distance between the (iBu)₇POSS moiety and the active catalytic site will be an important factor.

New POSS ligands using old POSS-synthon: The POSS synthon that was used for the synthesis of the three different TPP-POSS ligands can likely be used for preparation of other phosphine ligands. One suggestion is a DPPE-POSS (DPPE = 1,2-bis(diphenylphosphino)-ethane) ligand according to the suggested synthetic scheme in Figure 4-12 below.

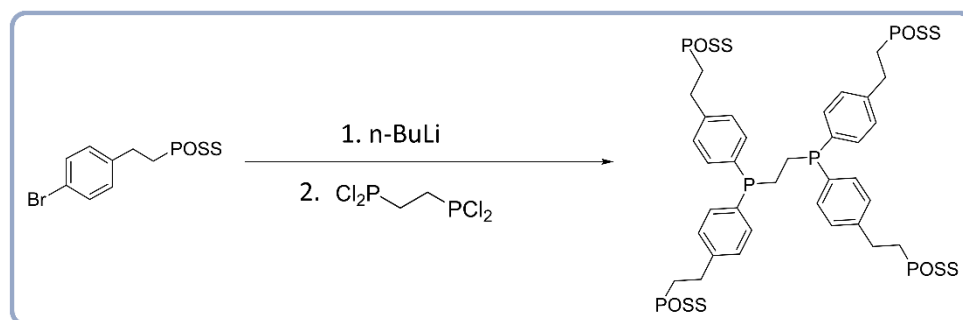


Figure 4-12: Potential POSS-modified DPPE ligand. It can be synthesised from the Br-aryl-ethyl-(iBu)₇POSS synthon and commercially available 1,2-bis(dichlorophosphino)ethane.

The phosphine chloride that is part of the above synthetic scheme is commercially available, which makes the synthesis of said ligand relatively straight forward. Also, XantPOSS contains four POSS cages, but its synthesis is considerably more complicated. The unmodified DPPE ligand is a small bite-angle bidentate phosphine ligand. Unmodified DPPE is very active and selective in Rh-catalysed hydroformylation of butadiene^[372], Pd-catalysed telomerisation of butadiene with alcohols^[373], Pd-catalysed hydroaminomethylation of terpenes,^[374] Pd-

catalysed amidotelomerisation^[375] to name a few. Important is to not forget that installing the POSS cage so close to the phosphor and the active site of the catalyst is likely to impair both, electronic and steric effects upon the ligand. Hence, favourable catalytic properties of such a POSS-modified DPPE ligand must be investigated experimentally.

POSS-modified Buchwald ligands: Apart from the classical TPP (and Xantphos-type) ligand(s), there are also other classes of ligands that can be considered generally applicable. For monodentate phosphine ligands the class of bulky dialkylphosphino-biaryl ligands (aka “Buchwald ligands”) are generally highly active in various Pd-catalysed cross-coupling reactions, and some of them are also extremely resistant towards oxidation while in solution, exposed to O₂ and at elevated temperature.^[186] A ligand that maintains its high activity/selectivity as well as longevity would be highly justifiable for MWE. Furthermore, since Pd-type homogeneous catalysts are generally prone to deactivate through Pd-cluster formation,^[376] the sensible approach is to MWE a ligand that will be applied in Pd systems in an individual manner and not via polymers/dendrimers. The argument here is that an individual MWE (which can arguably be achieved with e.g. POSS) of each ligand/Pd species would distribute the Pd-atoms as far apart from the next Pd-atom inside a solution while a polymer/dendrimer approach would concentrate the Pd-atoms to the vicinity of the polymer/dendrimer. A suggestion for a potential synthetic scheme towards a POSS-enlarged Buchwald ligand is presented in Figure 4-13 below.

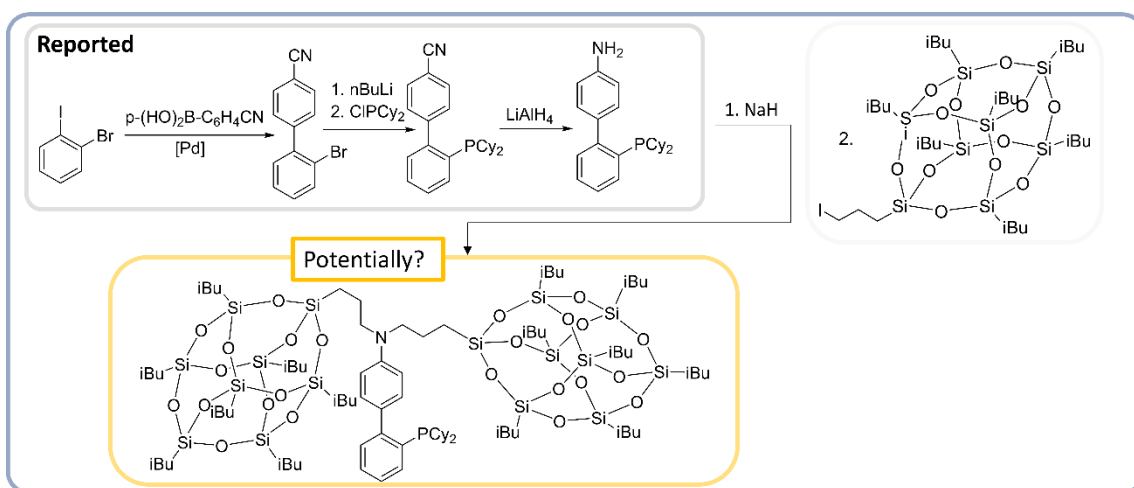


Figure 4-13: Potential synthetic protocol for a POSS-enlarged Buchwald type ligand.

If such a ligand is realised, it would also make sense to explore the tolerance of the POSS cage towards various bases that are commonly used in Pd-catalysed coupling reactions. It has been described that strong bases lead to the destruction of POSS cages.

4.5. Experimental

4.5.1. Materials

Chemicals used in the reaction were purchased from Acros Chemicals, deuteron, Hybrid Plastics, Fisher Chemicals, Merck, Sigma Aldrich, Umicore or VWR. Solvents used in the reactions were dried by activated molecular sieves and then degassed in an ultrasonic bath while bubbling argon for 45 minutes. The tetrahydrofuran (THF) and Et₂O used for the ligand synthesis was dried and degassed by distilling it over sodium and benzophenone. 1-octene used in Rh-catalysed hydroformylation was run through a plug of aluminium oxide to remove peroxides.

4.5.2. Setup

See section E. for details about the setup (autoclave and ceramic membrane loop reactor used in the experiments).

4.5.3. Analytical methods

NMR: Measured using Bruker AV Avance III HD (400MHz or 600 MHz). The relative uncertainty for reported molar ratios is estimated at $\pm 5\%$ for ¹H-NMR and $\pm 10\%$ for ³¹P-NMR.

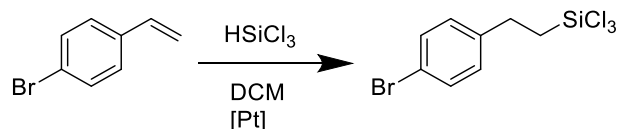
GC-FID: Measured on an Agilent Technologies 7890A GC System. Quantitative analysis of reaction mixtures was performed via GC-FID using dodecane as an internal standard to account for injection volume variances and detector drift. Response factors were determined using five-point calibration curves ($R^2 > 0.999$). Based on the precision of the autosampler and the reproducibility of sample preparation, the relative standard deviation (RSD) for conversions and yields is estimated at $\pm 2.5\%$. For instance, a reported conversion of 95% carries a trustiness region of approximately ± 2.4 percentage points. This level of uncertainty is considered standard for the evaluation of kinetic trends in homogeneous catalysis. See section E. on page X for details about the GC methodology.

ICP-OES: The results of the samples for retention were determined with an ICP-OES of type iris intrepid ICP from Thermos Elemental with a radial and axial evaluation. The full amount of permeate and retentate were concentrated on a rotary evaporator prior to sample preparation for the ICP-OES measurement. For membrane retention values (e.g., reported as 99%), the uncertainty was minimized by concentrating permeate samples to ensure metal content remained significantly above the Limit of Quantification (LOQ). Based on the propagation of a conservative 5% relative standard deviation (RSD) for ICP-OES sample preparation and

analysis, the absolute uncertainty for a 99% retention value is estimated to be approximately $\pm 0.1\%$. See section E. on page X for details about ICP sample preparation methodology.

4.5.4. Synthesis of compounds

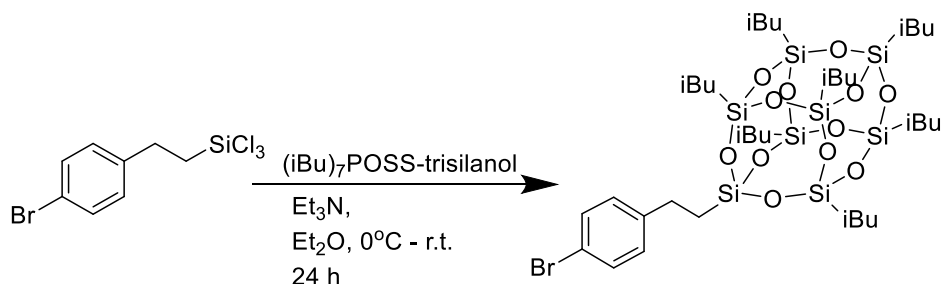
Synthesis of (4-bromo-phenyl)-ethyl-trichlorosilane



To a dry Schlenk flask fitted with a stirrer bar and a screw cap septum was added 4-bromostyrene (3.78 g, 20.65 mmol). Dry DCM (100 ml) was then added to make a solution. $(\text{Bu}_4\text{N})\text{PtCl}_6$ (5 mg, 7.8 μmol) was then quickly added and the mixture was left to stir for about 30 min. An excess of trichlorosilane (15 ml) was then slowly added to the reaction mixture, which was then left to stir at room temperature for about 20 h. The progress of the reaction was monitored by ^1H -NMR and when it was complete the excess trichlorosilane and DCM were removed in vacuo using a cold trap. The product was obtained almost quantitatively as a slightly yellowish oil and was used without any further purification.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.44 (d, $J = 8.2$ Hz, 2H), 7.10 (d, $J = 8.2$ Hz, 2H), 2.86 (m, 2H), 1.73 (m, 2H).

Synthesis of (4-bromo-phenyl)-ethyl-(iBu)₇POSS



In a dry 500 ml Schlenk flask fitted with a stirrer bar was charged $(\text{iBu})_7\text{POSS-trisilanol}$ (23.7 mmol, 18.76 g), the POSS material was left to dry under high vacuum for a few hours before continuing. Dry Et_2O was then added to the Schlenk flask making a clear solution, which was then put on an ice bath to keep the temperature close to 0°C . The intermediate silane product “(4-bromo-phenyl)-ethyl-trichlorosilane” was dissolved in dry Et_2O and added to the POSS solution. Et_3N (18 ml) was then added dropwise to the reaction mixture and a creamy white precipitate formed. More Et_2O was added to the reaction mixture if it became too thick from precipitate. The reaction was left to stir overnight while slowly warming to room temperature. The mixture was washed twice with 1N $\text{HCl}_{(\text{aq})}$, the organic phase was dried over MgSO_4 and

concentrated. The crude product was run through a short plug of silica (5 cm). After concentrating the filtrate, a white solid product was yielded and used without any further purification.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.39 (d, $J = 6.6$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 2H), 2.66 (m, 2H), 1.86 (m, 7H), 0.95 (d, $J = 6.6$ Hz, 42H), 0.60 (d, $J = 7$ Hz, 14H)

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 143.33, 131.31, 129.69, 119.31, 28.50, 25.70, 2.88, 22.5, 14.20

Synthesis of TPP-POSS-1, 2 and 3

(4-bromo-phenyl)-ethyl-(iBu) $_7$ POSS (5 g, 5.09 mmol) was dissolved in THF (50 ml) and the solution was cooled to -78°C . n-BuLi (1.6 M in hexanes, 3.4 ml, 5.5 mmol) was added dropwise to the solution and the mixture was stirred at this temperature for 1 h. PPh_2Cl (1.12 g, 0.91 ml, 5.09 mmol) or PhPCl_2 (0.45 g, 0.34 ml, 2.545 mmol) or PCl_3 (0.3 g, 0.19 ml, 1.69 mmol) was added dropwise. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The next day the solvents were removed in vacuo using cold traps. The product was extracted from the remaining solid with toluene/hexane (1:1, 150 ml) and washed with degassed water. The organic phase was dried over MgSO_4 . The solvents were removed in vacuo. Further purification was done by dissolving the product in a small amount of toluene and then adding MeOH to the solution until a precipitate is formed. Leave the solution in a fridge for an hour and then filter off the precipitate (product).

TPP-POSS-3:

^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.24 (dd, $J = 12.4$ Hz, $J = 14.4$ Hz, 12H), 2.69 (m, 6H), 1.79 (sept. $J = 13.6$, 6.8 Hz, 42H), 0.89 (d, $J = 6.7$ Hz, 132H), 0.54 (d, $J = 6.1$ Hz, 42H).

^{13}C NMR (151 MHz, CDCl_3) δ (ppm): 145.16, 133.81, 127.94, 125.30, 28.71, 25.72, 23.88, 22.52, 14.08.

^{31}P NMR (243 MHz, CDCl_3) δ (ppm): -7.71 (s).

TPP-POSS-2:

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.21 – 6.96 (m, 13H), 2.69 – 2.56 (m, 4H), 1.79 (dp, $J = 13.4$, 6.7 Hz, 14H), 0.88 (d, $J = 6.8$ Hz, 88H), 0.53 (d, $J = 7.1$ Hz, 28H).

^{13}C NMR (151 MHz, CDCl_3) δ (ppm): 145.32, 133.95, 128.07, 125.32, 28.76, 25.73, 23.90, 22.54, 14.09.

^{31}P NMR (243 MHz, CDCl_3) δ (ppm): -6.94 (s).

TPP-POSS-1:

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.32 – 6.91 (m, 14H), 2.74 – 2.52 (m, 2H), 1.78 (dh, $J = 13.3$, 6.3 Hz, 7H), 0.88 (dd, $J = 6.6$, 2.0 Hz, 44H), 0.52 (t, $J = 7.2$ Hz, 14H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 145.47, 143.34, 133.77, 131.34, 129.72, 128.41, 128.07, 119.34, 28.54, 25.74, 25.72, 23.91, 22.54, 14.24.

^{31}P NMR (243 MHz, CDCl_3) δ (ppm): -6.18 (s)

Issues with the Synthesis of TPP-POSS Ligands

The synthesis of these ligands was only accomplished once, despite numerous attempts at reproducing the synthesis. No conclusion could be made whereupon the missing and decisive parameter was, but MALDI-MS of different later batches of synthesised 4-bromo-phenyl-ethyl-(iBu)₇POSS showed that only minor quantities of the product ion were ever present. Both TLC and NMR spectra looked fine, although it was recognised that in the ¹H-NMR spectrum, very small strange peaks were present in the region around 1.37 ppm which could not be explained to be water. A potential explanation could be that the corner-capping reaction consistently failed to fully close all corners of the POSS cage, leaving a significant number of Si-OH groups open. It was learned while writing this thesis that POSS material can only be guaranteed dry by azeotropic distillation with toluene. Not even keeping POSS at 90°C and under high vacuum will remove all moisture!

4.5.5. *Rh-catalysed hydroformylation of 1-octene*

Batch autoclave Rh-catalysed hydroformylation

The ligands TPP, TPP-POSS-1,2 and 3 were applied in Rh-catalysed hydroformylation of 1-octene in batch autoclave reactors described in E.4. Also, the general operational methodology described therein was applied herein. Conditions: Rh(acac)(CO)₂ (0.029 mmol, 7.5 mg); Ligand (0.145 mmol); 1-octene (116 mmol, 18.25 ml); Rh:L:1-octene = 1:5:4000; Internal standard = n-dodecane (8,7 mmol, 2 ml); solvent = toluene (43 ml); 80°C; 20 bar; CO:H₂ = 1:1; N=700 rpm.

Added to the pot: catalyst solution (Rh(acac)(CO)₂ (0.029 mmol) TPP-POSS ligand (0.145 mmol) dissolved in 21 ml Toluene) was introduced first, followed by n-dodecane (8.7 mmol, internal standard) and then the extra toluene (22 ml). Added to the dropping funnel: 1-octene (116 mmol). After adding everything to the reactors, preformation was performed (700 rpm, 80°C at 18 bar H₂:CO = 1:1) for 1-2 hours. Final adjustment to the desired reaction set-points (700 rpm, 80°C, 20 bar syngas) were then made. 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. Samples were withdrawn from the reactors at regular intervals using the sample device. A few seconds before each sample, the pipes of the sample device were flushed by discarding a small

volume of reaction mass through it. Collected samples were analysed by GC-FID. The set-points of each experiment (T, p, rpm) were kept static.

Continuous Rh-Catalysed Hydroformylation

The three TPP-POSS ligands were investigated for their catalytic properties in a continuous flow ceramic nanofiltration membrane reactor described in E.5. Each experiment was conducted for about 24 hours. The permeate was continuously collected into a flask throughout the experiment, fresh substrate solution was pumped into the reactor on command from a level sensor. Sampling was done during the first 7 h of the experiment, then the reactor was left on overnight and more samples were collected from around the 19th hour onward. Conditions: 80°C and 20 bar syngas ($\text{CO:H}_2 = 1:1$), substrate: 1.92 M 1-octene in toluene, catalyst: M:L = 1:5, $\text{Rh}(\text{acac})(\text{CO})_2$ (15 mg, 0.058 mmol) with TPP-POSS (0.290 mmol), start of reaction when valve to the dropping funnel was opened after reaching a steady membrane flux at the set reaction conditions. Degassing of liquids was done in Schlenk-flasks using simultaneous sonication and argon bubbling for about 30 min – 1 h. Preparations and transfers of solutions and liquids were done by using standard Schlenk-techniques. The general preparation of the reactor was done according to the description in E.5.

The catalyst solution was prepared by weighing out both $\text{Rh}(\text{acac})(\text{CO})_2$ (15 mg, 0.058 mmol) and TPP-POSS ligand (0.290 mmol) dry into a single Schlenk flask fitted with a stirrer bar to which toluene (14 ml) was added. After stirring this solution for about 30 min, it was introduced into the dropping funnel of the reactor from the upper valve under a slow flow of argon using a long reaching needle (reusable 30 cm). The reactor was then heated to the reaction temperature (80°C), when this had been reached the reactor was pressurised with synthesis gas ($\text{H}_2:\text{CO} = 1:1$). The membrane was always free to permeate, and the permeated volume was made up by fresh substrate solution via the HPLC-pump, which was operating on feedback from the level sensor of the reactor. When the reactor had reached a steady state of permeation at the desired reaction temperature and pressure, the valve to the dropping funnel was opened so that the catalyst solution entered the substrate solution inside the reactor and the reaction was considered to have started ($t = 0$). Samples were taken from the permeate stream at regular intervals (every 30 min) and analysed by GC-FID using the method of internal standard (dodecane). The permeate was collected into a bottle standing on a balance, and the substrate was kept inside another bottle also standing on a balance. The change in mass over time of permeate and substrate was thus recorded. At the end of an experiment, the total volume of all the solutions were measured separately (mass and volume). These solutions were the pre-

catalyst addition permeate and the post-catalyst addition permeate. These were then concentrated down on a rotary evaporator and again measured for mass and volume. The two permeate solutions as well as un-altered sample from the end of the reaction reactor solution were then submitted for ICP analysis (P and Rh).

Chapter 5: XantPOSS-2 and NixantPOSS

5.1. Abstract

This chapter is about the molecular weight enlargement of Xantphos-type ligands. Two different designs of Xantphos-type ligands modified with POSS cages were attempted. Both designs had the POSS cages attached to the rear of the backbone, away from their active sites. The first approach of a Xantphos-POSS type ligand design had two POSS cages attached at the 2,7-position of the ligand backbone. Unfortunately, the complete synthesis of this ligand was never realised. The second approach of a POSS-modified Xantphos-type ligand was based upon the late-stage modification of Nixantphos, where a POSS synthon was grafted to the secondary amine resulting in the ligand “NixantPOSS”. This design proved highly successful as it was achievable through a one pot reaction using standard reactants, ambient temperature and gave an excellent yield of the enlarged ligand. The resulting ligand, named NixantPOSS, was characterised by NMR and MALDI-MS. This new ligand has excellent solubility in toluene and other solvents. Applied in the Rh-catalysed hydroformylation of 1-octene reaction it showed activity and selectivity almost on-par with the unmodified Nixantphos, and considerably better than Xantphos. Finally, the ligand was investigated for its rejection by ceramic nanofiltration membrane and compared with its unmodified parent compound. A significant improvement in its rejection was achieved due to the MWE.

5.2. Introduction

This chapter is the second part of the work towards further the use of POSS as MWE-unit for phosphine ligands. The main point of this chapter was to explore if a POSS-modification in the rear of the ligand backbone has a less adverse effect upon the TOF compared to having the POSS modification close to the active site of the catalyst (see XantPOSS by Janssen and Vogt et al.^[126]).

5.3. Results and Discussion

Molecular weight enlargement of Xantphos-type ligands using polyhedral oligomeric silsesquioxane (POSS) as the MWE-unit was attempted. Two different approaches were explored, whereby Xantphos or Nixantphos were modified by grafting (iBu)₇POSS to their ligand backbones. In both cases the POSS cages were grafted at the rear of the ligand backbones, away from the binding site of the ligands, see Figure 5-1 below for the target ligands.

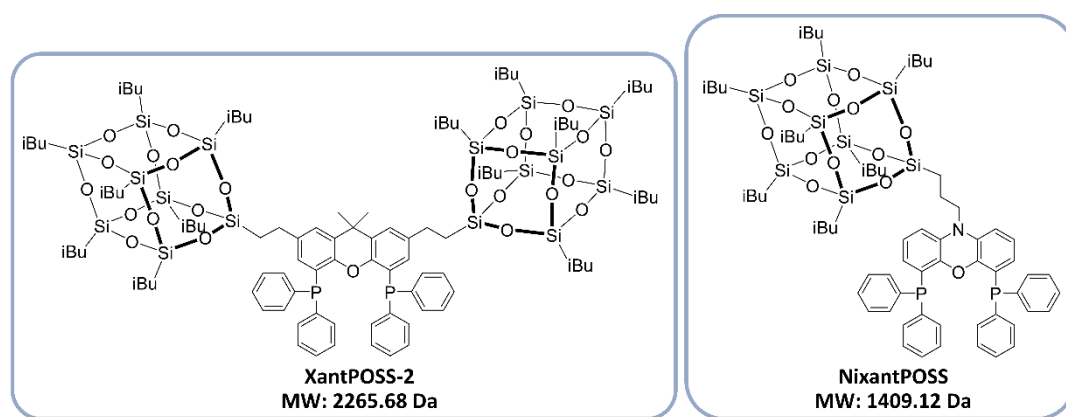


Figure 5-1: Structure of XantPOSS-2 and NixantPOSS

Choosing the back of the backbone as the anchor site of the POSS-cages was to minimise the risk of any adverse effects that MWE might have upon the activity and selectivity of a resulting catalyst complex.

5.3.1. XantPOSS-2

Although the full synthesis of XantPOSS-2 was never successful, it is suitable to still present that work and include it in the discussion. The proposed synthetic scheme for the Xantphos based di-POSS ligand “XantPOSS-2” is presented in Figure 5-2 below.

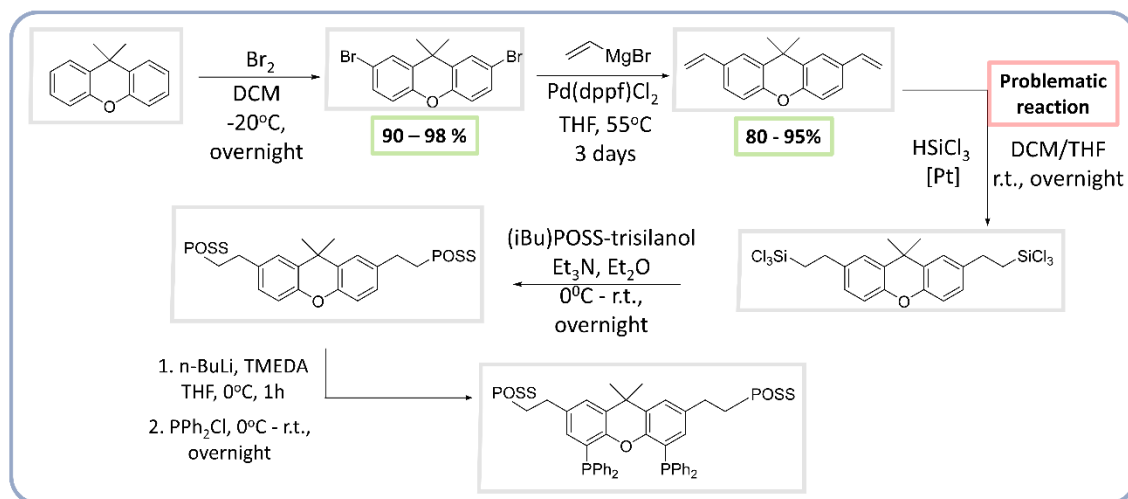


Figure 5-2: Suggested synthetic protocol to access XantPOSS-2

The bromination of 9,9-dimethylxanthene is straightforward and gives a yield of 2,7-dibromo-9,9-dimethylxanthene around 90-98%. The Kumada coupling of the vinyl-Grignard reagent with the brominated backbone is best performed at 55°C for 3 days using Pd(dppf)Cl₂ as catalyst, freshly distilled THF (from Na/benzophenone) and rigorous exclusion of air and moisture. Progress of the reaction is best observed using GC-MS, which can easily distinguish between starting material, mono-bromo-mono-vinyl- and di-vinyl-xanthene (DVX). The

intermediate product “DVX” is prone to polymerize, especially under acidic conditions, in concentrated form and at elevated temperatures. The best yield after workup of the Kumada reaction was 95%, although it was more common with yields around 80%. The next step in the synthesis was a double hydrosilylation of the two vinyl groups. The reaction used a platinum-based catalyst and HSiCl_3 as the silane. The success of the hydrosilylation reaction was found to be very unpredictable for this divinylxanthene substrate. First, it was recognised that higher concentrations of DVX in the reaction mixture significantly increase the risks of it oligomerising/polymerising. Different reaction protocols were explored investigating different parameters that potentially were decisive for the success of the reaction. Such parameters included the type of catalyst ($(\text{Bu}_4\text{N})_2\text{PtCl}_6$, Karstedts, $\text{Pt}(\text{NHC})$ -type and PtO_2); catalyst loading; solvents and solvent combinations (toluene, Et_2O , DCM, THF); the ratio between vinyl:silane (1:1.3, 1:2, 1:4, 1:6, 1:20) and the order by which components were added. None of the sets of experiments performed generated results that could show any effects of any of the above-mentioned parameters. In the majority of cases very little could be observed to have happened when it was sampled and analysed by ^1H -NMR, but in those instances where something did happen a complete/near complete conversion of the substrate was observed together with the formation of the desired product peaks, see Figure 5-3 for ^1H -NMR spectra.

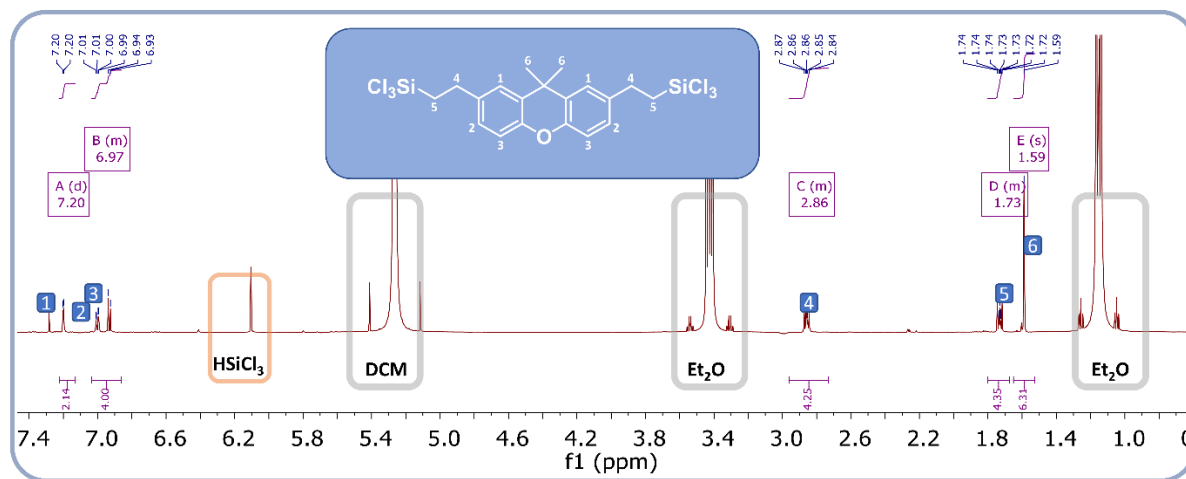


Figure 5-3: ^1H -NMR of a reaction mixture sample from the hydrosilylation reaction of divinylxanthene, (601 MHz, Chloroform- d).
Reaction conditions: divinylxanthene (100mg, 0.38 mmol), DCM (3 ml), Et_2O (2 ml), $(\text{Bu}_4\text{N})_2\text{PtCl}_6$ (125 ppm Pt to vinyl), HSiCl_3 (0.2 ml, 1.98 mmol). vinyl:silane = 1:2.6.

In the specific case of the reaction results presented above, the observed full conversion to the desired product was only realised after the third sample on the third day (one sample per day), where the previous samples had shown only a few percent of conversion and yield at all. It is discussed in the literature that Pt-catalysed hydrosilylation reactions can suffer from

unpredictable induction periods and the need for small amounts of oxygen in order for the catalyst to become activated.^[377] The degree to which the hydrosilylation acts unpredictably is also highly dependent upon the substrate and silane used. The so called “oxygen-effect” can have a decisive influence upon a Pt-catalysed hydrosilylation system where no activity is observed under completely inert conditions, but can start reacting vigorously when the “right amount” of oxygen is being introduced.^[378] Having an insufficient amount or an excess of oxygen can in both cases result in inactive species.^[377] Due to the erratic behaviour of this hydrosilylation reaction and a few signs pointing towards the importance of the “oxygen-effect”, further experiments were devised trying to design a reaction protocol that allowed better control of the introduction of oxygen into the reaction mixture. The reaction mixture was prepared under inert conditions in the designated reaction vessel. Finally a calcium chloride drying tube was attached to the vessel while flowing a steady stream of argon. The last thing was to stop the flow of argon so that the inert atmosphere of argon inside the reaction vessel could slowly diffuse out through the drying tube while air from the outside could slowly diffuse in. Over time, this would then allow the “perfect” concentration of oxygen to be reached. For each new reaction, it is recommended that the drying tube is loaded with fresh CaCl₂. Older sources of CaCl₂ will hold water, which will react with the relatively volatile HSiCl₃ and result in a blockage of the tube. Despite these measures, the success rate was not guaranteed. Not all hydrosilylation reactions that reacted were suitable for further use as there was also a risk that the vinyl substrates polymerised and/or oligomerised. If a successful hydrosilylation produced a clean silane intermediate product, it was worked-up by evaporating all the volatiles (solvents and excess HSiCl₃). The remaining di-silane-xanthene intermediate was then left as a light yellow oil that was then reacted in a corner capping reaction as shown in Figure 5-2 to give the air and moisture stable intermediate 2,7-diethyl-di(iBu)₇POSS-9,9-dimethylxanthene. The last reaction is a di-lithiation and reaction with the phosphine chloride, which was never successfully realised to produce a pure product. One of the better attempts at the last reaction gave two strong signals in the ³¹P-NMR at -13.99 and -16.04 ppm, one of which might be the one of the desired XantPOSS-2 product. This can be compared with the ³¹P-NMR of Xantphos at -17.5ppm. This is then suggesting that installing the POSS cages at the 2,7-position of the backbone in this way still has an influence upon the electronic properties of the phosphor, which is seemingly becoming slightly less electron rich as the chemical shift is moved slightly upfield. The impact upon the ligand’s catalytic properties is potentially that it would exhibit a higher activity than Xantphos in the Rh-catalysed hydroformylation. This would be due to reduced phosphor basicity and reduced phosphor electron donation to empty metal orbitals,

which then leads to reduced π -back bonding to the CO ligands of the Rh-resting state complex. Hence, the CO ligand would therefore become slightly more labile, which would favour more Rh-complexes to participate in the catalytic cycle instead of being idle as Rh-resting state complexes. Overall, it must be recognised that the proposed synthesis of XantPOSS-2 is rather long (5 steps) and involves highly unpredictable reactions and unstable intermediates, but the intended product ligand might very well have good potential to be an active and selective POSS-modified Xantphos-type ligand bearing the POSS-modification in the rear of the backbone.

5.3.2. NixantPOSS

The other approach to POSS-modification of a Xantphos-type ligand in the rear of the backbone was suggested to be done via the secondary amine of the Nixantphos ligand. The secondary amine can be deprotonated by NaH and then reacted with different benzyl and alkyl halides as is presented in Figure 5-4 below.

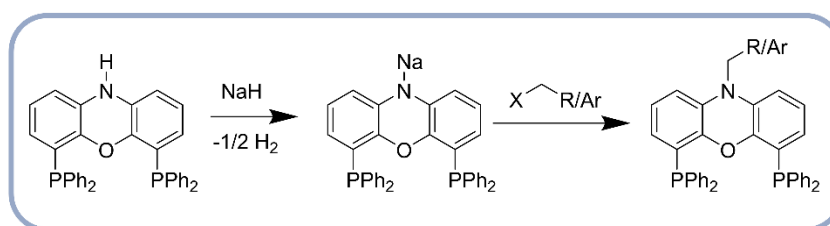


Figure 5-4: Deprotonation of Nixantphos and reaction with an alkyl- or benzyl- halide.

Thus, a similar synthetic scheme was envisioned, whereby a POSS synthon could be installed. Different sources use slightly different conditions; some use DMF^[128] while others have used THF as the solvent^[379]. Generally DMF is not a good solvent for dissolving (iBu)₇POSS containing compounds while THF is, hence the choice of solvent was THF. It is necessary to thoroughly exclude oxygen while working with Nixantphos in solution. Performing reactions in lab-scale at room temperature rather than at elevated temperature makes the exclusion of oxygen much easier as no reflux condenser is then required. Furthermore, not working at elevated temperature also reduces the risk of the NaH causing decomposition of the POSS cage (NaH is a relatively strong base). Hence, the deprotonation step at room temperature and at elevated temperature was investigated, as well as the subsequent reaction with an electrophile.

5.3.3. Using *N*-phenyl-2-naphtylamine as a Model Amine for Nixantphos

To find a suitable reaction protocol for the late stage MWE of Nixantphos, a model amine was initially used in place of Nixantphos. The selection of a model amine came down to *N*-phenyl-

2-naphtylamine, which is presented in Figure 5-5 below, right side, together with Nixantphos, left side.

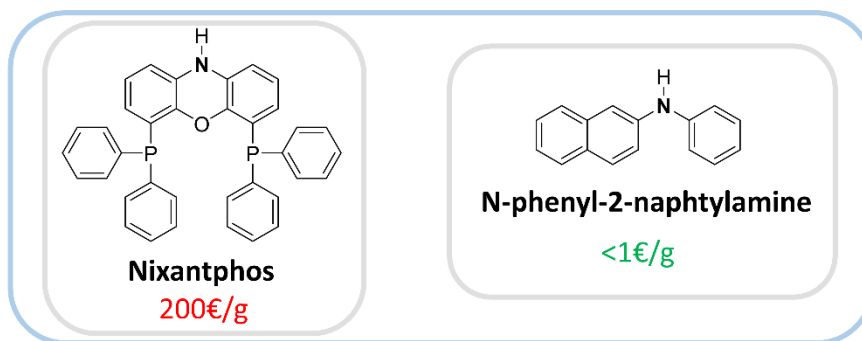


Figure 5-5: Structure of Nixantphos and N-phenyl-2-naphtylamine

Both molecules are diaryl secondary amines, but the model amine costs only 1€/g, a fraction of the price of Nixantphos at 200€/g. The model amine also contains protons with characteristic chemical shifts that were easy to study with ^1H -NMR when following the progress of a deprotonation reaction. This has been highlighted in Figure 5-6 below.

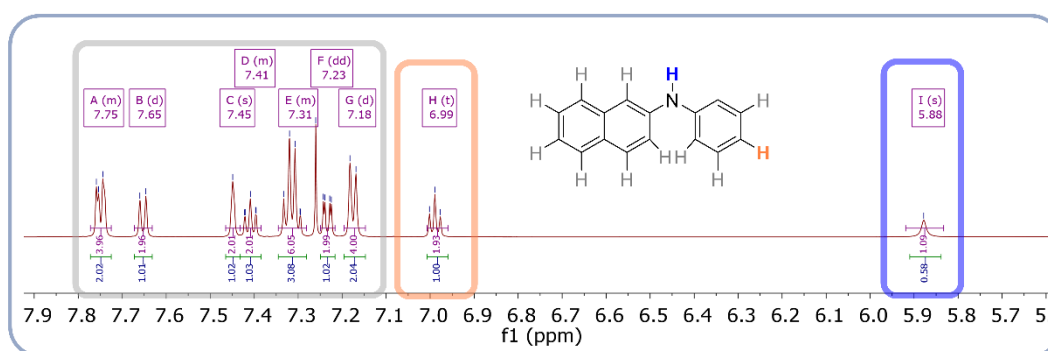


Figure 5-6: ^1H -NMR of N-phenyl-2-naphtylamine, (CDCl_3 , 400 MHz).

The relative integral of the coloured protons allows the progress of the deprotonation of the amine to be tracked.

5.3.4. Preparing POSS-Synthons

While exploring the deprotonation scheme, also appropriate POSS containing electrophiles were investigated. Three different POSS-containing electrophiles were identified, which are presented in Figure 5-7 below.

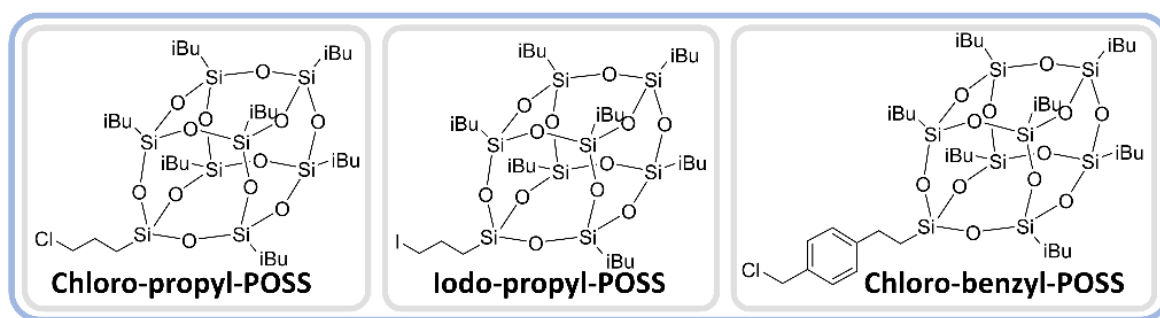


Figure 5-7: Three different POSS-synthons investigated for grafting to Nixantphos.

The synthesis of the three different POSS-synthons is presented in Figure 5-8 below. The first two POSS-synthons are 3-chloro-propyl-POSS and 3-iodo-propyl-POSS and were synthesised from the starting material 3-chloro-propyl-trimethoxysilane, which was reacted with the POSS-trisilanol using tetrabutylammonium hydroxide as a catalyst. After workup, the product 3-chloro-propyl-(iBu)₇POSS was received in 91% yield. A Finkelstein reaction was performed to gain the iodo-substituted derivative, the pure product was received at 89% yield after workup.

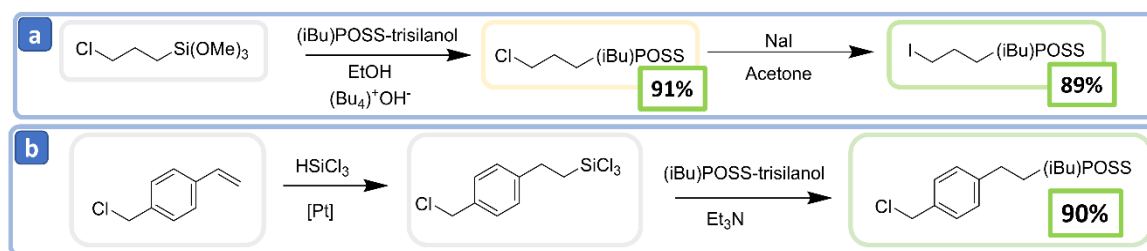


Figure 5-8: a: Synthesis of the POSS-synthons

(Top): chloro- and iodo-propyl-(iBu)₇POSS; (Bottom): synthesis of chloro-benzyl-ethyl-(iBu)₇POSS

The last POSS-synthon was prepared from the starting material 4-vinylbenzyl chloride, which was hydrosilylated with trichlorosilane using a Pt-catalyst. The intermediate silane was then reacted with (iBu)₇POSS-trisilanol to gain the product chloro-benzyl-(iBu)₇POSS in 90% yield after purification.

5.3.5. Deprotonation of Model Amine and Reaction with POSS-Synthon

The deprotonation of N-phenyl-2-naphtylamine by NaH in THF at room temperature or at elevated temperature and how well the various electrophiles managed to react with the deprotonated amine was investigated. Samples were withdrawn from the reaction mixture at various times and quickly quenched in D₂O. The quenched samples were then filtered through a plug of silica, volatiles were evaporated and submitted for ¹H-NMR analysis (CDCl₃). Integration of the amine N-H proton at 5.88 ppm (singlet) was compared with the Ar-H (¹H) at 6.99 ppm (doublet). The reaction between the deprotonated amine and the electrophiles was followed in a similar fashion. Here the two protons next to the halogen in the POSS-synthon

were compared with the two protons next to the amine in the products. When it comes to the amine-propyl-POSS products, it is highly important that all THF has been evaporated from the samples before an NMR is prepared, as both THF and the protons of the product show a ^1H -triplet at 3.76ppm. The results from these two experiments are presented in Table 6 below.

Table 6: The progress of deprotonation of model-amine and grafting of POSS-synthons. Reaction progress monitored by ^1H -NMR.

Reaction step	Amine proton left [%]	benzyl-POSS reacted [%]	Reaction step	Amine protons left [%]	propyl-POSS reacted	
					Cl [%]	I [%]
Amine + NaH, rt, 30 min	96	-	Amine + NaH, rt, 15 min	44	-	-
Amine + NaH + POSS, 0 °C, 1 h	98	2	Amine + NaH + POSS, 0 °C, 2 h	90	16	27
amine + NaH + POSS, rt, 16 h	69	58	amine + NaH + POSS, rt, 16 h	58	9	93
amine + NaH + POSS, 60°C, 72 h	90	85	amine + NaH + POSS, rt, 88 h	94	53	100

Clearly, the deprotonation of the amine happened within minutes at room temperature and the subsequent reaction with the electrophiles progressed satisfyingly for the chloro-benzyl-POSS and best for iodo-propyl-POSS. The chloro-propyl-POSS showed very little conversion even after an extended period.

5.3.6. Amine-POSS Stability Test

Benzyl groups are extensively used as protection groups for amines; hence, many suitable protocols for their instalment do exist. However, a potential warning against using the benzyl synthon as MWE-unit of Nixantphos would be that the standard protocol for deprotecting a benzyl-amine is to apply H_2 and a Pd-catalyst (reducing conditions). And since there are many reactions making use of reducing conditions that would benefit from a MWE-Nixantphos ligand, it would be preferred if it is safeguarded that the MWE-group does not get cleaved off the first thing that happens when subjugated to such conditions. Therefore, the POSS-modified model amines were isolated and their long-term stability under typical Rh-catalysed hydroformylation conditions was investigated in autoclave reactors for 1 week under reaction conditions (20 bar; $\text{CO}:\text{H}_2 = 1:1$; 90°C ; $\text{Rh}/\text{TPP} = 1:5$). No decomposition of the amines or the POSS cages was observed with NMR analysis at the end of this.

5.3.7. Synthesis of NixantPOSS

After the initial investigations using the model amine, it was concluded that the synthesis of NixantPOSS could be attempted as a one-pot reaction using NaH in THF at room temperature and 3-iodo-propyl-POSS as the electrophile. Because heating was not required, the reaction

could be performed in a long neck Schlenk flask with only an argon balloon on-top. A simple setup has a smaller risk of oxygen contamination and is therefore preferred when working with air sensitive compounds (e.g. phosphines). The reaction used freshly distilled THF from Na/Benzophenone (O_2 and H_2O free). After 3 days of stirring the first sample was withdrawn and analysed by 1H -NMR, indicating complete conversion of the iodo-propyl-POSS. The reaction was worked-up by first removing the THF giving a crude product that was then dissolved in cyclohexane/toluene and washed with water. After evaporating all solvents, a brown/green product resulted, which was characterised by NMR (1H , ^{13}C , ^{29}Si , ^{31}P) presented in Figure 5-9 below.

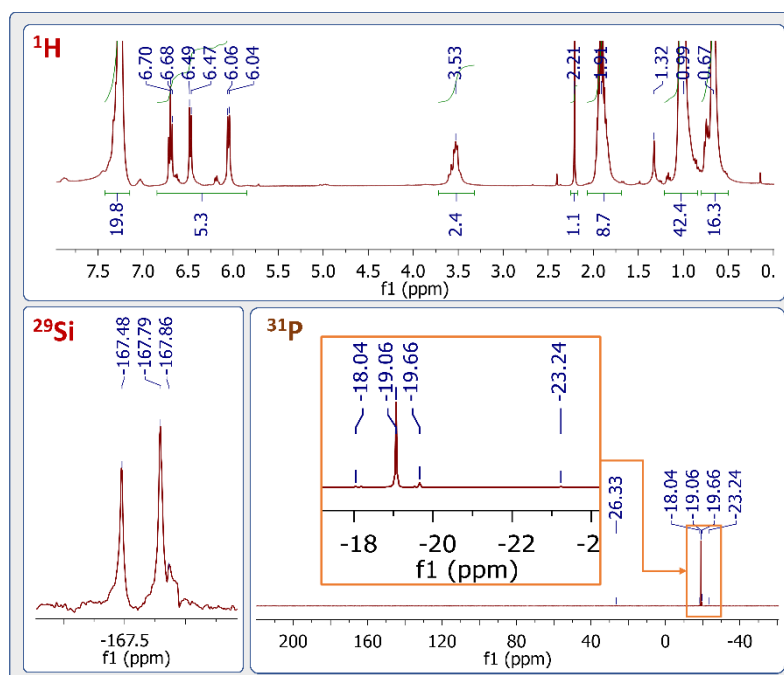


Figure 5-9: The 1H - ^{29}Si - and ^{31}P -NMR spectra of NixantPOSS, ($CDCl_3$, 400MHz).

For the NMR analysis the sample was prepared under inert conditions using degassed $CDCl_3$ and a specially designed Schlenk tube (See supporting information, section E.1. for details) in order to safeguard against oxygen. The ^{31}P -NMR spectra show that the product contained very little amount of phosphine oxide (+26.33 ppm) or other phosphor containing impurities while the vast majority shows up as one type of phosphine with a single peak at -19.05 ppm, which is only slightly downfield of unmodified Nixantphos (-18.86 ppm). The ^{29}Si -NMR show the typical pattern of a fully closed POSS cage with one corner different from the others, hence two large and one small singlets. The 1H -NMR shows an acceptable integration. NixantPOSS was also characterised by MALDI-MS, which is presented in Figure 5-10 below.

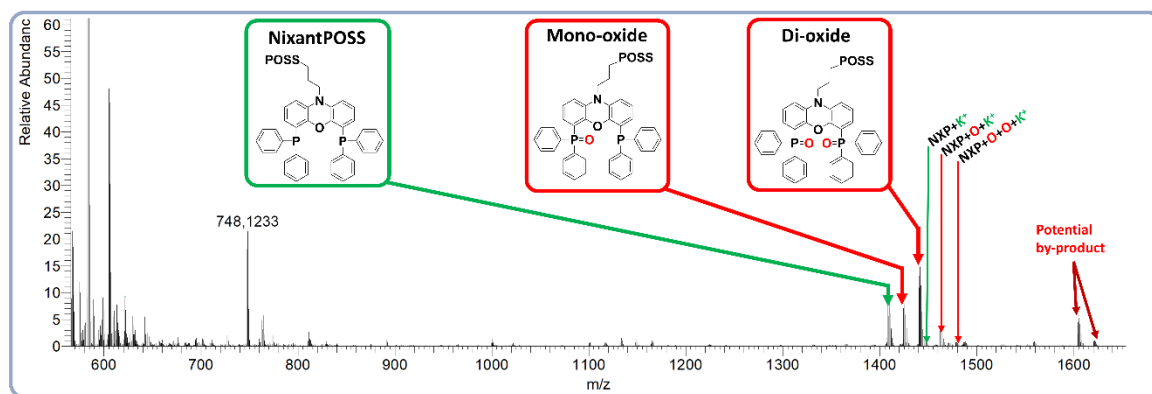


Figure 5-10: The MALDI-MS spectra of NixantPOSS.

The mass spectrum from the MALDI-MS analysis shows several different peaks at lower m/z , which can be assigned to the matrix itself or possible fractioning products. At higher m/z , there are three larger clusters of ions, which can be assigned to the product NixantPOSS, NixantPOSS-mono-oxide and NixantPOSS-di-oxide. The oxidation of the phosphines happened because the sample was not prepared under inert conditions, not analysed until 7 days after preparation and while being stored at room temperature. Clearly, NixantPOSS is prone to oxidation when in solution, even at room temperature. In the MALDI-MS spectra there are a few peaks coming above the already identified product peaks, those peaks can also be assigned to be products but come at a higher m/z due to the presence of K^+ . The slightly larger ion clusters at 1605.41 m/z and 1620.40 m/z are possibly the species presented in Figure 5-11 below but no further evidence exist other than that they have masses that matches those of the ion peaks in the MALDI-MS.

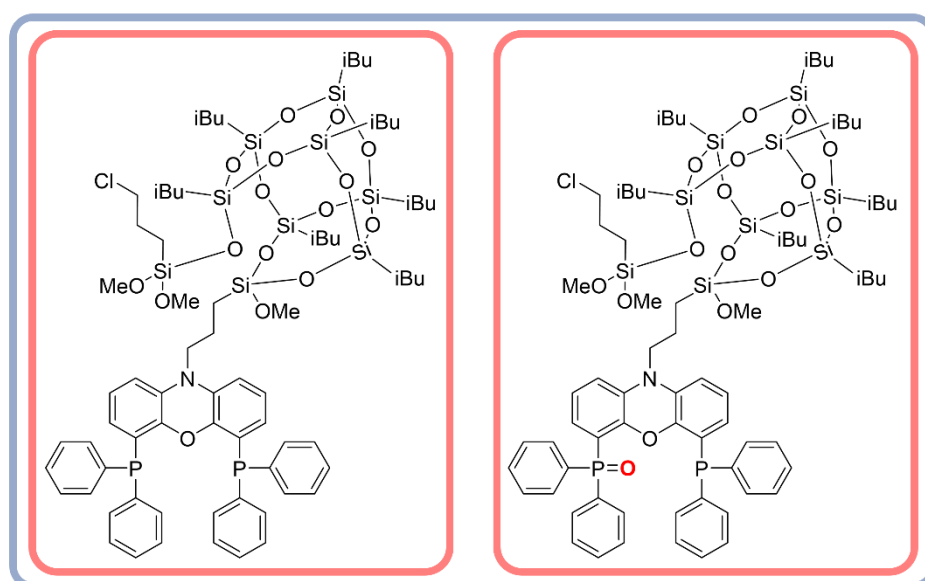


Figure 5-11: Potential by-products associated with ion peaks in the MALDI-MS spectrum.

The existence of these suggested by-products would have their origin in the corner-capping reaction between (iBu)₇POSS-trisilanol and 3-chloro-propyl-trimethoxysilane for the preparation of the 3-chloro-propyl-POSS (section 5.3.4.). It is suggested that the corner-cap reaction was at times in the reaction mixture slightly imbalanced whereupon two methoxysilane molecules reacted with one POSS-trisilanol molecule, resulting in a product with two chloro-propyl parts and one POSS cage. Despite the presence of these ion signals in the MALDI-MS spectra, the largest ion signals are those of the desired product. Furthermore, MALDI-MS is not a quantitative technique but rather a qualitative. Hence, the application of this ligand in catalysis and membrane nanofiltration rejection experiments was followed.

5.3.8. Solubility of NixantPOSS

The Xantphos-type ligands are known to have limited solubility in many of the solvents typically used in hydroformylation processes (toluene, pure substrate, product aldehyde) and have strictly limited solubility in ethers, ketones and/or condensation products of the aldehydes that can form during hydroformylation process.^[380] A low ligand solubility can therefore set limits upon production intensification efforts. It was estimated by van Leeuwen et al. that a minimum solubility of 58 mmol/L is required for large-scale application of Xantphos-type ligands in hydroformylation.^[380] With the introduction of a (iBu)₇POSS cage onto a molecule it is common that the overall solubility in nonpolar solvents will significantly increase, a feature that adds great value to this new ligand. Therefore, the solubility of Nixantphos and NixantPOSS in toluene was compared, the results of which are presented in Figure 5-12 below.

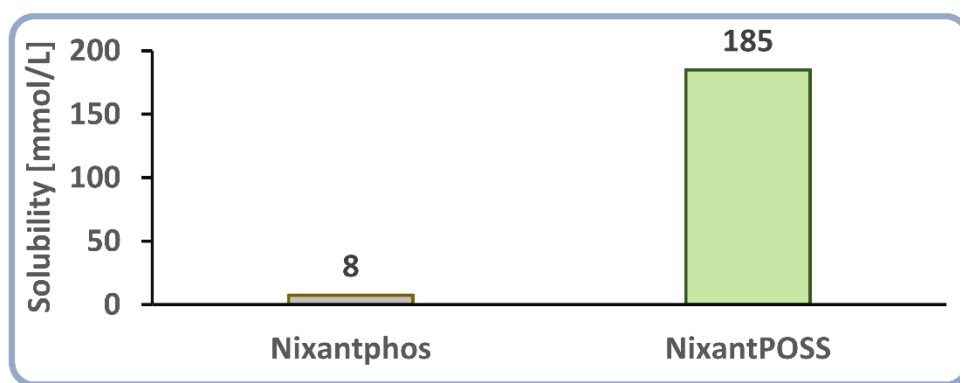


Figure 5-12: The solubility of Nixantphos and NixantPOSS in toluene measured at room temperature (ca 20°C).

The introduction of the (iBu)₇POSS cage into Nixantphos increased the ligand's solubility in toluene by almost 25 times to 185 mmol/L at 20°C, significantly beyond the threshold of 58 mmol/L. The solubility of NixantPOSS in toluene was comparable to the better ones in a set of phenoxaphosphino-modified Xantphos-type ligands synthesised by van Leeuwen et al. (60 –

500 mmol/L).^[380] The increase in solubility that (iBu)₇POSS brings about can be rationalised by the sterically bulky iBu-groups on the POSS cage. These introduce steric repulsion that interferes with the π - π stacking interactions between the aromatic parts of the ligand. The iBu-groups also represent many possible conformations, adding to the configurational entropy of the system. Furthermore, the solubility of NixantPOSS in a selection of other solvents was also investigated, two different concentrations were investigated (2 and 0.2 mmol/L) at two different temperatures (20 and 100°C). The higher concentration of 2 mmol/L was chosen as this is in the ligand concentration range of many hydroformylation protocols. The experiments were performed in (high) pressure glass vessels with Teflon screw cap lids and solubility was assessed by visual inspection. The results from these experiments are presented in Table 7 below.

Table 7: Solubility of NixantPOSS in different solvents assessed by visual inspection.

Solvent	c = 2 mmol/L		c = 0.2 mmol/L	
	20°C	100°C	20°C	100°C
Methanol	✗	✗	✗	✗
Acetonitrile	✗	✗	✗	✗
Dimethylformamide	✗	✓	✗	✓
Ethanol	✗	✓	✗	✓
Iso-propanol	✗	✓	✗	✓
Butanol	✗	✓	✗	✓
Chloroform	✓	✓	✓	✓
Dichloromethane	✓	✓	✓	✓
Tetrahydrofuran	✓	✓	✓	✓
Toluene	✓	✓	✓	✓
Cyclohexane	✓	✓	✓	✓

NixantPOSS is soluble in all medium to non-polar solvents at both high and lower concentrations at room temperature. The more **polar** solvents did not dissolve NixantPOSS very well at room temperature but did so at elevated temperature. Only acetonitrile and methanol were completely unable to dissolve NixantPOSS at either concentration even at an elevated temperature.

5.3.9. Rh-Catalysed Hydroformylation of 1-octene in Batch Autoclaves

The NixantPOSS ligand was investigated for its catalytic properties (activity and selectivity) and compared with its unmodified mother-ligand Nixantphos as well as the classical Xantphos ligand in Rh-catalysed hydroformylation of 1-octene. In hydroformylation the ligand will be exposed to challenging reaction conditions (20 bar CO:H₂ = 1:1, 90°C) and will give a good first indication if the MWE-approach has potential. The 1-octene substrate is a good model compound to represent medium long-chained alkenes. The batch autoclave reactions were

performed in stainless steel autoclaves described in section E.4. on page XI. Samples were taken from the reaction mixture at regular intervals in the beginning of the reaction so that the turnover frequency could be determined. The reactions were then left to react overnight until completion, and final samples were collected before shutdown (~1400 min). The reaction profile showing the production of the desired linear aldehyde over time is presented in Figure 5-13 below.

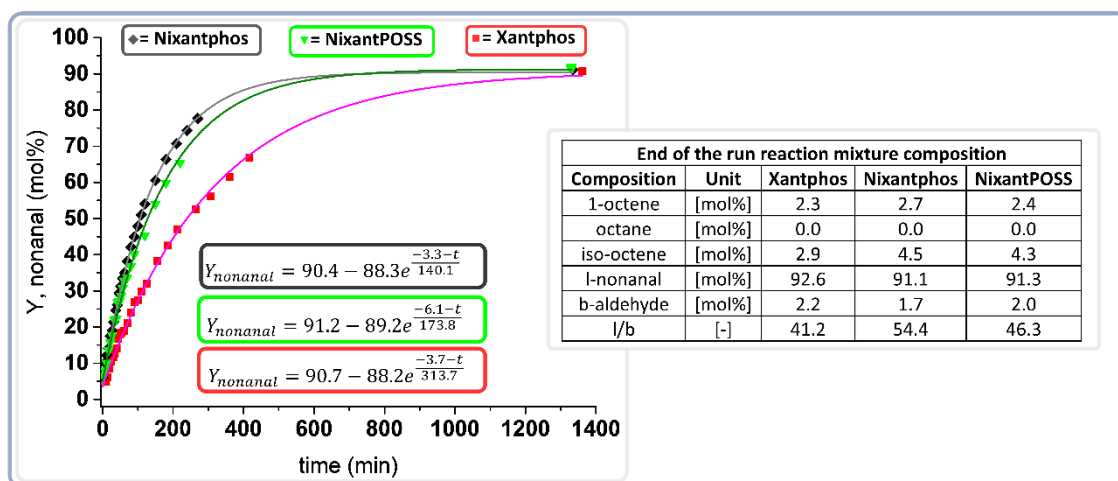


Figure 5-13: Rh-catalysed hydroformylation of 1-octene in batch autoclave reactions. Conditions: 20 bar synthesis gas ($\text{CO}:\text{H}_2 = 1:1$), 90°C , Toluene (43 mL), 1-octene (116 mmol), $\text{Rh}(\text{acac})(\text{CO})_2$ (0.029 mmol), Ligand (0.145 mmol). Rh:L:S = 1:5:4000. Samples were analysed by GC-FID using the method of internal standard (IS = dodecane). Left side: Reaction profiles of Y_{nonanal} (mol%) vs. time with fitted functions with the general formula: $Y = Y_0 + A_1 e^{-(x-x_0)/t_1}$; Right side: End of the reaction ($t = 1400$ min) mixture composition.

To each reaction profile was an exponential function fitted, which is also displayed within the left figure. The overall results are that Nixantphos is a considerably more active ligand than Xantphos while NixantPOSS is only slightly less active than Nixantphos. The end-of-the-run ($t \sim 1400$ min) reaction mixture composition of all three experiments is presented in the table that is part of Figure 5-13 above. All three ligands showed typical conversion and selectivity towards the linear nonanal that is expected from Xantphos-type ligands with l/b ratios between 40 – 60. Both Nixantphos and NixantPOSS showed a slightly higher degree of isomerisation than Xantphos, while the amount of hydrogenation product octane was almost not detected. Thus, the POSS-modification of Nixantphos resulted in a very small reduction in activity and no significant change in selectivity. To get numerical information about activity, the TOF of the ligands was calculated based on the derivatives of the fitted exponential functions. The TOF of the ligands as a function of yield of l-nonanal is presented in a graph and a table included in Figure 5-14 below.

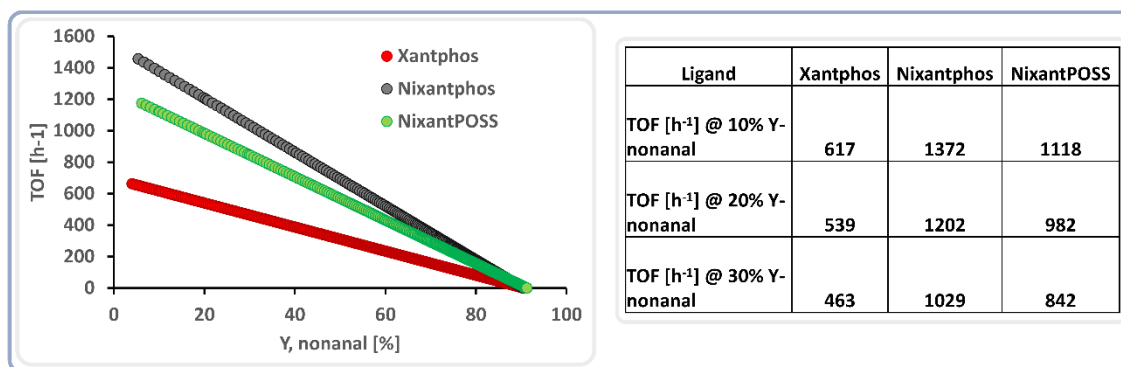


Figure 5-14: TOF as a function of Y_{aldehyde} for the three ligands Xantphos, Nixantphos and NixantPOSS. For the Rh-catalysed hydroformylation of 1-octene.

Although the TOF of NixantPOSS is 18% lower than that of Nixantphos, it is still 81% more active than Xantphos, and overall, one of the lowest reductions in activity for a MWE ligand applied in Rh-catalysed hydroformylation. The selectivity of NixantPOSS remained unchanged from Nixantphos. It is important to compare the results of NixantPOSS with those of the POSS-modified Xantphos ligand (XantPOSS) reported by Vogt et al. (shown in Figure 2-18e. The XantPOSS ligand showed an almost 38% reduction in TOF compared to its unmodified Xantphos ligand when applied in Rh-catalysed hydroformylation. The POSS cages of XantPOSS were grafted very close to the active site of the catalyst, but it also had four of them, while NixantPOSS has only been grafted with one POSS cage.

5.3.10. Continuous Hydroformylation in Ceramic Membrane Loop Reactor

The ceramic membrane loop reactor that was used in these experiments is described in the supporting information, page XII, section E.5. Initial work with the loop reactor was done with Xantphos to provide a benchmark for the rejection of an unmodified Xantphos-type ligand. A set of rejection experiments of Xantphos dissolved in only toluene were performed, where either temperature or cross-membrane pressure was changed between each experiment. The results from those experiments are presented in Figure 5-15 below.

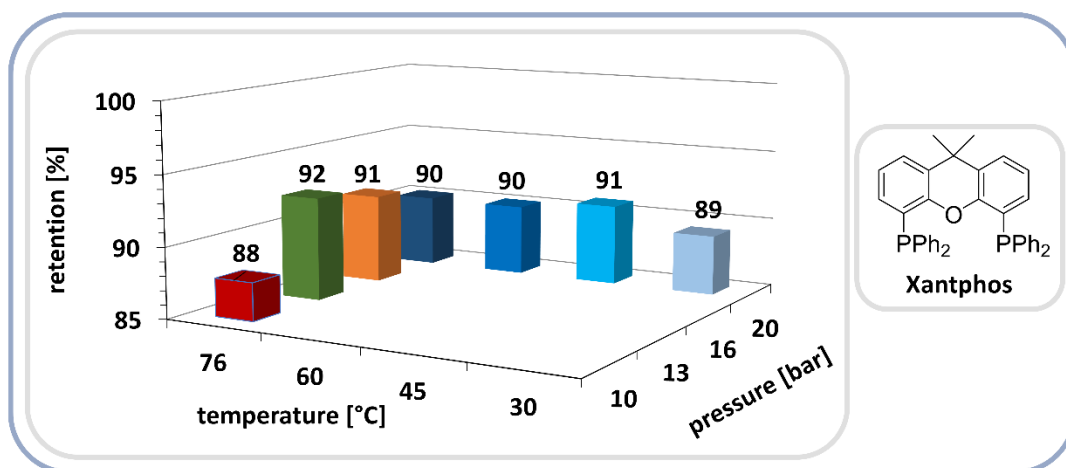


Figure 5-15: The rejection of Xantphos in toluene by a 450 Da MWCO ceramic nanofiltration membrane. The ceramic nanofiltration membranes was purchased from Inopor GmbH Germany. It had a pore size of 0.9 nm and a MWCO = 450 Da (www.inopor.com).

There was no measurable effect on rejection by changing the temperature or the cross-membrane pressure. The rejection was in all experiments measured to be between 88% - 92% which is slightly less than what Dreimann et al. determined in rejection of Xantphos by a polymeric nanofiltration membrane ($R_P = 95\%$), although those results were from a hydroformylation reaction mixture. After the rejection studies of Xantphos in toluene, the full catalytic hydroformylation system was applied in the loop reactor. During the continuous flow experiment, samples were taken from the permeate stream at regular intervals and analysed by GC-FID. The results of this initial continuously operated Rh/Xantphos-catalysed hydroformylation of 1-octene experiment is presented in Figure 5-16 below.

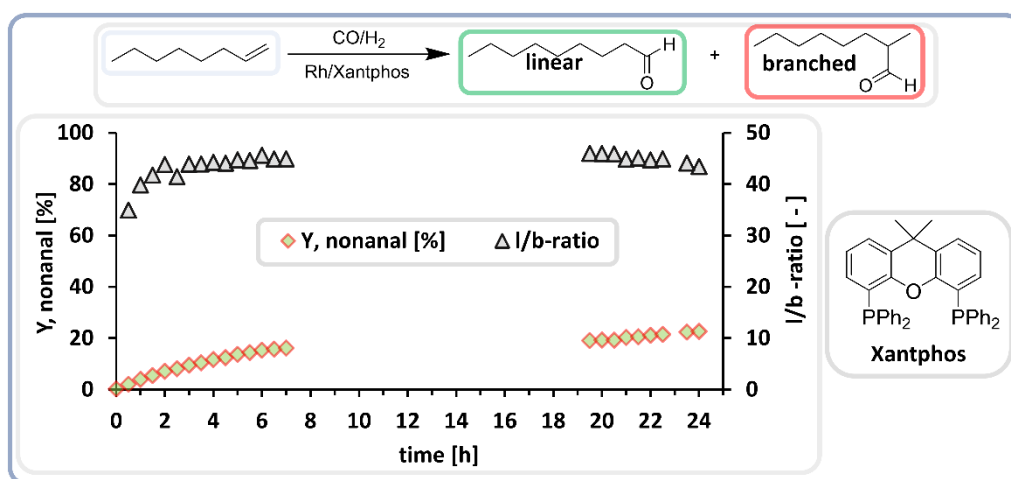


Figure 5-16: Continuous Rh/Xantphos-catalysed hydroformylation of 1-octene. Performed in a continuous flow ceramic OSN membrane loop reactor. Conditions: 80 °C and 20 bar ($\text{CO}:\text{H}_2 = 1:1$), substrate: 1.92 M 1-octene in toluene, catalyst: $M:L = 1:2$, $\text{Rh}(\text{acac})(\text{CO})_2$ (30 mg, 0.116 mmol) with Xantphos (134.24 mg, 0.232 mmol), started reaction after reaching steady membrane permeation, experiment time: 24 h. The ceramic nanofiltration membranes was purchased from Inopor GmbH Germany. It had a pore size of 0.9 nm and a MWCO = 450 Da (www.inopor.com).

The continuous Rh/Xantphos-catalysed hydroformylation of 1-octene system was stable throughout the 24 h it was operated, during which time 1.4 reactor volumes of product solution had permeated through the membrane. This was not enough time for the system to reach steady-state operation. However, the continuously high l/b ratio of the product aldehydes permeating the membrane attest that the methodology used for preparing the reactor with catalyst and substrate solutions was adequate. After the experiment, the rejection of P and Rh was measured using ICP-OES on the concentrated permeate solution. The results are presented in Figure 5-17 below.

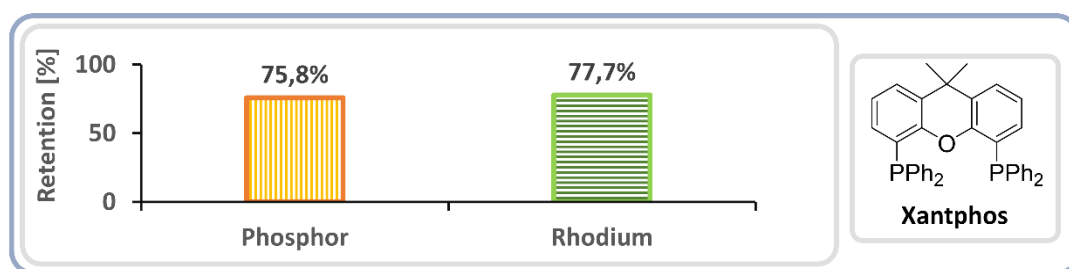


Figure 5-17: The rejection of Rh and P from the continuous Rh/Xantphos experiment.

Performed in a ceramic nanofiltration membrane loop reactor. The ceramic nanofiltration membranes was purchased from Inopor GmbH Germany. It had a pore size of 0.9 nm and a MWCO = 450 Da (www.inopor.com).

The rejection of Xantphos and Rh by the ceramic nanofiltration membrane during continuous hydroformylation was very low, compared to the rejection experiments constituting only Xantphos in toluene. It is known that the rejection of solutes can vary greatly when changing the composition of the solution, adding new solutes, changing the membrane. Making such changes can have a large effect on how the components (solvent, membrane and solute) will interact with each other and therefore how well certain solutes will be rejected by a membrane, see Figure 2-36 for an illustrative example. It is clearly not enough to study the rejection of a solute in a simplified system and expect that the rejection results will hold true in the full catalytic system. When it was time to study the rejection of NixantPOSS, the full hydroformylation system was applied directly. The results of this experiment are presented in Figure 5-18 below.

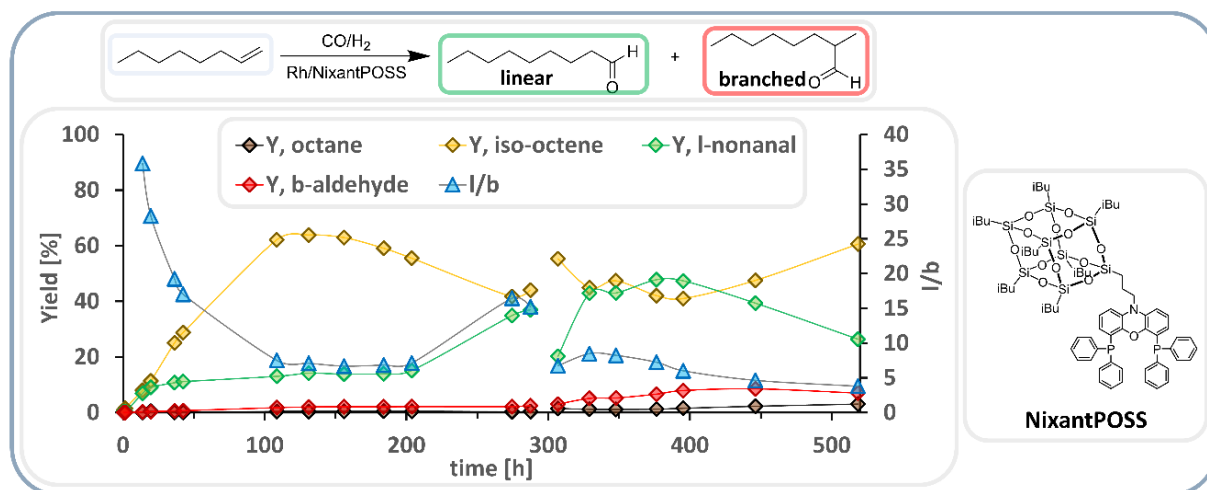


Figure 5-18: Continuous Rh/NixantPOSS hydroformylation of 1-octene.

Performed in a continuous OSN loop reactor fitted with a ceramic nanofiltration membrane (MWCO = 450 Da, inopor). Conditions: Rh(acac)(CO)₂ (15 mg, 0.058 mmol), NixantPOSS (326 mg, 0.232 mmol), 1.6M 1-octene in toluene substrate solution; Reactor volume = 220 ml; S:Rh:L = 6000:1:5; 90°C, 20 bar syngas (CO:H₂ = 1:1). The ceramic nanofiltration membranes was purchased from Inopor GmbH Germany. It had a pore size of 0.9 nm and a MWCO = 450 Da (www.inopor.com).

A total of 4.2 reactor volumes were permeated through the membrane during this continuous experiment. The system never reached any stable steady state in terms of conversion where all reaction mixture components were at stable levels. The yield of iso-octene was consistently very high and fluctuating, always above 40% after 100 h of operation. The yield of nonanal was on the other hand consistently very low, although it was arguably stable at 10-14% up until 200 h of operation. The yield of branched aldehydes was at a satisfying low level until 288 h (2.5 reactor volumes), where the reactor was shut down and degassed due to maintenance work of the surrounding lab infrastructure. The reactor was left with a blanket of argon for 19 h until it could be re-pressurised with synthesis gas and heated up again, $t = 307$ h. After the re-start, the yield of both branched and linear aldehydes initially increased, but the yield of linear aldehyde soon started to drop. The overall effect upon the l/b ratio was a steady decline and the last sample taken at $t = 518$ h had a $l/b = 3.8$. A possible explanation for the low hydroformylation activity and the high isomerisation activity is that the loop reactor had issues with the gas/liquid mixing and insufficient amount of synthesis gas was able to dissolve into the liquid phase. In the catalytic cycle (see Figure 2-9 on page 13) the Rh-complex faces a competition between CO association (leading to hydroformylation) and β -hydrogen abstraction (leading to isomerisation). A low CO concentration thus favours isomerisation, which is well known for hydroformylation reactions. The continuous Rh/Xantphos hydroformylation experiment was conducted at an early stage in the work with the loop reactor. After the Xantphos experiments, a set of Rh/Biphephos experiments were then conducted in the loop

reactor (see Chapter 6: section 6.3.2.) before the experiment with the NixantPOSS. It is believed that the Biphephos/Rh experiments resulted in deposits inside the loop reactor that caused restrictions to the passage of liquid through a nozzle that is responsible for gas/liquid mixing. The last continuous Rh/Biphephos hydroformylation experiment conducted in the loop reactor produced very similar results to the continuous Rh/NixantPOSS hydroformylation experiment presented above with a very low hydroformylation activity, albeit a high isomerisation activity that is expected for Biphephos. The total amount of collected permeate from the continuous Rh/NixantPOSS experiment was concentrated and analysed by ICP-OES to determine the membrane rejection of Rh and P which is presented in Figure 5-19 below.

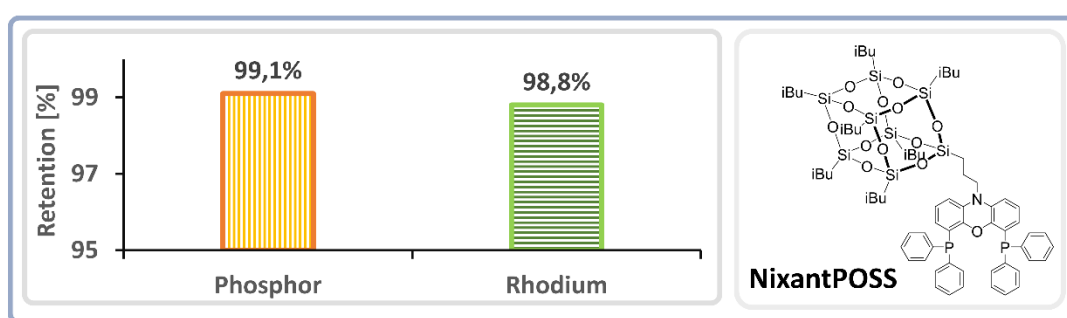


Figure 5-19: The rejection of Rh and P from the continuous Rh/NixantPOSS experiment. Performed in a ceramic nanofiltration membrane loop reactor. Membrane: inopor 450.

These results suggest a high rejection of close to 99% for both Rh and P. The mass balance of P and Rh introduced to the reactor vs. what was possible to be accounted for at the end of the experiment matched. Overall, the continuous flow hydroformylation experiment in the ceramic nanofiltration membrane loop reactor for the Rh-NixantPOSS system provided ambiguous results. The system showed a very low hydroformylation activity and a very high isomerisation activity, two factors that are indicative of insufficient CO solvation in the reaction mixture. The initial l/b ratio of around 20 was acceptable but no way near what was measured in the batch autoclave experiments. After the re-start-up at $t = 307$ h the system started to produce larger quantities of the branched aldehyde. During the shutdown period (lasting 19 h) the reactor was released of its synthesis gas pressure and kept with an atmosphere of argon. It is possible that this caused larger quantities of Rh-clusters (see Figure 2-6 on page 10) to form during this period without any protective CO-blanket. Rh-clusters can be active but unselective in hydroformylation^[381]. It is also possible that the NixantPOSS ligands inside the reactor got oxidised over time and that the methodology for preparing and operating the reactor under inert conditions was compromised. Despite the disappointing continuous catalytic results, the

rejection results for both Rh and P were close to 99%, which is a significant improvement for Xantphos-type ligands.

5.4. Conclusions and Outlook

Two different MWE Xantphos-type ligands were attempted to be synthesised, XantPOSS-2 and NixantPOSS. The XantPOSS-2 ligand was never successfully synthesised due to issues with a hydrosilylation reaction, and thus a very limited access to the following intermediate to work with for the final reaction steps of the synthesis. Another negative point of XantPOSS-2 is the number of synthetic steps involved in the synthesis. The ligand Nixantphos was on the other hand successfully MWE with a POSS synthon in a simple one pot reaction using standard reagents, yielding NixantPOSS in 94% isolated yield. This new ligand was characterised by NMR and MALDI-MS. The solubility in nonpolar solvents was excellent while it was also soluble in many other slightly more polar solvents. Nixantphos was more than twice as active as Xantphos in Rh-catalysed hydroformylation of 1-octene performed in batch autoclave reactors. NixantPOSS showed the same selectivity as Nixantphos and only an 18% reduction in TOF as compared to Nixantphos. This is supporting the idea that MWE in the rear of the ligand backbone is a suitable approach. The application of NixantPOSS in a continuous ceramic nanofiltration membrane loop reactor did not give reliable results. It is suggested that the reactor was unable to properly provide the necessary gas-liquid mixing. Nevertheless, the ceramic membrane gave a 99% rejection of both P and Rh after permeating 4.2 reactor volumes. This can be compared with the rejection results from the continuous hydroformylation with Rh/Xantphos that resulted in 76% for P and 78% for Rh. Hence, (iBu)₇POSS was an excellent MWE-unit as it significantly increases the size and rejection of this type of ligand, it was easily installed on Nixantphos, it enhanced the ligand solubility, it did not influence the ligands selectivity and caused only a smaller reduction in the catalytic activity. Nevertheless, the rejection by a ceramic nanofiltration membrane and application of the ligand in continuous catalytic systems must be further investigated as the loop reactor setup used within this work is suspected to have been compromised to an unknown extent and thus was not fully operational as intended.

Suggestions for future developments: Here follows some suggestions for potential future exploration related to the material presented within this chapter.

More polar solvent system: To further enhance the rejection of NixantPOSS by a polar ceramic nanofiltration membrane it is worth investigating the use of more polar solvents and/or solvent mixtures. This approach is based upon the assumption that NixantPOSS mainly

permeates a ceramic nanofiltration membrane via the diffusion mechanism. Using a solvent system that has a stronger affinity and interaction with the membrane could therefore help interfere with the NixantPOSS-membrane interaction, and therefore increase its rejection. This was illustrated in Figure 2-36 and in Figure 2-37.

Two step synthesis: POSS-modification could also start at the very cheap and readily available 10-H-phenoxazine backbone. After MWE at the secondary amine, the backbone is lithiated and reacted with the diphenyl-chlorophosphine. This route of synthesis has been presented in Figure 5-20 below.

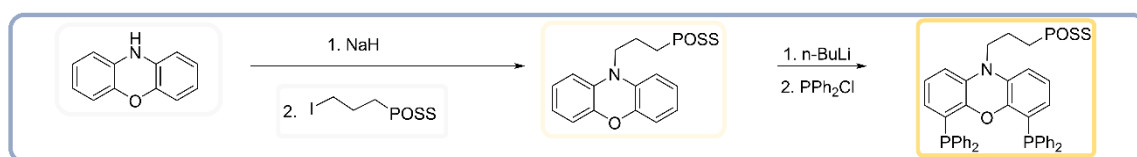


Figure 5-20: Potential two step synthetic route to access NixantPOSS (excluding synthetic steps necessary to prepare POSS synthon).

Xantphos-polymer: An intermediate in the synthetic scheme towards XantPOSS-2 named Di-vinyl-xanthene (DVX) is susceptible to polymerisation. It is here suggested that DVX can be selectively polymerised and incorporated into polymers, then lithiated and reacted with appropriate phosphine chloride to produce polymer-incorporated Xantphos ligands, see Figure 5-21 below.

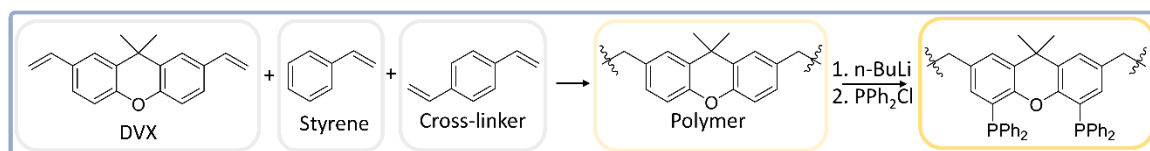


Figure 5-21: Potential synthesis of a polymer bound Xantphos ligand.

POSS-modified BINAP: BINAP is one of the most successful known ligands, being chiral and highly useful ligand for asymmetric catalysis^[382]. Below is presented a suggested POSS-modified BINAP ligand, the majority of the synthesis is based on already published synthetic procedures applied in the synthesis of a polymer bound BINAP ligand^[383].

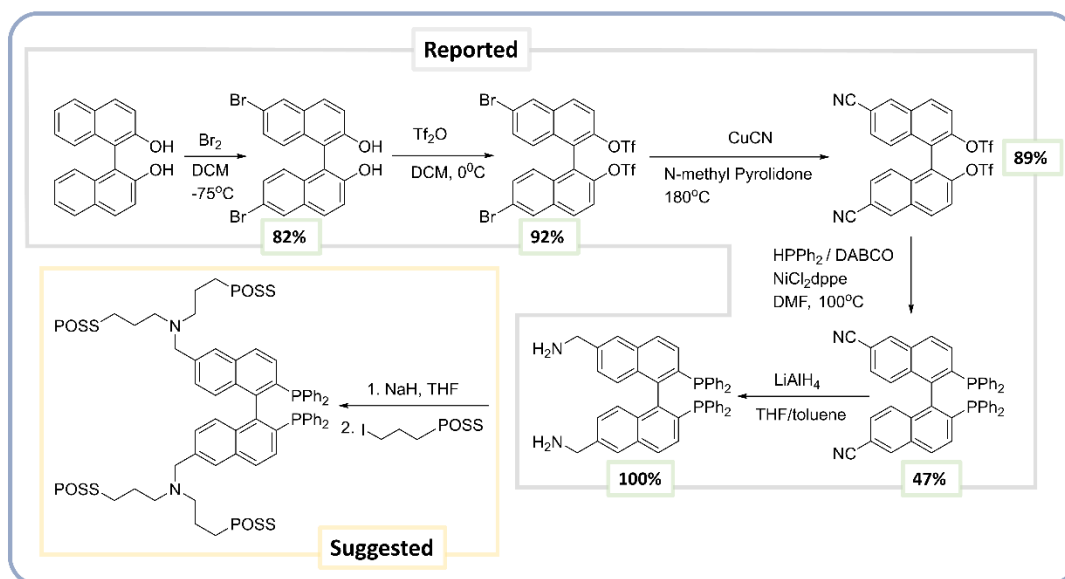


Figure 5-22: Potential synthesis of a POSS-modified BINAP ligand.

The above suggestion is only one of many potential pathways available for installation of POSS onto BINAP, much more inspiration for potential synthetic approaches can be found in a review article.^[382]

The suggestions made above are only a representation of a few potential ways that POSS could be introduced to a Xantphos-type ligand. It is important to keep in mind that the potential for success is higher for synthetic routes that contain fewer steps, are high yielding, use cheap chemicals and reactants and are easy to perform.

5.5. Experimental

5.5.1. Materials

Chemicals used in the reaction were purchased from abcr, Acros Chemicals, deuteron, Hybrid Plastics, Fisher Chemicals, Merck, Sigma Aldrich, Umicore or VWR. Solvents used in the reactions were dried by activated molecular sieves and then degassed in an ultrasonic bath while bubbling argon for 45 minutes. The tetrahydrofuran (THF) used for the ligand synthesis was dried and degassed by distilling it over sodium and benzophenone. 1-octene used in Rh-catalysed hydroformylation was run through a plug of aluminium oxide to remove peroxides.

5.5.2. Setup

See section E. on page X for details about the setup (autoclave and ceramic membrane loop reactor)

5.5.3. Analytical methods

NMR: Measured using Bruker AV Avance III HD (400MHz or 600 MHz). The relative uncertainty for reported molar ratios is estimated at $\pm 5\%$ for ^1H -NMR and $\pm 10\%$ for ^{31}P -NMR.

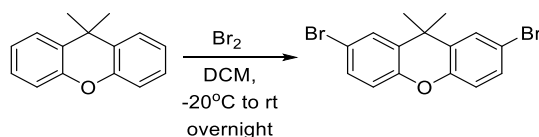
GC-FID: Measured on an Agilent Technologies 7890A GC System. Quantitative analysis of reaction mixtures was performed via GC-FID using dodecane as an internal standard to account for injection volume variances and detector drift. Response factors were determined using five-point calibration curves ($R^2 > 0.999$). Based on the precision of the autosampler and the reproducibility of sample preparation, the relative standard deviation (RSD) for conversions and yields is estimated at $\pm 2.5\%$. For instance, a reported conversion of 95% carries a trustiness region of approximately ± 2.4 percentage points. This level of uncertainty is considered standard for the evaluation of kinetic trends in homogeneous catalysis. See section E. on page X for details about the GC methodology.

ICP-OES: The results of the samples for retention were determined with an ICP-OES of type iris intrepid ICP from Thermos Elemental with a radial and axial evaluation. The full amount of permeate and retentate were concentrated on a rotary evaporator prior to sample preparation for the ICP-OES measurement. For membrane retention values (e.g., reported as 99%), the uncertainty was minimized by concentrating permeate samples to ensure metal content remained significantly above the Limit of Quantification (LOQ). Based on the propagation of a conservative 5% relative standard deviation (RSD) for ICP-OES sample preparation and analysis, the absolute uncertainty for a 99% retention value is estimated to be approximately $\pm 0.1\%$. See section E. on page X for details about ICP sample preparation methodology.

Melting points (T_{melt}): Measured with “BÜCHI melting Point B-450”.

5.5.4. Synthesis of Compounds

Synthesis of 2,7-dibromo-9,9-dimethylxanthene



9,9'-Di-methylxanthene (48 mmol, 10 g) was dissolved in dichloromethane (100 mL) and cooled to -20°C before bromine (2.8 equiv., 3.5 mL, 67 mmol) was added all at once using a measuring cylinder. The solution was then allowed to come to room temperature and was stirred overnight. The excess bromine was quenched by addition of a saturated aqueous sodium sulphite solution (80 mL) and the organic layer was extracted. The aqueous layer was further

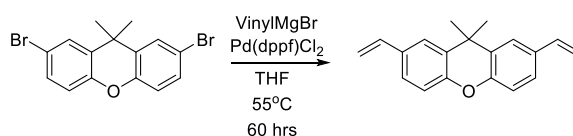
washed with dichloromethane and all the organic layers were collected and dried over magnesium sulphate. The drying agent was then filtered off and the solvents were removed in vacuum. The crude product was purified in a short silica/cyclohexane column using only cyclohexane as solvent. Yield 96%.

^1H NMR (601 MHz, Chloroform-*d*) δ 7.46 (dd, J = 7.8, 1.6 Hz, 2H), 7.24 (ddd, J = 8.2, 7.3, 1.6 Hz, 2H), 7.15 – 7.06 (m, 4H), 1.68 (s, 6H).

^{13}C -{ ^1H } NMR (CDCl_3 , 100 MHz): δ 149.1 (s), 131.5 (s), 130.7 (s), 129.0 (s), 118.2 (s), 115.8 (s), 34.6 (s), 32.2 (s).

T_{melt} : 96-98 °C

Synthesis of 2,7-divinyl-9,9-dimethylxanthene

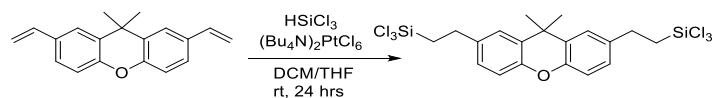


2,7-dibromo-9,9-dimethylxanthene (6.1 g, 16.7 mmol) and Pd(dppf)Cl₂ (160 mg, 0.22 mmol) was placed in a dry 1L Schlenk-flask containing a stirrer bar. The flask was evacuated and filled with argon three times. THF (400 ml, freshly distilled from Na/benzophenone) was added to the flask to dissolve the material. VinylMgBr (50 ml 1 M in THF, 50 mmol) was added to the solution while stirring at room temperature resulting in a deep blood-red solution. The reaction mixture was heated to 55°C for 60 h, after which full conversion had been achieved according to GC-MS (reaction mixture had now a deep orange/yellow colour). The reaction mixture was added to 600 ml cyclohexane and 1 ml of water to quench. The combined mixture was filtered through a 3 cm plug of celite and washed with cyclohexane, the collected filtrate was concentrated on a rotary evaporator to roughly 300 ml at which point more precipitate had formed. The mixture was filtered through a 1-2 cm plug of celite and washed with cyclohexane. The collected filtrate was concentrated on a rotary evaporator down to 10 ml. The remaining solution was left to evaporate overnight resulting in the product forming long white needle like crystals. Yield 80-95%.

^1H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.37 (m, 2H), 7.29 (ddd, J = 8.4, 2.1, 0.5 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.70 (dd, J = 17.6, 10.9 Hz, 2H), 5.66 (dd, J = 17.6, 0.9 Hz, 2H), 5.18 (dd, J = 10.9, 0.9 Hz, 2H), 1.65 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 149.91, 136.34, 132.74, 129.69, 124.99, 124.43, 116.51, 112.19, 33.97, 32.50.

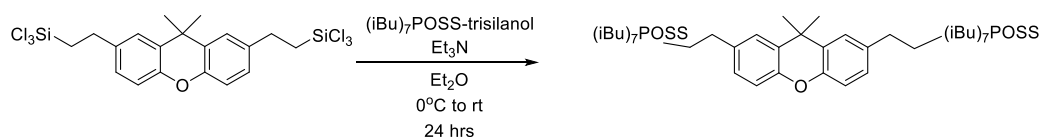
Synthesis of 2,7-diethyltrichlorosilane-9,9-dimethylxanthene



DVX (1 g, 3.8 mmol) was placed in a heat-gun dried, argon-filled Schlenk flask fitted with a rubber septum Schott screw-cap. The flask was evacuated and refilled with argon. DCM (dry, 30 ml) and Et₂O (dry, 20 ml) were added to dissolve the DVX. (Bu₄N)₂PtCl₆ (0.05 M in DCM, 0.2 ml to give 500 ppm Pt to DVX) was added to the solution and finally HSiCl₃ (2 ml, 19.8 mmol) was added to the reaction mixture. Under a steady slow flow of argon, the screw cap was exchanged for a CaCl₂ drying tube, the argon flow was then stopped, and the reaction mixture was left to stir at room temperature for 24 h. A sample was then taken and analysed by ¹H-NMR to follow the progress of the reaction. When the reaction was complete, all the solvent and excess silane were evaporated using reduced pressure, cold traps and a lukewarm water bath. The crude product remained in the flask as slightly yellow oil and was used without further purification assuming full conversion and yield.

¹H NMR (601 MHz, Chloroform-d) δ 7.28 (s, 1H), 7.20 (d, J = 2.2 Hz, 5H), 7.00 (dd, J = 8.3, 2.2 Hz, 5H), 6.93 (d, J = 8.2 Hz, 4H), 2.90 – 2.79 (m, 9H), 1.79 – 1.68 (m, 9H), 1.59 (s, 14H). ¹³C NMR (125 MHz, Chloroform-d) δ 152.40, 135.61, 133.66, 132.53, 127.48, 124.33, 124.27, 115.57, 114.50, 35.84, 31.21. (predicted ¹³C-NMR in MestReNova)

Synthesis of 2,7-diethyl-di(iBu)₇POSS-9,9-dimethylxanthene



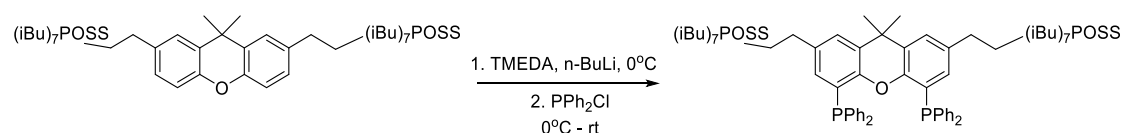
The di-silane-xanthene intermediate was dissolved in dry Et₂O (distilled from Na and benzophenone). (iBu)₇POSS-trisilanol (2.1 equivalent) was dissolved in dry Et₂O. The POSS solution was cooled to 0°C. The di-silane-xanthene solution and dry Et₃N (7 equivalents) were slowly added simultaneously to the di-silane-xanthene solution while maintaining the temperature at 0°C. After everything had been added, the reaction mixture was allowed to warm to room temperature while stirring overnight. 1 N of HCl relative to Et₃N was added to the reaction mixture together with deuterated water. The mixture was transferred to a separation funnel and the organic phase was collected. The aqueous phase was extracted twice with Et₂O. The combined organic phase was dried with MgSO₄, filtered and concentrated on the rotary evaporator. A short silica column using only cyclohexane was done.

^1H NMR (400 MHz, Chloroform- d) δ 7.22 (q, J = 2.7 Hz, 2H), 7.05 (dt, J = 6.3, 3.1 Hz, 2H), 7.01 – 6.94 (m, 2H), 2.82 – 2.64 (m, 4H), 1.90 (dq, J = 13.4, 6.7 Hz, 14H), 1.65 (s, 6H), 1.53 – 1.37 (m, 7H), 1.00 (t, J = 6.8 Hz, 88H), 0.72 – 0.60 (m, 28H).

^{13}C NMR (101 MHz, Chloroform- d) δ 148.70, 138.86, 129.75, 126.64, 125.12, 116.13, 34.07, 32.30, 28.58, 25.72, 23.89, 22.48, 14.68.

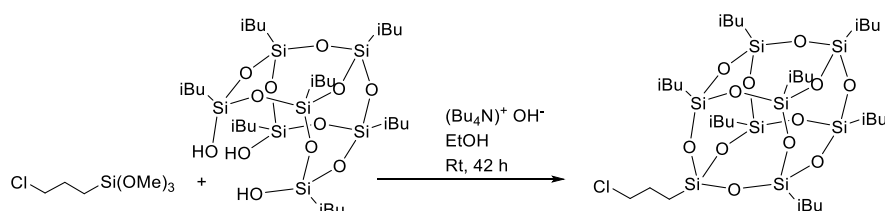
^{29}Si NMR (80 MHz, CDCl_3) δ -67.60, -67.86, -68.13.

Synthesis of XantPOSS-2



In a heat-gun dried, argon-filled Schlenk-flask containing a stirrer bar was DPX (1 g, 0.53 mmol) dissolved in 10 ml Et_2O (distilled from Na and benzophenone). TMEDA (0.2 ml, 1.38 mmol) was added at 0°C . $n\text{-BuLi}$ (1.6 M in hexane, 0.86 ml, 1.38 mmol) was then added dropwise at 0°C resulting in an intense blood-red colour of the reaction mixture to develop. After 1 hour of stirring at 0°C , a solution of ClPPh_2 in Et_2O (0.25 ml, 1.38 mmol in 2 ml Et_2O) was added dropwise resulting in the gradual shift in colour from red to orange to yellow to faint yellow. The reaction was left to warm to room temperature and stirred overnight. The reaction mixture was added to a separation funnel and an aqueous workup was performed using degassed solvents. No pure product was obtained, but it is believed that the ^{31}P -NMR of the product is either -13.99 or -16.04 ppm.

Synthesis of 3-chloro-propyl-(iBu) $_7$ POSS



In a 250 ml Schlenk flask (iBu) $_7$ POSS-trisilanol (25.2 mml, 19.94 g) was dissolved in dried ethanol (125 ml) under an argon atmosphere. 3-Chloro-propyl-trimethoxysilane (25.2 mmol, 4.68 ml) and tetrabutylammonium-hydroxide (1 M in MeOH, 0.52 mmol, 0.14 ml) were added. The white solution was stirred for 90 h while a white solid suspended. The solvent was removed and the remaining solid was washed with acetonitrile (200 ml) and then dried under vacuum.

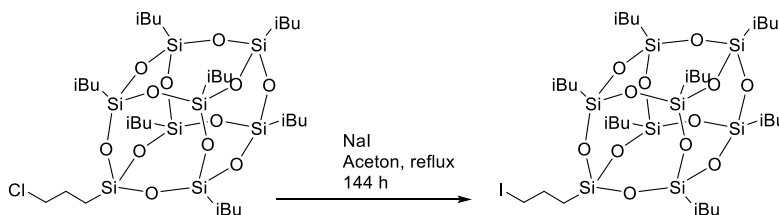
^1H NMR (400 MHz, CDCl_3) δ = 3.52 (t, J =6.9, 2H, 1), 1.96-1.76 (m, 9H, 5), 0.96 (dd, J =6.7, 1.2, 42H, 6), 0.80-0.67 (m, 2H, 2), 0.61 (dd, J =7.1, 3.2, 14H, 3;4) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 47.37 (s), 26.65 (s), 25.86 (d, J =2.7), 24.05 (d, J =3.4), 22.64 (d, J =6.1), 9.95 (s) ppm.

^{29}Si NMR (80 MHz, CDCl_3) $\delta = -67.59$ (s), -67.88 (s) ppm.

$T_{\text{melt}} = 245^\circ\text{C}$

Synthesis of 3-iodo-propyl-(iBu) $_7$ POSS



In a large 1 L round bottom flask with a stirrer bar 3-chloro-propyl-(iBu) $_7$ POSS (18.7 mmol, 16.7 g) and sodium iodide (187 mmol, 28 g) were dissolved in acetone (800 ml) and refluxed at 70°C for 144 h. A white precipitate formed through the course of the reaction. The solvent was removed under reduced pressure. The solid that remained was washed with deionized water. A white solid product remained, which was dried under vacuum. After drying an off-white solid remained, total yield was 89%.

^1H NMR (400 MHz, CDCl_3) $\delta = 3.20$ (t, $J=7.1$, 1H, 1-I), 2.03-1.72 (m, 9H, 5), 1.08-0.86 (m, 42H, 6), 0.79-0.68 (m, 2H, 2), 0.61 (dd, $J=7.0$, 3.5, 14H, 4) ppm.

^{13}C NMR (101 MHz, CDCl_3) $\delta = 47.34$ (s), 27.76 (s), 26.64 (s), 25.85 (d, $J=2.6$), 24.04 (d, $J=3.6$), 22.64 (d, $J=5.8$), 14.01 (s), 10.25 (s), 9.94 (s) ppm.

^{29}Si NMR (80 MHz, CDCl_3) $\delta = -67.59$ (s), -67.88 (s) ppm.

$T_{\text{melt}} = 241^\circ\text{C}$

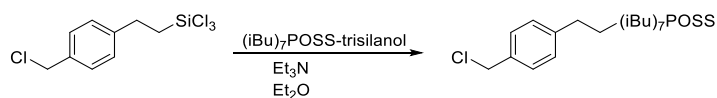
Synthesis of (4-ethyl-trichlorosilyl)benzyl chloride



$(\text{Bu}_4\text{N})_2\text{PtCl}_6$ (4.3 mg, 4.8 μmol) was added to a solution of 4-vinylbenzyl chloride (5 ml, 5.415 g, 35.48 mmol) in DCM. After stirring for 30 min, excess trichlorosilane (10 mL) was added. The reaction mixture was stirred at room temperature, and the progress is monitored by ^1H -NMR. (The reaction was complete in 18 h). The solvent and the excess trichlorosilane were removed in vacuo and the product was directly used in the (next reaction assuming full yield) of corner-capping by (iBu) $_7$ POSS-trisilanol.

^1H NMR (601 MHz, Chloroform- d) δ 7.37 (d, $J = 7.7$ Hz, 2H), 7.24 (d, $J = 7.8$ Hz, 2H), 4.61 (s, 2H), 2.98 – 2.84 (m, 2H), 1.84 – 1.73 (m, 2H).

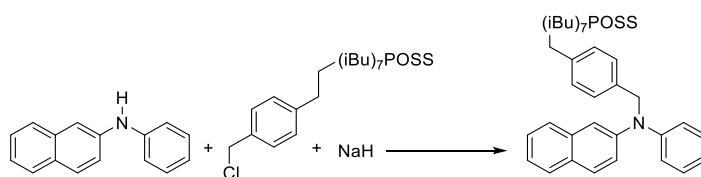
Synthesis of 4-Chloro-benzyl-ethyl(iBu) $_7$ POSS



The product 4-ethyl-trichlorosilyl benzyl chloride (35.48 mmol) still present in the previous Schlenk-flask stored under argon was dissolved in dry Et₂O. In a different flask (iBu)₇POSS-trisilanol (28 g, 35.48 mmol) was dissolved in dry Et₂O. The two solutions were combined in a larger Schlenk-flask at 0°C, after this Et₃N (30 ml, 37.7 mmol) was added dropwise. A white precipitate formed, and the reaction mixture became creamy. It stirred for 16 h after which 1 N of 1 M HCl was added to quench excess base. Aqueous workup then followed, the organic phase was evaporated and a crude white solid resulted. A short silica column using only cyclohexane and subsequent drying of the product gave a pure white solid at 90% yield based on the 4-vinylbenzyl chloride.

¹H NMR (601 MHz, Chloroform-d) δ 7.34 – 7.29 (m, 2H), 7.23 – 7.18 (m, 2H), 4.59 (s, 2H), 2.77 – 2.71 (m, 2H), 1.98 – 1.76 (m, 7H), 0.99 (dt, J = 6.6, 1.4 Hz, 44H), 0.66 – 0.59 (m, 14H).

Coupling N-Phenyl-2-naphtylamine and 4-Chloro-benzyl-ethyl(iBu)₇POSS



Sodium hydride (98 mg, 4.08 mmol) was suspended in freshly distilled THF (20 ml), the suspension was stirred for 20 min. At the same time N-Phenyl-2-naphtylamine (984 mg, 4.08 mmol) was dissolved in freshly distilled THF (20 ml). The amine solution was then transferred to the NaH suspension. The reaction mixture was stirred for 15 min at room temperature and a sample was taken and quenched in D₂O for ¹H-NMR analysis. The reaction mixture was then heated up to 65°C over two hours and then cooled down to 0°C and another sample was taken and prepared as before. A solution of 4-chloro-benzyl-ethyl(iBu)₇POSS (1906 mg, 2.17 mmol) was dissolved in freshly distilled THF (10 ml) and added to the reaction mixture which was left stirring for 1 h at 0°C. A sample was taken and prepared as before. The reaction was allowed to warm to room temperature and left stirring for 15 h after which another sample was taken and prepared as before. The reaction was then heated to 80°C for 24 h and a last sample was taken and prepared as before. The solvent was then removed under vacuum and a brown solid was received. The solid was washed with methanol multiple times until a light brown solid remained (1159 mg), 51% yield.

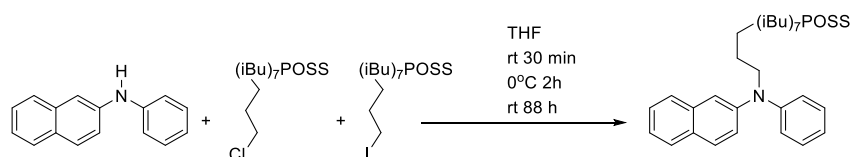
^1H NMR (400 MHz, CDCl_3) δ = 7.79-7.57 (m, 3H, 13-16), 7.37 (d, J =11.3, 2H, 10), 7.34-7.27 (m, 4H, 9;17;18), 7.25-7.09 (m, 4H 2;3;12), 6.97 (t, J =7.1, 1H, 11), 5.10 (s, 1H, 1), 4.58 (s, 1H, 1-Cl), 2.76-2.61 (m, 2H, 4), 1.86 (ddd, J =9.9, 8.3, 5.0, 7H, 7), 0.95 (dt, J =17.8, 9.0, 42H, 8), 0.71-0.47 (m, 14H, 5;6) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 148.95{142.82 (m), 135.57 (d, J =159.6), 130.14{125.93 (m), 122.28 (dd, J =148.0, 120.7), 115.74 (s), 56.41 (s), 29.25 (d, J =120.3), 25.84 (s), 24.02 (d, J =2.9), 22.61 (d, J =7.5), 14.45 (s) ppm.

^{29}Si NMR (80 MHz, CDCl_3) δ = -67.60 (s), -67.88 (s) ppm.

T_{melt} =123 °C

Synthesis of N-Phenyl-2-naphtylamine-propyl-(iBu)₇POSS



Sodium hydride (100 mg, 4.17 mmol) was suspended in THF (15 ml), the suspension was stirred for 15 min. A solution of N-phenyl-2-naphtyl-amine (820 mg, 3.74 mmol) in distilled THF (15 mL) was then added to the suspension. The mixture was stirred for 15 min and a sample was withdrawn, quenched with D_2O and submitted for ^1H -NMR analysis. The solution was cooled to 0°C and a solution containing a mix of 3-iodo-propyl-*i*Bu₇-POSS (45 %, 782 mg, 0.79 mmol) and 3-chloro-propyl-*i*Bu₇-POSS (55 %, 956 mg, 1.06 mmol) dissolved in THF (10 mL) was added. The solution was stirred for 2 h at 0°C before another sample was taken and prepared as before. The solution was warmed up to room temperature and stirred for 16 h. Another sample was then taken and prepared as before. The solution was stirred for another 72 h at room temperature before a last sample was taken and prepared as before. Workup: The solvents were evaporated under vacuum and the remaining solid was washed with methanol until a green brown sticky solid remained. The product was at this stage still very impure (purity: 40%), and a low product yield of 6%.

^1H NMR (400 MHz, CDCl_3) δ = 7.77-7.72 (m, 3H, 11;14), 7.65 (d, J =8.6, 2H, 12;13), 7.46-7.37 (m, 3H, 8), 7.35-7.27 (m, 3H, 7;17;18), 7.25-7.15 (m, 5H,), 6.98 (t, J =7.3, 2H, 7;9;10), 5.89 (s, 1H, NH), 3.83-3.75 (m, 1H, 1), 3.56-3.46 (m, 1H, 1-Cl), 2.02 (s, 4H, 5), 1.25 (d, J =5.8, 7H, 5), 1.01-0.76 (m, 42H, 6), 0.67-0.50 (m, 14H, 3;4) ppm.

^{13}C NMR (400 MHz, CDCl_3) δ = 141.00 (s), 134.76 (s), 129.57 (s), 129.32 (s), 127.78 (s), 126.60 (d, J =3.6), 123.62 (s), 121.55 (s), 120.18 (s), 118.41 (s), 111.70 (s), 29.85 (s), 25.84 (s), 24.00 (s), 22.63 (s) ppm.

^{29}Si NMR (400 MHz, CDCl_3) δ = -67.58, -67.87 ppm.

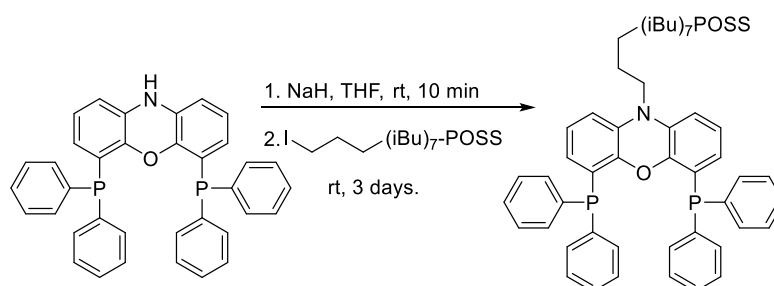
Difficulties with Deprotonation Reaction

It must be highlighted that difficulties with the deprotonation will occur when the quality of the NaH has been compromised due to insufficiently dry storage. Although the NaH might seem to be highly active at a first glance when tested with e.g. water (fizzing upon contact with water), it is possible that a significant amount of the surface of the NaH particles is covered with enough NaOH as a result of reaction with moisture to block the NaH from reacting with the protons of any dissolved amine. This was realised when an old source of NaH was used at a later stage to reproduce the deprotonation. Only after buying a new quantity of NaH the deprotonation was successfully reproduced.

Stability Test Under Hydroformylation Conditions

The POSS-modified N-phenyl-2-naphtylamine, triphenylphosphine and Rh(acac)(CO)₂ were dissolved in degassed toluene (8.5 ml). The solution was introduced against a controlled argon flow into a 15 ml pressure reactor containing a stirrer bar. The reactor was pressurised with syngas (CO:H₂ = 1:1, 20 bar) and heated to 90°C for 148 h, N = 350 rpm.

Synthesis of NixantPOSS



Nixantphos (1.93 mmol, 1063 mg), sodium hydride (7.50 mmol, 200 mg) and 3-iodo-propyl-*i*Bu₇-POSS (1.93 mmol, 1902 mg) was weighed out into an argon-filled 100 ml Schlenk flask fitted with a stirrer bar. THF (50 ml) was added to the flask making a suspension. The reaction mixture was stirred for 72 h. The solvent was removed under vacuum and the remaining solid was re-dissolved in a degassed mix of cyclohexane and toluene (1:1, 40 ml). The solution was washed with degassed water (3 x 40 ml). The phases were separated, and the organic phase was removed under vacuum giving a brown green solid (1.808 mmol, 2547 mg), 94% yield.

¹H NMR (600 MHz, CDCl₃) δ = 7.26 (s, 19H, 1;2;3), 6.70 (t, J=7.8, 1H, 4), 6.49 (d, J=7.8, 1H, 6), 6.07 (d, J=7.3, 1H, 5), 3.53 (d, J=7.7, 1H, 7), 2.39 (s, 1H), 2.01 {1.91 (m, 6H, 9;10), 1.34 (s, 2H), 1.03 (dd, J=11.7, 6.6, 42H, 12), 0.70 (d, J=6.9, 13H, 11) ppm. ¹³C NMR (151 MHz, CDCl₃) δ = 133.95 (t, J=10.8), 128.24 (dd, J=15.1, 3.9), 25.82 (d, J=3.3), 23.99 (d, J=8.3), 22.58 (d, J=5.7) ppm.

²⁹Si NMR (119 MHz, CDCl₃) δ = -67.39, -67.70 ppm.

^{31}P NMR (243 MHz, CDCl_3) $\delta = -18.98$ ppm.

$T_{\text{decompose}} = 170-190$ °C

5.5.5. Rh-catalysed hydroformylation of 1-octene

Batch autoclave Rh-Catalysed Hydroformylation

All batch autoclave experiments were conducted in autoclaves described in E.4. where also the reparation procedure of the reactors can be found. Ratio used in the reactions was Rh:L:S = 1:5:4000. One single reactor (reactor 1) was used during these experiments. The catalyst solution was prepared by weighing out both $\text{Rh}(\text{acac})(\text{CO})_2$ (7.5 mg, 0.029 mmol) and the relevant ligand (0.145 mmol) dry into a single Schlenk-flask fitted with a stirrer bar to which toluene (13 ml) was added, the solution was left to stir for about 20 min or until everything had dissolved. The catalyst solution was transferred to the pot of the reactor together with additional toluene (30 ml). 1-Octene (18.2 ml, 116 mmol) was added to the dropping funnel. After adding everything to the reactors, preformation was performed (700 rpm, 80°C at 18 bar $\text{H}_2:\text{CO} = 1:1$) for 1-2 hours. Final adjustment to the desired reaction set-points (90°C, 20 bar $\text{H}_2:\text{CO} = 1:1$, 700 rpm) were then made, 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. Samples were withdrawn from the reactors at regular intervals using the sample device. A few seconds before each sample, the pipes of the sample device were flushed by discarding a small volume of reaction mass through it. Collected samples were analysed by GC-FID using the method of internal standard (IS = dodecane). The set-points of each experiment (T, p, rpm) were kept static.

Continuous Rh-Catalysed Hydroformylation

The ceramic membrane loop reactor used in these experiments is described in E.5. The reactor was also prepared according to the procedure described in E.5. A catalyst solution was prepared by weighing out both $\text{Rh}(\text{acac})(\text{CO})_2$ (14.8 mg, 0.057 mmol) and Biphephos (226.6 mg, 0.288 mmol) dry into a single Schlenk-flask fitted with a stirrer bar to which toluene (14 ml) was added. After stirring this solution for about 30 min it was introduced into the dropping funnel of the reactor from the upper valve under a slow flow of argon. The reactor was then heated to the reaction temperature (90°C), when this had been reached the reactor was pressurised with synthesis gas ($\text{H}_2:\text{CO} = 1:1$) to 20 bar. The membrane was always free to permeate, and the permeated volume was made up by fresh substrate solution via the HPLC-pump, which was operating on feedback from the level sensor of the reactor. When the reactor had reached a steady state of permeation after reached the set reaction temperature and pressure, the valve to the dropping funnel was opened so that the catalyst solution entered the substrate solution

inside the reactor and the reaction was considered to have started ($t = 0$). Samples were taken from the permeate stream at regular intervals which were analysed by GC-FID using the method of internal standard (dodecane). The permeate was collected into a bottle standing on a balance, and the substrate was kept inside another bottle also standing on a balance. The change in mass over time of permeate and substrate was thus recorded. At the end of an experiment the total volume of all the solutions were measured separately (mass and volume). These solutions were the pre-catalyst addition permeate and the post-catalyst addition permeate. These were then concentrated down on a rotary evaporator and again measured for mass and volume. The permeate solution as well as un-altered sample from the end of the reaction reactor solution were then submitted for ICP analysis (P and Rh).

Chapter 6: Long-Term Stability of Biphephos

6.1. Abstract

Phosphite ligands can build highly active and selective homogeneous transition metal catalyst systems. It is therefore a standing desire to achieve a system where such an active and selective ligand can be straightforwardly separated and recycled in a continuous process, also for less volatile products. The idea of molecular weight enlargement to facilitate a more efficient nanofiltration separation process is a running theme in this thesis, and the idea of applying this concept onto phosphite ligands was naturally floated. However, to justify the synthesis of a MWE phosphite ligand, it would be necessary to first be able to show that such a type of ligand can be successfully applied in a continuous flow experiment. Phosphites are difficult to use in continuous processes, as they are prone to various decomposition reactions (*vide supra*). Hence, before any synthesis was to be initiated, it was decided that it would be necessary to first prove that a continuous flow system constituting phosphite ligands could be mastered and understood. To study the stability of a continuously operated phosphite system the ligand Biphephos was chosen. Biphephos is a wide bite-angle bidentate bulky phosphite ligand with good activity and high selectivity towards the linear aldehydes when applied in Rh-catalysed hydroformylation of terminal and internal alkenes. This ligand is also rather large with a molecular weight of 786 Da, which was theorised to be enough for high performance nanofiltration membranes to reject it. This chapter tells the story about the application of Rh/Biphephos as the catalyst in a continuous flow ceramic nanofiltration membrane reactor for the continuous hydroformylation of 1-octene. Initial autoclave experiments were performed to show reproducibility of already reported results and to confirm the optimal temperature setting for the reaction (90°C). Not until the system was applied in the continuous flow loop reactor the sensitive nature of Biphephos became fully clear. Biphephos is prone to hydrolyse in the presence of acids, and the hydrolysis products are phosphonic acids, which resulted in autocatalytic decomposition. Biphephos is also prone to oxidation under certain conditions. It was found in (patent) literature that various additives can act as acid scavengers and therefore stabilise the phosphites.^[162,163,165,208–214] Based on earlier reports cyclohexene oxide, Et₃N and 2,2,6,6-tetramethylpiperidine were chosen to be further investigated for their stabilising potential. The effect of these additives upon the stability of Biphephos was investigated by use of ³¹P-NMR. The best stability was achieved with a lower equivalent of additives, while higher concentrations increasingly stimulate more decomposition product formation from Biphephos.

During these investigations it was also discovered that the order in which the ligand and the metal are dissolved and mixed together had an impact upon oxidation of the phosphite ligand. Finally, it was shown that the level of inertness inside the reaction setup after it has been loaded, and before heating has been initiated, can be significantly improved by application of “pressure de-pressure” cycles using oxygen free gas.

6.2. Introduction

This chapter is part of the work towards further the use of POSS as MWE-unit for phosphite ligands. However, it is futile to try and show the benefits of a MWE phosphite ligand as compared to an unmodified ligand if the long-term stability of such a ligand cannot be controlled. Phosphite ligands are difficult to use in continuous processes, as they are prone to various decomposition reactions (*vide supra*). Hence, the main goal of this chapter is to explore, which parameters have the largest influence upon phosphite ligand's stability when exposed to reaction conditions, and how to best maintain control over those parameters. Rh/Biphephos-catalysed hydroformylation of 1-octene was chosen as the model reaction to be studied for this purpose as it allows the stability of the ligand to be indirectly interpreted from the product distribution that results from the reaction. Information about the l/b ratio is very useful as it gives indirect information about the stability of the system and when the system is about to break down. The breakdown of the system is defined as the point where the system loses its specific activity and selectivity towards the linear aldehyde product, which for Biphephos is typically l/b-ratio = 50 to 100.

6.3. Results and Discussion

Batch autoclave experiments were used to explore the effect of temperature upon the reaction and to find a suitable temperature for the consecutive work. The reaction system was then transferred into a continuous flow ceramic membrane loop reactor to study the system under more dynamic reaction conditions over a longer period. The effect of a few different parameters was investigated but very few conclusions could be made from those experiments. The system was brought back to be studied in batch autoclave reactions but again the results from changing the parameters were giving very scattered results. The stability of the Biphephos ligand was therefore thoroughly studied using ^{31}P -NMR experiments that allowed better control over conditions and parameters. A final set of batch autoclave experiments were conducted that incorporated all the findings and could successfully show that the stability of Biphephos had been brought under control.

6.3.1. Batch Autoclave Experiments – Temperature as a Variable

The first goal of this project was to make sure that results from the literature could be reproduced. An initial set of batch autoclave experiments were performed with temperature as the only variable. The conditions were standard Rh-catalysed hydroformylation conditions (75 – 110 °C, 20 bar synthesis gas $\text{CO}:\text{H}_2 = 1:1$). The autoclaves (described in section E.4.) were charged with a catalyst solution. The catalyst solution had been prepared by dissolving Biphephos and $\text{Rh}(\text{acac})(\text{CO})_2$ at the same time in the same flask. The yield of linear nonanal over time as well as the l/b over time for these experiments is presented in Figure 6-1 below.

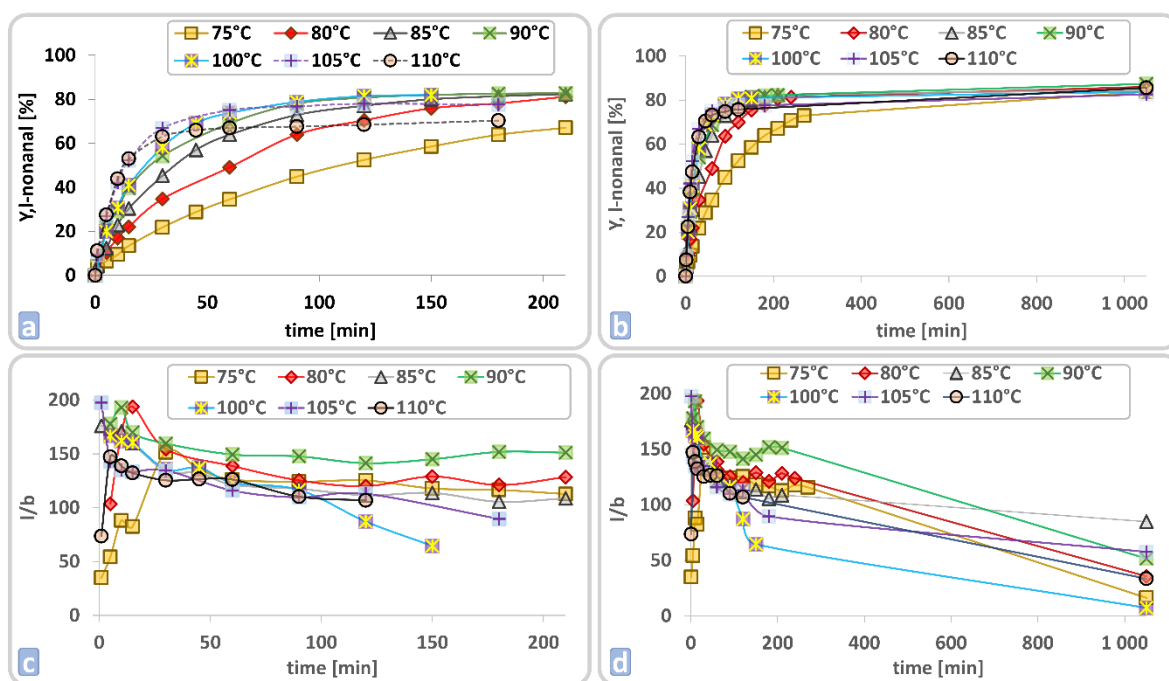


Figure 6-1: Effect of temperature in the Rh/Biphephos-catalysed hydroformylation of 1-octene. (a and b): The yield of l-nonanal over time at different temperatures. (c and d): The l/b ratio over time at different temperatures. Conditions: 90°C; 20 bar $\text{CO}:\text{H}_2 = 1:1$; 700 rpm; $\text{Rh}:\text{L}:1\text{-octene} = 1:5:6000$; $\text{Rh}(\text{acac})(\text{CO})_2$ 2.9 mg, 0.0111 mmol; Biphephos 43.8mg, 0.0557 mmol; 1-octene 10.5 ml, 67.4 mmol; solvent = toluene 41 ml; 2 h preformation (80 °C, 18 bar).

After the last samples had been taken at the day of the experiment, the reactions were left on overnight for a final sample to be taken the next day ($t = 1050$ min). The l/b ratio was seemingly a bit random and no correlation can be observed between l/b ratio and temperature. For a target yield of l-nonanal of 80% a temperature of 90 – 100°C would allow this to be reached the fastest which is consistent with the results reported by Brunsch.^[384] The reaction mixture composition at 120 min from all the experiments is presented in Table 8 below. In all experiments the yield of branched aldehyde after 120 min of reaction was less than 1% giving l/b ratios >100.

Table 8: Reaction mixture composition at 120 min in the Rh/Biphephos catalysed hydroformylation of 1-octene.

Temperature [°C]	75	80	85	90	100	105	110
Y, 1-octene [%]	20	8	4	3	2	2	2
Y, octane [%]	2	2	2	3	3	4	4
Y, iso-Octene [%]	25	19	16	14	14	16	18
Y, l-Nonanal [%]	52	70	77	80	81	78	76
Y, b-Nonanal [%]	0	<1	<1	<1	<1	<1	<1
I/b	125	120	112	141	87	113	107

Analysis by GC-FID using internal standard (dodecane). Conditions: Rh:L:1-octene = 1:5:6000. Rh(acac)(CO)₂ 2.9mg, 0.0111 mmol; Biphephos 43.8 mg, 0.0557 mmol; 1-octene 10.5 ml, 67.4 mmol; CO/H₂ = 1:1; P = 20 bar; solvent = toluene 41 ml; 2 h preformation (80 °C, 18 bar).

From the obtained results it was decided that 90°C was the most suitable temperature to use for further studies of the system in the ceramic membrane loop reactor, as this resulted in the highest yield of l-nonanal in the shortest time.

6.3.2. Continuous Flow Experiments in Ceramic Nanofiltration Membrane Loop Reactor

After the optimum temperature of 90°C was confirmed with autoclave batch experiments for the Rh/Biphephos catalysed hydroformylation of 1-octene system, it was time to test the system in the continuous flow ceramic nanofiltration membrane loop reactor, which is described in the supporting information, section E.5. . A total of 7 continuous flow experiments were performed in the loop reactor. These experiments are summarised in Table 9 below.

Table 9: Summary of the initial 7 continuous flow ceramic membrane loop reactor experiments performed.

Exp.	Purification of 1-octene	Sol. H ₂ O conc. [ppm]	Drying of Toluene	Additive	Residence time [min]	Experiment online [h]	Stable [h]
1	None	54	X	X	299	50	X
2	Percolated through Al ₂ O ₃	60	X	X	345	35	10
3	Percolated through Al ₂ O ₃	500	X	X	338	10	5
4	Percolated through Al ₂ O ₃	8	molecular sieves	X	477	12	6
5	Percolated through Al ₂ O ₃	63	X	Tinuvin 770	1280	15	9
6	Percolated through Al ₂ O ₃	64	X	Et ₃ N	313	35	10
7	Percolated through Al ₂ O ₃	66	X	CHO	338	130	X or 130

All these experiments had their catalyst solution prepared by co-dissolving the Biphephos and Rh-precursor together.

Chargin of reaction mass into the reactor was done by Schlenk-technique. CHO = cyclohexene oxide. Tinuvin® 770 = Bis(2,2,6,6-tetramethyl-4-piperidyl) sebacate. Membrane: inopor TiO₂, 450 Da MWCO.

These experiments used Rh/Biphephos catalyst solutions prepared according to what later became known as a “non-ideal” preparation method. In this, Biphephos and Rh-precursor were weighed out into the same flask and dissolved together (more about this in section 6.3.4.). Samples were taken from the permeate stream at regular intervals and analysed by GC-FID to

generate data about the permeate composition. The amount of leaching of P and Rh in the permeate was determined by ICP-OES analysis of the concentrated permeate solution and calculated against the amount of P and Rh that had been initially charged into the reactor. The reaction mixture present inside the reactor at the end of the experiment was analysed by ICP to determine the remaining quantity of P and Rh still in solution inside the reactor. This allowed a mass-balance evaluation of the total amount of P and Rh loaded to the reactor vs. the quantity of P and Rh that was possible to be accounted for via the ICP analysis of the permeate and the reactor content. The first 4 continuous experiments used no additives but investigated the effect of using non-purified vs purified substrate and if the water content had an impact upon the stability of the system. The first experiment used 1-octene taken directly from a few months old opened metal canister. The second experiment had the same 1-octene percolated through a plug of Al_2O_3 to remove impurities (e.g. peroxides). All future experiments used the purified 1-octene. The third experiment deliberately used wetted toluene and the fourth experiment used dried toluene (over molecular sieves). The permeate compositions and l/b ratio as a function of time and residence time (τ) from these first four continuous experiments are presented in Figure 6-2 below.

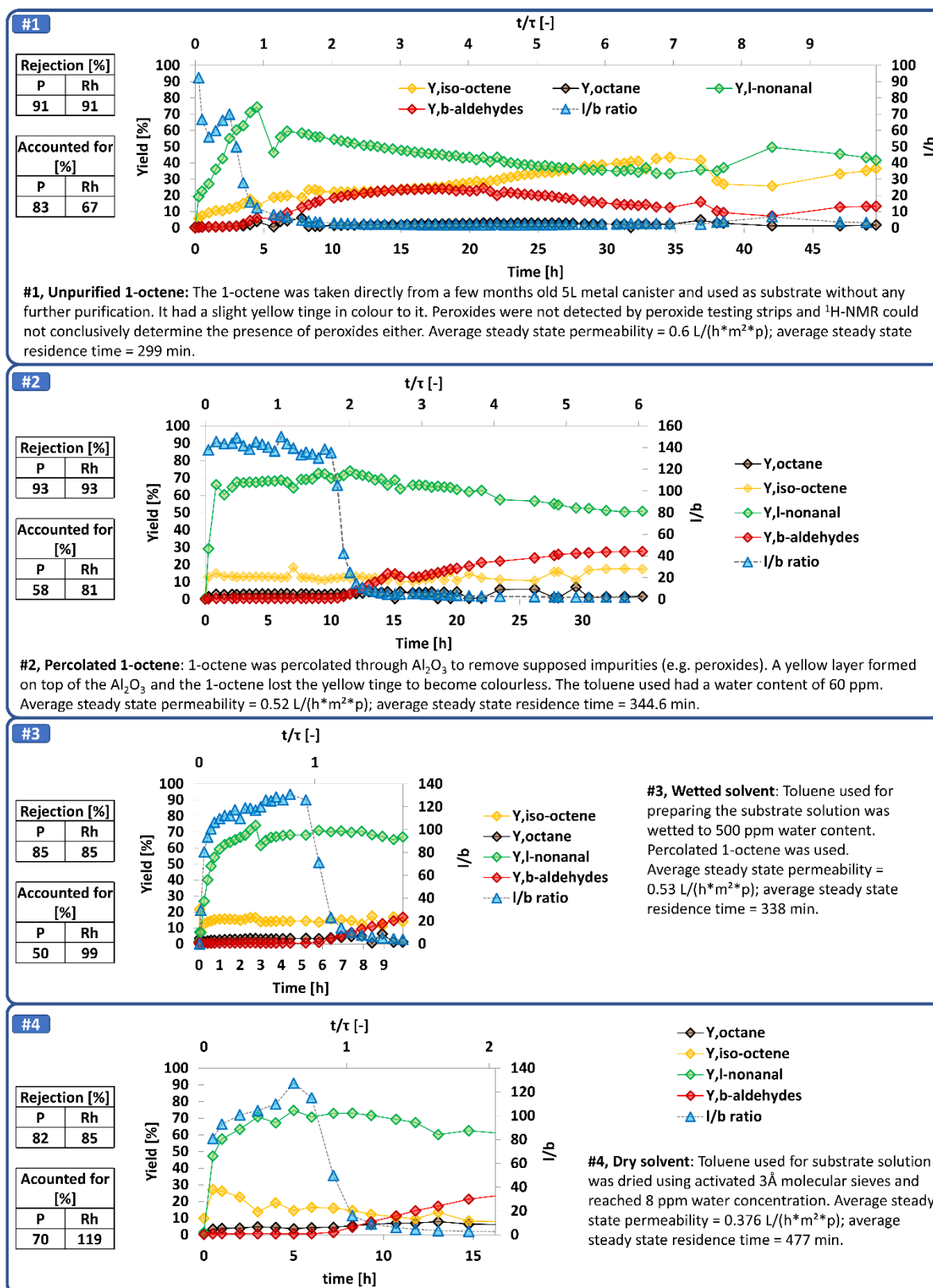


Figure 6-2: Continuous Rh/Biphephos-catalysed hydroformylation of 1-octene, reaction #1-4. Performed in a ceramic membrane loop reactor. General conditions: $T = 90^\circ\text{C}$; $P = 20 \text{ bar}$; $\text{CO}/\text{H}_2 = 1:1$; $\text{Rh}:\text{L}:1\text{-octene} = 1:5:6000$; Catalyst solution: $\text{Rh}(\text{acac})(\text{CO})_2$ (14.8 mg, 0.057 mmol); Biphephos (226.6 mg, 0.288 mmol) in toluene (14 ml); Substrate solution: 1.6 M 1-octene in toluene. Reactor volume = 220 ml. Membrane: inopor TiO_2 , 450 Da MWCO.

Continuous experiment #1: The 1-octene used in the first continuous experiment (Figure 6-2, #1) had a slight yellow tinge in colour. Peroxide testing strips were unable to detect any peroxides and ^1H -NMR could only vaguely identify the presence of suspected peroxide protons. Initially the system was selectively producing only linear nonanal, but soon lost selectivity and the l/b ratio quickly dropped from >100 down to 2. A stable steady state operation was never fully reached in this experiment. The calculated rejection of both P and Rh was 91%. The P and Rh that was accounted for by the ICP measurements of the solutions (permeate and reactor solution at the end of the experiment) were at 83 and 67% respectively.

Continuous experiment #2: In the second experiment, the 1-octene substrate had been percolated through a short column of Al_2O_3 . The 1-octene did leave a distinctive layer of yellow coloration on the top part of the alumina, while also coming out completely colourless at the bottom of the column. The continuous hydroformylation experiment showed a clear improvement of the stability of the system as a steady and selective production of nonanal (l/b~140) was maintained for 10 h before the l/b ratio fell. The rejection of both P and Rh reached 93%, which is slightly higher than what was measured in #1. The quantity of P and Rh that was possible to be accounted for was only 58% for P and 81% for Rh. Almost half of the P that was originally introduced into the reactor was therefore not accounted for in the collected solutions.

Continuous experiment #3: The third experiment was devised to explore the impact, which an enhanced concentration of water in the reaction mass would have upon the stability of the system. Continuous experiment #3 used wetted solvent (500 ppm water) as compared to experiment #2 (60 ppm water). The result was that the l/b ratio dropped after around 6 h, or one residence time into the experiment, which was roughly half the time of experiment #2. Thus, this experiment is suggesting that a tenfold increase of water concentration in the toluene merely induced halving of the time of stable operation. The rejection of P and Rh in this experiment was at 85% for both P and Rh, which is now a significant drop compared to #1 and #2. The amount of P accounted for was 50% while Rh reached 99%.

Continuous experiment #4: To further investigate the effect of water, a fourth experiment was devised that used “dry” toluene (8 ppm water). The drying was accomplished using activated 3 Å molecular sieves. The stability of #4 (8 ppm water) lasted significantly shorter than #2 (60 ppm water). It must be recognised that drying solvents with molecular sieves will always result in some dust particles from the molecular sieves becoming dispersed in the solvent! It is also known that molecular sieves are slightly acidic, e.g. they are very capable of catalysing aldol

condensation of aldehydes or ketones. Hence, it is possible that the reduction in the system stability that was observed in #4 was the result of the presence of such acidic molecular sieve debris. Overall, the stability of the continuous Rh/Biphephos-catalysed hydroformylation system is not primarily governed by the water concentration! The rejection of P and Rh was at 82 and 85%, similar to #3. The P and Rh accounted for was 70 and 119%, a marked increase for both compared to previous experiments. Noticeable is that more Rh was accounted for than had been introduced at the beginning of the experiment.

Continuous experiments with additives: Since the majority of the different decomposition reactions that phosphites are susceptible to are catalysed by acids, the next set of experiments were designed to try and combat the presence of any acids by applying acid scavengers. The continuous experiments #5-7 were therefore designed to investigate three different additives for their stabilising effects of the Rh/Biphephos system. The three additives that were used are presented in Figure 6-3 below.

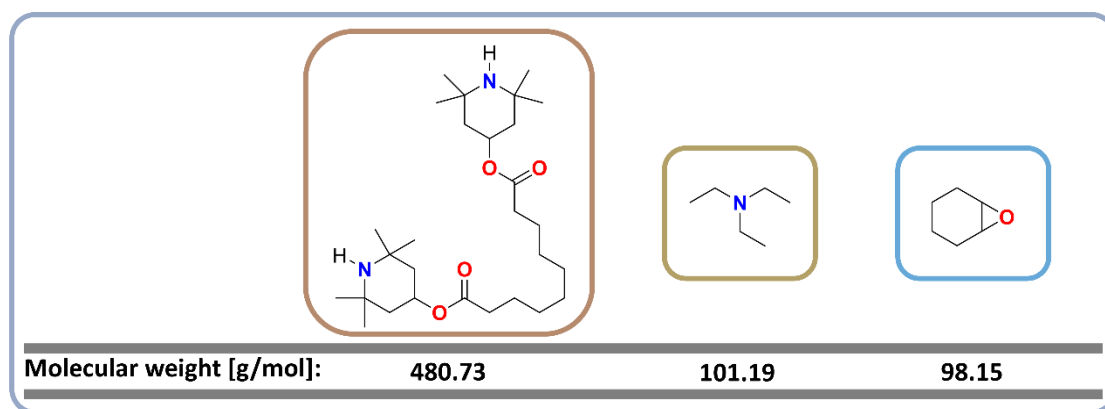


Figure 6-3: Stabilisers investigated in the continuous Rh/Biphephos-catalysed hydroformylation of 1-octene. (Left): bis(2,2,6,6-Tetramethylpiperidyl) sebacate (“Tinuvin 770”); (Middle): Triethylamine (Et_3N); (Right): cyclohexene oxide (CHO).

The three stabilisers are **a)** bis(2,2,6,6-Tetramethylpiperidyl) sebacate – a hindered secondary amine, also known as “Tinuvin® 770”. **b)** Et_3N – a tertiary amine and **c)** cyclohexane oxide – an epoxide. These have all been reported to possess excellent stabilising effects on phosphites used in Rh-catalysed hydroformylation of alkenes (vida supra).^[161,165,208] Each additive was therefore applied in a separate continuous hydroformylation experiment. The permeate compositions as a function of time and residence time (τ) from these three continuous experiments #5-7 are presented in Figure 6-4 below.

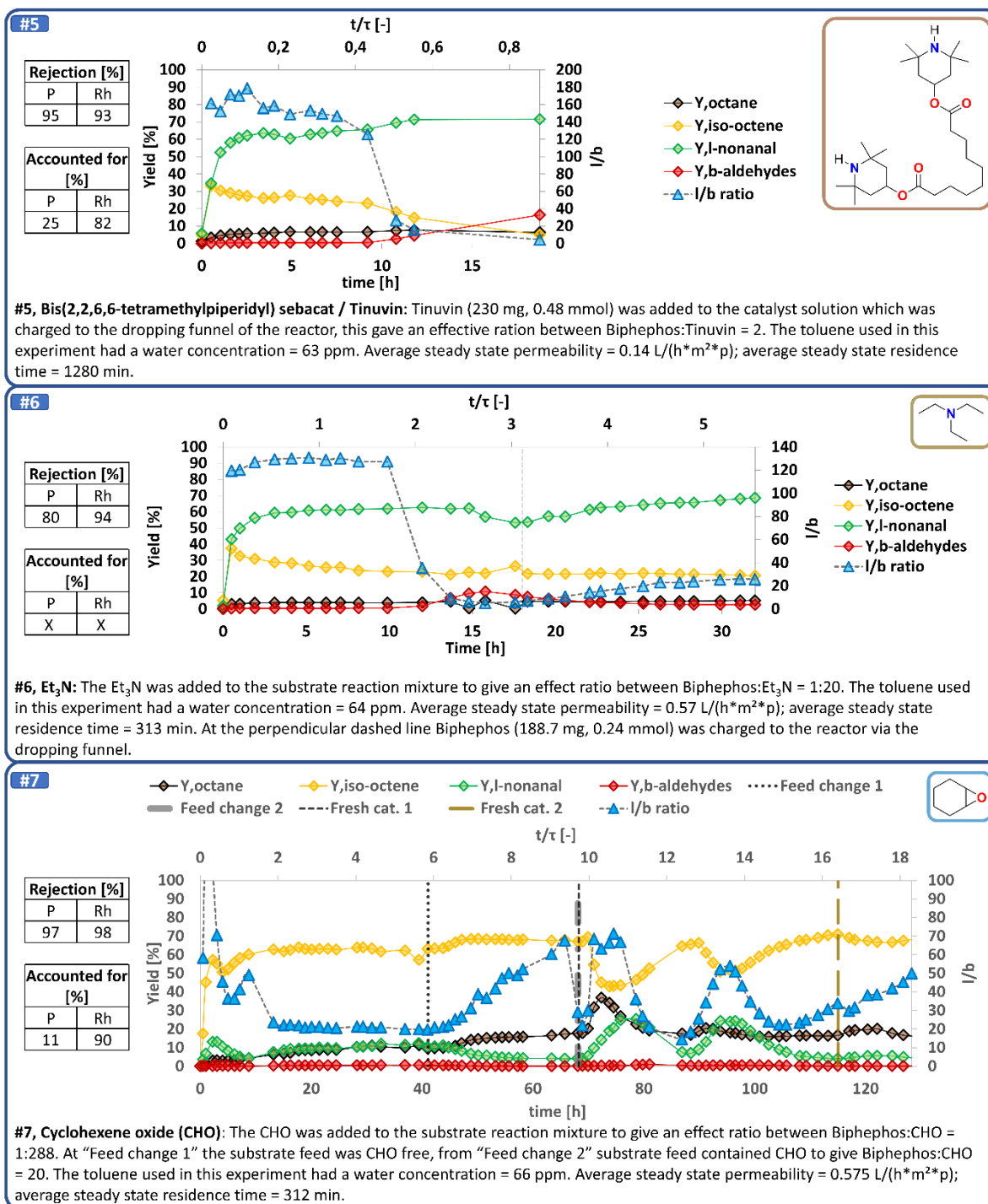


Figure 6-4: Continuous Rh/Biphephos-catalysed hydroformylation of 1-octene with stabilizers, reaction #5-7. (#5, top = Tinuvin; #6, middle = Et₃N; #7, bottom = cyclohexene oxide). General conditions: T = 90 °C; P = 20 bar; CO/H₂ = 1:1, Rh:L:1-octene = 1:5:7300; Rh(acac)(CO)₂ 12.38 mg, 0.048 mmol; Biphephos 188,72 mg, 0.240 mmol; 1.6 M 1-octene in toluene.

Continuous experiment #5: The secondary amine bis(2,2,6,6-Tetramethylpiperidyl) sebacate also known by its trade name Tinuvin® 770, has a large molecular weight (480.72 Da). It was theorised that it would be rejected by nanofiltration membranes to a certain extent. Tinuvin® 770 was therefore administered to the reactor as part of the catalyst solution in a one-time

charge to give an initial ratio Biphephos:Tinuvin = 1:2. The permeability of the ceramic nanofiltration membrane was severely reduced ($0.14 \text{ L}/(\text{h}\cdot\text{m}^2\cdot\text{p})$) during this experiment resulting in a residence time of 1280 min. It is possible that Tinuvin® 770 clogged up the pores of the membrane due to its large and elongated molecular size. The l/b ratio of the system was stable for about 7.5 h before it dropped and so this experiment could not prove that Tinuvin® provides any extra stability to the Rh/Biphephos system. The rejection of P was at 95% and that of Rh was slightly lower at 93%. The amount of P and Rh accounted for was 25 and 82%.

Continuous experiment #6: The next stabiliser was Et_3N , a tertiary amine and relatively small molecule. The Et_3N was present in the substrate solution to give a ratio of Biphephos: Et_3N = 1:20. Again, the selectivity of the system broke down after only 9.9 h of operation. The supposed stabilising effect of Et_3N was therefore not observed within this experiment. Soon after the system breakdown at $t = 11 \text{ h}$ a fresh charge of Biphephos was added to the reactor to test if selectivity could be regained. As can be seen, the permeate composition soon thereafter showed an increasing concentration of the linear aldehyde and a decreasing concentration of the branched aldehyde. Hence, using a makeup feed containing Biphephos could be a feasible solution to maintain a stable selectivity towards the linear aldehyde over a longer period. This approach of a ligand make-up was applied in the work of Dreimann and colleagues with their DMF/Dodecane TMS system.^[178,180,181] The rejection of P was 80% and the rejection of Rh was 94%.

Continuous experiment #7: The third additive that was explored was cyclohexene oxide (CHO). This has also been reported to be an effective phosphite stabiliser in Rh/phosphite catalysed hydroformylation systems.^[161] Because the previous two continuous experiments with additives (Tinuvin and Et_3N) did not result in improvements to the stability of the systems, the ratio between Biphephos:CHO was significantly increased to an initial ratio of 1:288. This was altered down in the course of the experiment. The CHO was present in the substrate solution as it was not being retained by the membrane. A few general observations can be stated about this experiment: the yield of nonanal was generally low, the yield of octane and iso-octene were generally high, but the l/b ratio was relatively stable over time. After 40 h of operation the continuous feeding of cyclohexene oxide was removed to observe what would happen when the effective concentration of cyclohexene oxide reduced due to wash-out through the membrane. A direct consequence was that the l/b ratio significantly increased while the yield of the linear aldehyde stabilised at a reduced level. After 65.7 h the l/b ratio had reached a maximum and was thereafter in a steep decline, which indicated that the system was

about to break down, possibly due to the effective concentration of CHO had reached a lower threshold limit. The feed to the reactor was therefore changed to again contain CHO, this time to give a ratio between Biphephos:CHO = 20. Soon after a second charge of Rh/Biphephos solution was also introduced to the reactor. The effect of these actions became something of rollercoaster as the system never managed to stabilise properly thereafter. Some issues with the substrate feed HPLC pump must also be recognised as a potential contributing factor to the instability. At 115 h (third vertical dashed line) fresh Biphephos was introduced to the reactor, due to the ongoing fluctuations in the system it is not possible to say if the changes after this event are directly linked to the addition of the Biphephos. The overall take home from this experiment is that the yield of nonanal was surprisingly low, the octane and iso-octene were high, the l/b ratio was low but always above 10. Cyclohexane oxide could arguably have a stabilising effect regarding the l/b ratio, but it is possible that it also had a negative effect upon the yield of linear aldehyde. The rejection of P was 97% and the rejection of Rh was 98%, the two highest measured rejection values so far. The amount of P accounted for was only 11% while the Rh accounted for was at 90%. It is possible that precipitates of P and Rh-rests had blocked the flow somewhere in the piping of the reactor, leading to bad inter loop mixing and/or insufficient gas-liquid mixing. This could then act as an explanation to why #7 was not able to reach any higher yield of l-nonanal, but still maintained a high isomerisation activity.

Overall, no long-term stable continuous flow system with Biphephos was achieved, although the best results were realised in the second experiment where the substrate had been purified and no other external measures had been taken. There was a systematic large gap in the amount of P introduced and the amount of P that was possible to be accounted for after an experiment, this has been illustrated in Figure 6-5 below.

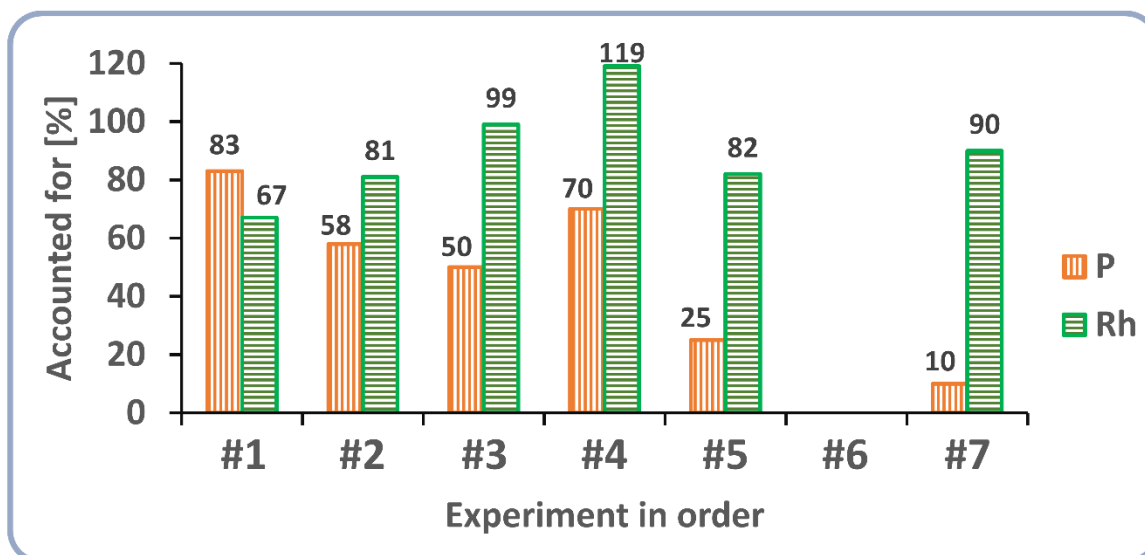


Figure 6-5: The P and Rh accounted for to be present in solution at the end of the different experiments (#1-7).

The amount of P that was possible to be accounted for was constantly dropping for each consecutive experiment (#4 being an exception), suggesting that the reactor was accumulating deposited P. The amount of Rh accounted for on the other hand was fluctuating. At a later stage the reactor was opened for inspection, a surprisingly large amount of brown precipitates was covering all the walls and pipes of the reactor, see Figure 6-6 below.

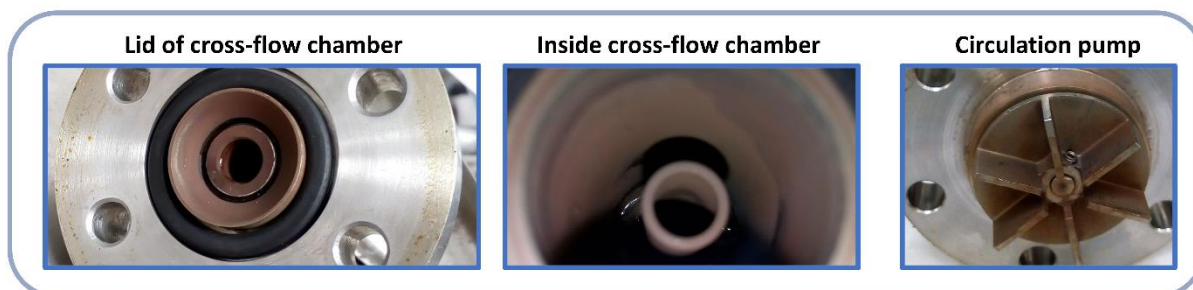


Figure 6-6: Brown precipitates covering the interior of the loop reactor after the last reaction #7.

Hence, it is fundamentally important that the surface that any reaction mixture will be in contact with is clean and well kept. Thus, it is highly recommended to have a look inside the reactor, pipes, pumps and other equipment belonging to the reactor after each run. It will require the setup to be dismantled after each run to properly perform this maintenance. For the deposits and precipitates that were identified to be present inside the reactor in this instance, a dilute aqueous solution of phosphoric acid (5-10%) together with a soft brush was found to be effective in removing it. The parts were then thoroughly rinsed with water. Before the cleaning, a sample was collected and sent for analysis by Energy-dispersive X-ray spectroscopy (EDX). This showed that the brown precipitate contained significant amounts of the elements

making up the stainless-steel alloy that the reactor was constructed from. Furthermore, large quantities of Rh were also detected. But where the missing phosphor ended up remains a mystery. It could be possible that it was once part of the brown precipitate but was later washed out during cleaning procedures using organic solvents, before a sample of the precipitate was analysed by the EDX spectrometer. Overall, the stability of Biphephos was beyond control in all of the continuous flow experiments, the mass-balance of phosphor and Rh between what was introduced into the reactor at the start of an experiment in dissolved form and what was accounted for to be present in solution by the end of an experiment always differed. Thus, the rejection results must be taken with healthy level of scepticism as it was not sure by this stage what had happened.

6.3.3. Autoclave Experiments with Additives

The continuous experiments with Tinuvin, Et₃N and CHO produced some interesting results that, to some extent, raised more questions than they answered. Therefore, these systems were further investigated in batch autoclave setups for sampling over time experiments. Since the high molecular weight HALS additive (Tinuvin® 770, Figure 6-3) caused a significant reduction of the membrane flux, it was decided to investigate a smaller molecular derivative of this additive that still contains the same essential functional group. Thus, 2,2,6,6-tetramethylpiperidine (TMP) was selected to represent a HALS in the further studies about their stabilising effects upon Biphephos. This additive, together with TEA and CHO are presented in Figure 6-7 below.

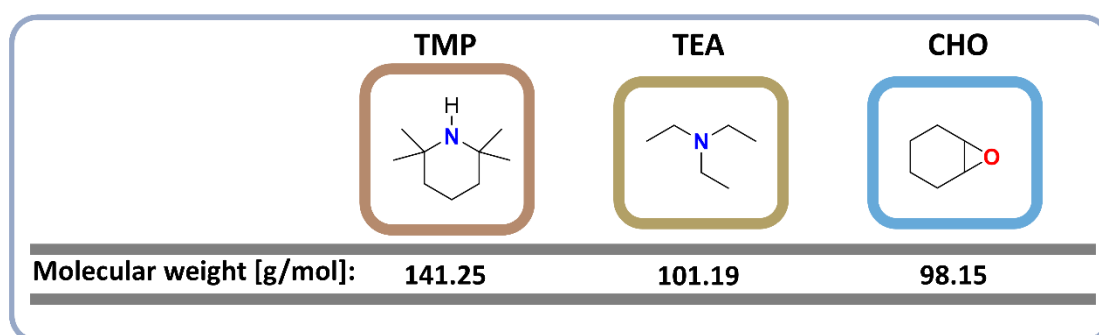


Figure 6-7: The three stabilisers being further investigated for Biphephos stabilisation.

(Left side): 2,2,6,6-tetramethylpiperidine (TMP), a hindered secondary amine, MW = 141.25 g/mol; (Middle): Et₃N (TEA), a tertiary amine, MW = 101.49; (Right side): cyclohexene oxide (CHO), an epoxide, MW = 98.15.

Batch autoclave experiments were therefore devised to investigate the 3 different additives, in 12 different ratios (Biphephos:additive = 1:0.01, 1:0.1, 1:0.5, 1:1, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256). All the reactions were prepared using standard Schlenk-technique. The reactions were sampled over time to generate reaction profiles, providing a dynamic overview of what happened through the course of each reaction. The l/b ratio is a key indicator, whether the Biphephos in the system is intact (l/b ~ 100) or if it has been significantly decomposed. If enough Biphephos decomposes, the system will eventually lose its selectivity (l/b << 100). The results from these experiments are presented in Figure 6-8 below.

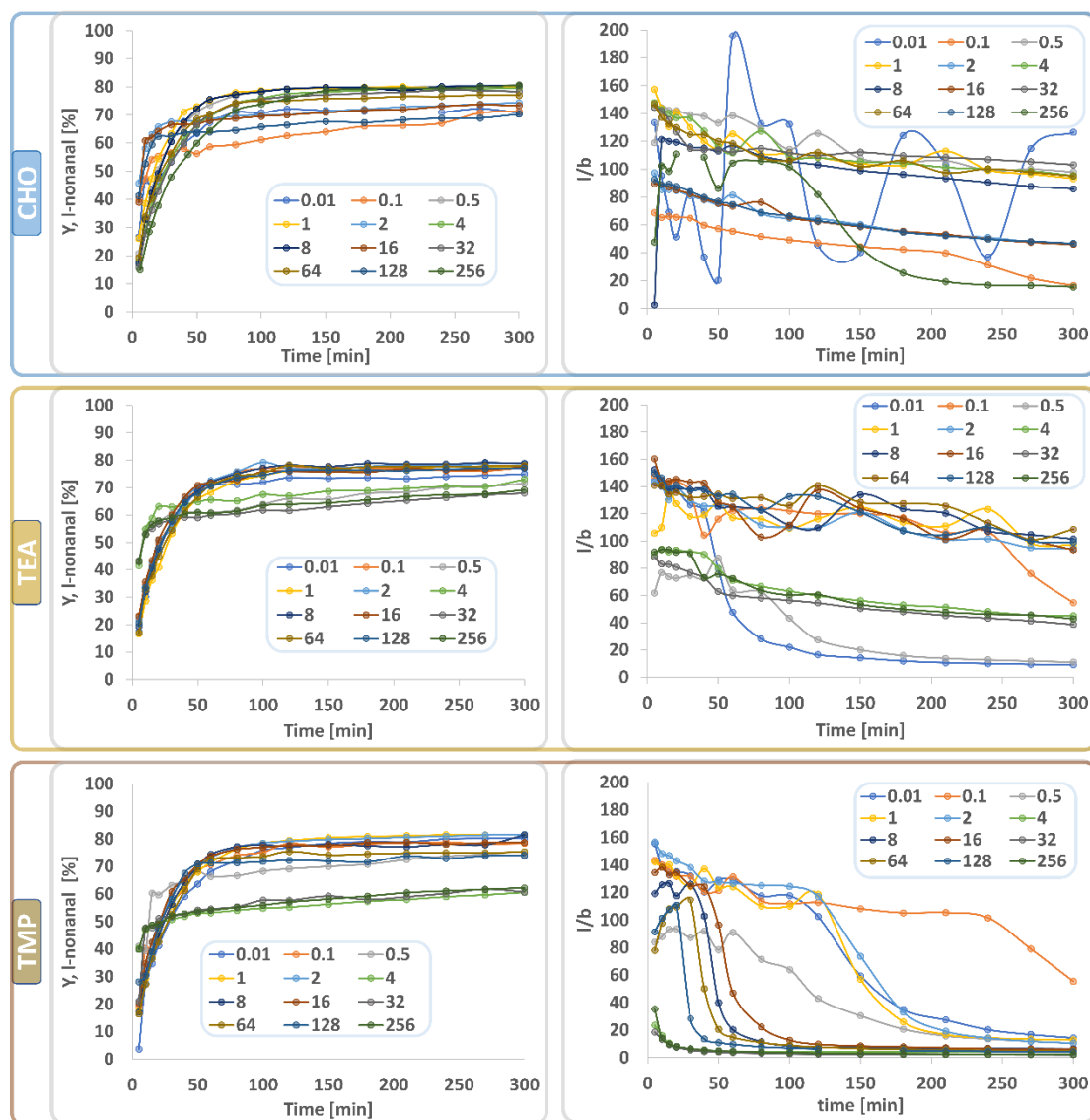


Figure 6-8: Rh/Biphephos-catalysed hydroformylation of 1-octene in batch autoclave in presence of stabilisers. Conditions: Rh:L:1-octene = 1:5:5:6000. Rh(acac)(CO)₂ 2.9 mg, 0.0111 mmol; Biphephos 43.8 mg, 0.0557 mmol; 1-octene 10.5 ml, 67.4 mmol; CO:H₂ = 1:1; P = 20 bar; solvent = toluene 41 ml; 2 h preformation @ 80 °C, 18 bar CO:H₂ = 1:1. The numbers represent the ratio of the additive relative to Biphephos.

At a first glance, it seems like none of the additive-containing systems generated any predictably stable systems. In all cases, no real trend can be observed; the onset of the full breakdown of the selectivity of the systems seemed to have happened at random. This suggests that there was still a parameter that was not under control. Nevertheless, none of the additives had any effect upon increased yield of other by-products (octane, nonanol or aldol condensation products).

6.3.4. ³¹P-NMR Studies

Before ruling out the potential stabilising effect the additives TEA, CHO and TMP have on Biphephos and any catalytic system of Biphephos, a set of simplified Biphephos/additive solutions were studied by ³¹P-NMR. The ³¹P-NMR peak of Biphephos relative to phosphonic acid comes at 145 ppm, while oxidation decomposition products come at around -4 and 0 ppm,^[385] hydrolysis decomposition products come at round 2 - 20 ppm.^[386] The general idea was to study the relative stability of Biphephos against hydrolysis in solutions containing the different additives in varying amounts as they were exposed to “reaction conditions” of 90 °C for extended periods of time, while intermittently being analysed by ³¹P-NMR. All the Biphephos solutions were deliberately prepared in a non-inert atmosphere; hence, no special care was taken to exclude air from contacting any of the sample solutions that were prepared. This was done because it was believed that Biphephos would be stable against oxygen in the absence of any alkenes.

Premature decomposition of Biphephos, experiment 1: The first set of Biphephos solutions included Rh in a ratio Rh:Biphephos = 1:5. A Rh/Biphephos stock solution was prepared the same way as it had always been prepared for all the previous reactions that had been setup up to this moment. Both Biphephos and Rh(acac)(CO)₂ were weighed into the same flask containing a stirrer bar. Toluene was then added to dissolve both compounds simultaneously to make the stock solution. It was then recognised that some residue material in the stock solution was unable to fully dissolve, even after 2 h of continuous stirring. This was not new, as slightly turbid catalyst solutions had also previously been recognised but never fully investigated. At this point, no further attention was therefore paid to this, and the preparation of the various solutions containing different additives at different ratios was completed. The Rh/Biphephos/additive solutions together with toluene-d₈ were added to NMR tubes that were sealed with caps, parafilm and submitted for ³¹P-NMR analysis. The results from the ³¹P-NMR analyses are presented in Figure 6-9, left side below.

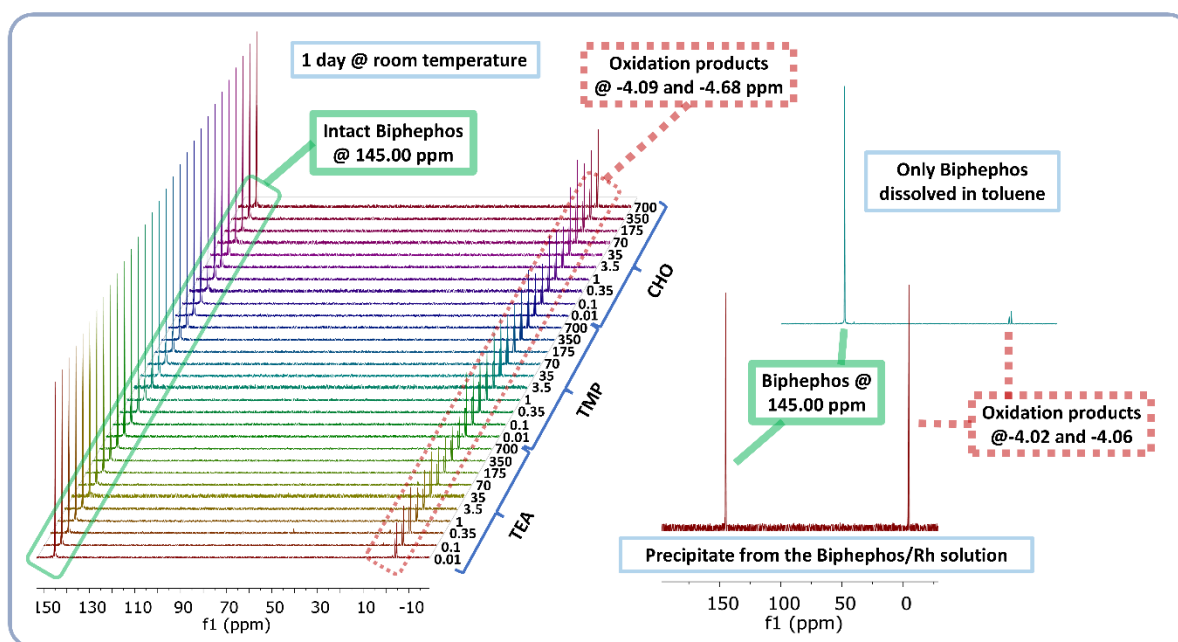


Figure 6-9: ^{31}P -NMR showing pre-mature decomposition of Biphephos due to Biphephos oxidation. Conditions: Rh:Biphephos = 1:5, weighed out into the same flask and dissolved simultaneously. The additives being Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene oxide (CHO). The numbers (0.01, 0.1, 0.35, 1, 3.5, 35, 70, 175, 350, 700) represent the number of molar equivalences of additive present relative to Biphephos. ^{31}P -NMR measured in toluene- d_8 , 500 MHz. Samples were prepared with no care taken to exclude air or water.

In all samples, a large quantity of the Biphephos had already at this stage been oxidized. It was feared that the source of Biphephos was of bad quality, so a solution of only Biphephos in toluene- d_8 was analysed by ^{31}P -NMR. This time (Figure 6-9, above right side, top), only small amounts of oxidation product peaks were present, meaning that the Biphephos was of good quality. Simultaneously to these events, the stock solutions used for preparing the initial series of NMRs also containing Rh precursor had been left in a fridge for 2 days, during which time larger quantities of precipitate had formed. The precipitate was analysed by ^{31}P -NMR (Figure 6-9, above right side, bottom), indicating large amount of Biphephos oxidation products.

Premature hydrolysis of Biphephos, experiment 2: To confirm the results in the initial set of Biphephos/Rh solutions, a new set of NMRs were prepared in the same way as before and analysed by ^{31}P -NMR. The results are presented in Figure 6-10 (left) below.

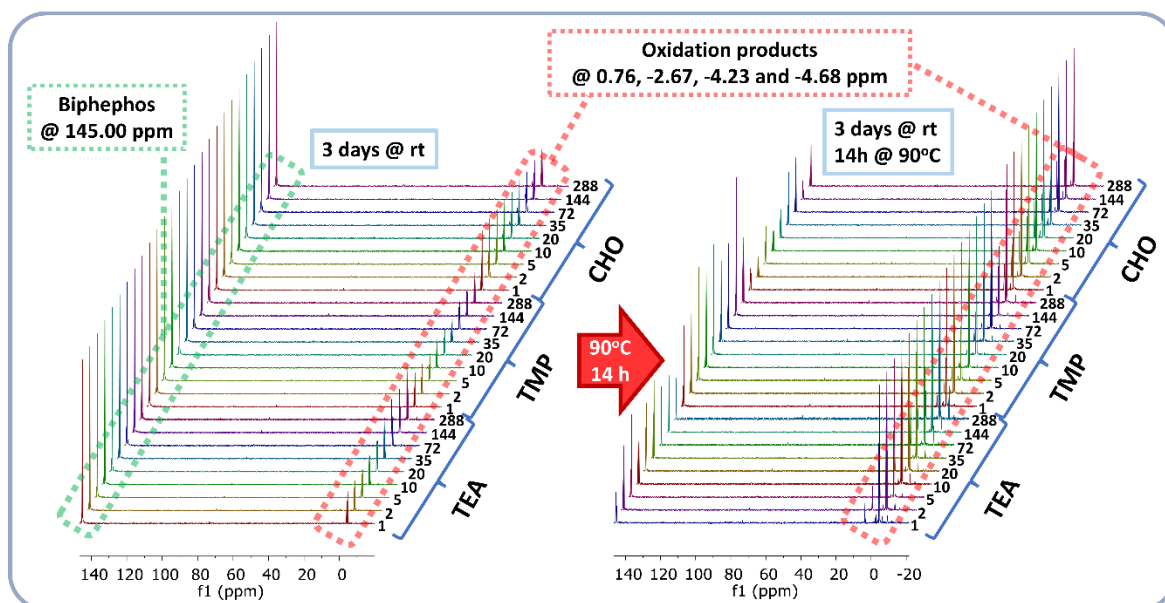


Figure 6-10: ^{31}P -NMR showing reproduced pre-mature hydrolysis of Biphephos due to wrong order of mixing. Conditions: Rh:Biphephos = 1:5, weighed out into the same flask and dissolved in toluene simultaneously. The additives being Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene oxide (CHO). The numbers (1, 2, 5, 10, 20, 35, 72, 144, 288) represent the number of molar equivalences of additive present relative to Biphephos. ^{31}P -NMR measured in toluene- d_8 , 600 MHz. Samples were prepared with no care taken to exclude air or water.

Like the previous experiment, large quantities of oxidation products of Biphephos were observed in this newly prepared set of solutions before they had been exposed to elevated temperatures. The experiment was then allowed to proceed according to protocol and the NMR tubes were heated at 90°C for 14 h before being resubmitted for another round of analysis by ^{31}P -NMR. The stacked ^{31}P -NMR spectra from the post heating are presented in Figure 6-10, right side. Clearly, after the treatment at 90°C for 14 h, all Biphephos solutions showed large amounts of oxidation products.

Rh-free additive-containing solutions: To prove that it was not the “stabilisers” or oxygen alone that caused the pre-mature oxidation decomposition, Rh-free Biphephos solutions containing the additives were made up under non-inert conditions and analysed by ^{31}P -NMR. The result from that set of experiments is presented in Figure 6-11 below.

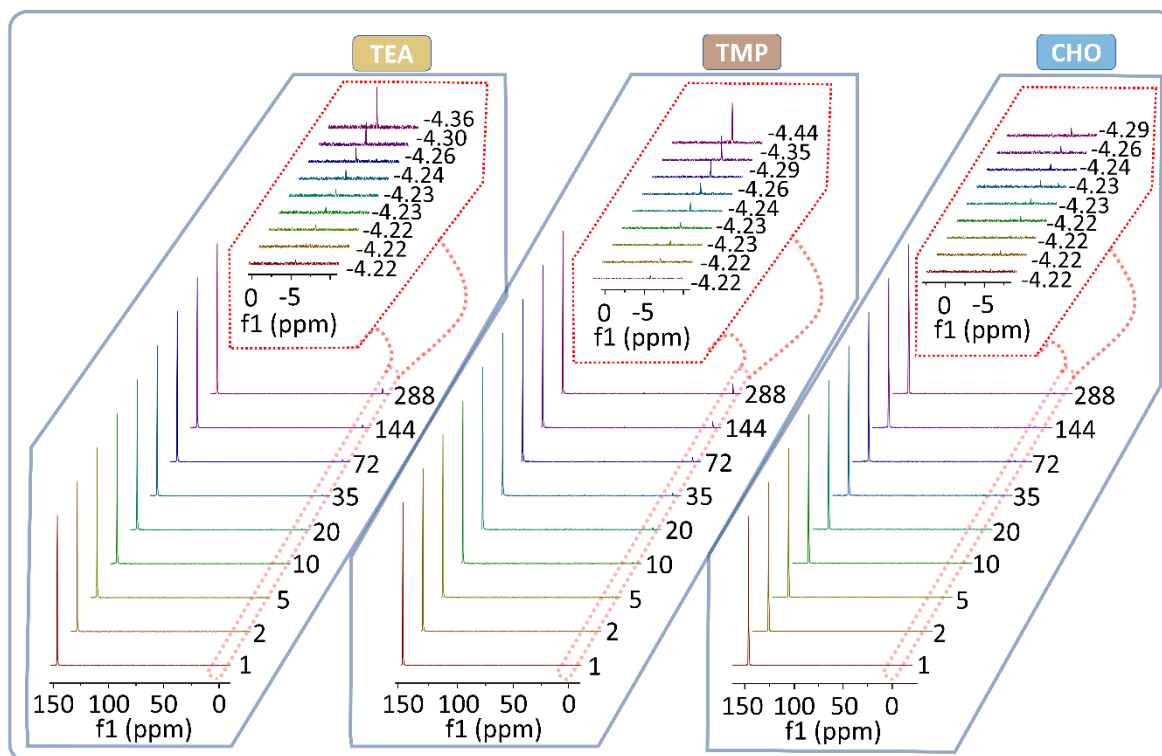


Figure 6-11: Biphephos with very small amount of oxidation decomposition products in Rh-free, stabiliser-containing solutions. Conditions: Rh-free, the additives being Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene oxide (CHO). The numbers (1, 2, 5, 10, 20, 35, 72, 144, 288) represent the number of molar equivalences of additive present relative to Biphephos. ^{31}P -NMR measured after 3 days at room temperature in toluene- d_8 , 600 MHz. Samples were prepared with no care taken to exclude air or water.

As can be seen, in the presence of the additives and in absence of rhodium under non-inert conditions, only very small quantities of oxidation decomposition products can be identified. A trend in increasing amount of oxidation decomposition with increasing amount of stabiliser is clearly observed for TEA and TMP. The amount of oxidation products that each sample contained was measured from the relative integral of the NMR peaks and is presented in Figure 6-12.

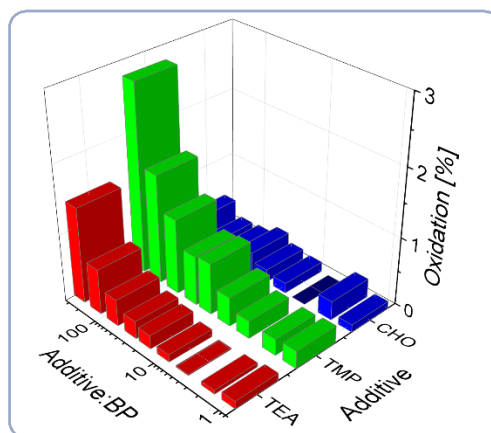


Figure 6-12: The amount of Biphephos being oxidised in various stabiliser-containing solutions. Conditions: Rh-free, the additives being Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene oxide (CHO). ^{31}P -NMR measured after 3 days at room temperature in toluene- d_8 . Samples were prepared with no care taken to exclude air or water.

An increased concentration of the amine-based stabilisers (TEA and TMP) resulted in an increased amount of oxidation products in these samples. The relative concentration of the epoxide stabiliser (CHO) had no significant effect upon the amount of oxidation. Notice that the samples were prepared under non-inert conditions and then stored for 3 days at room temperature before they were analysed by ^{31}P -NMR. A possible cause for the unwanted oxidation of the Biphephos was the presence of Rh, which has been reported to be a catalytically active metal in oxidation reactions.^[387,388]

Correct order of preparing a $\text{Rh}(\text{acac})(\text{CO})_2$ and Biphephos solution: A slightly revised method for preparing the Rh/Biphephos/additive solutions was investigated. Here, $\text{Rh}(\text{acac})(\text{CO})_2$ and Biphephos were dissolved separately, the Biphephos solution was then split up into 4 fractions to which the appropriate amount of additive and Rh-solution were added to give a ratio of Rh:Biphephos:additive = 1:5:25. The first set of stacked ^{31}P -NMR spectra presented in Figure 6-13 left side are those of Biphephos solutions that have only been exposed to “room temperature” conditions and analysed within 24 h from sample preparation.

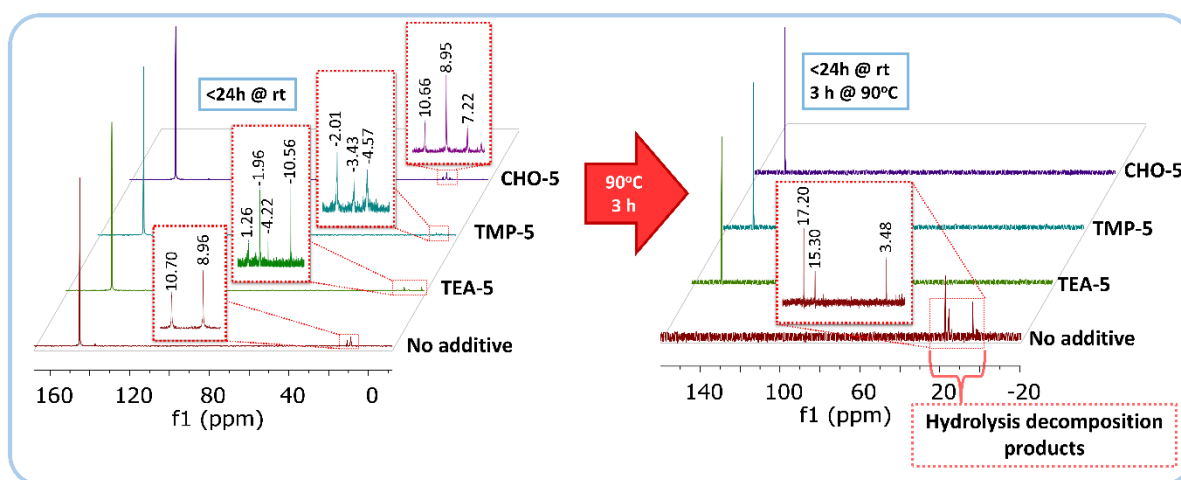


Figure 6-13: Biphephos with small amount of hydrolysis in Rh-containing solutions, correct order of mixing. Conditions: Biphephos and $\text{Rh}(\text{acac})(\text{CO})_2$ were dissolved separately, the Rh solution was added dropwise to the Biphephos solution and any stabilisers were then added. Analysis by ^{31}P -NMR before and after subjected to 90°C for 3 h. ^{31}P -NMR measured in toluene- d_8 , 600 MHz. Samples were prepared with no care taken to exclude air or water.

Only smaller quantities of decomposition products were observed within all the samples after they had been prepared and before they had been exposed to elevated temperature. After they had been subjected to heating at 90°C for 3 hours, all Biphephos solutions containing stabilisers had no decomposition product signals present, while the stabiliser-free Biphephos solution was completely decomposed, showing only hydrolysis peaks. It was thus shown that the order of dissolving the $\text{Rh}(\text{acac})(\text{CO})_2$ and Biphephos has an influence; presence of O_2 is not necessarily going to oxidize Biphephos, and using suitable additives prevents hydrolysis.

Effect of Biphephos:additive ratio: The next set of experiments went back to the idea of investigating the relative stability of Biphephos in toluene having different additives at different ratio to Biphephos. A set of solutions with varying Biphephos:additive ratios (1:1, 1:2, 1:5, 1:10, 1:20, 1:35, 1:72, 1:144 and 1:288) were prepared, with additive = TEA, TMP or CHO. The results from this investigation are presented in Figure 6-14 below.

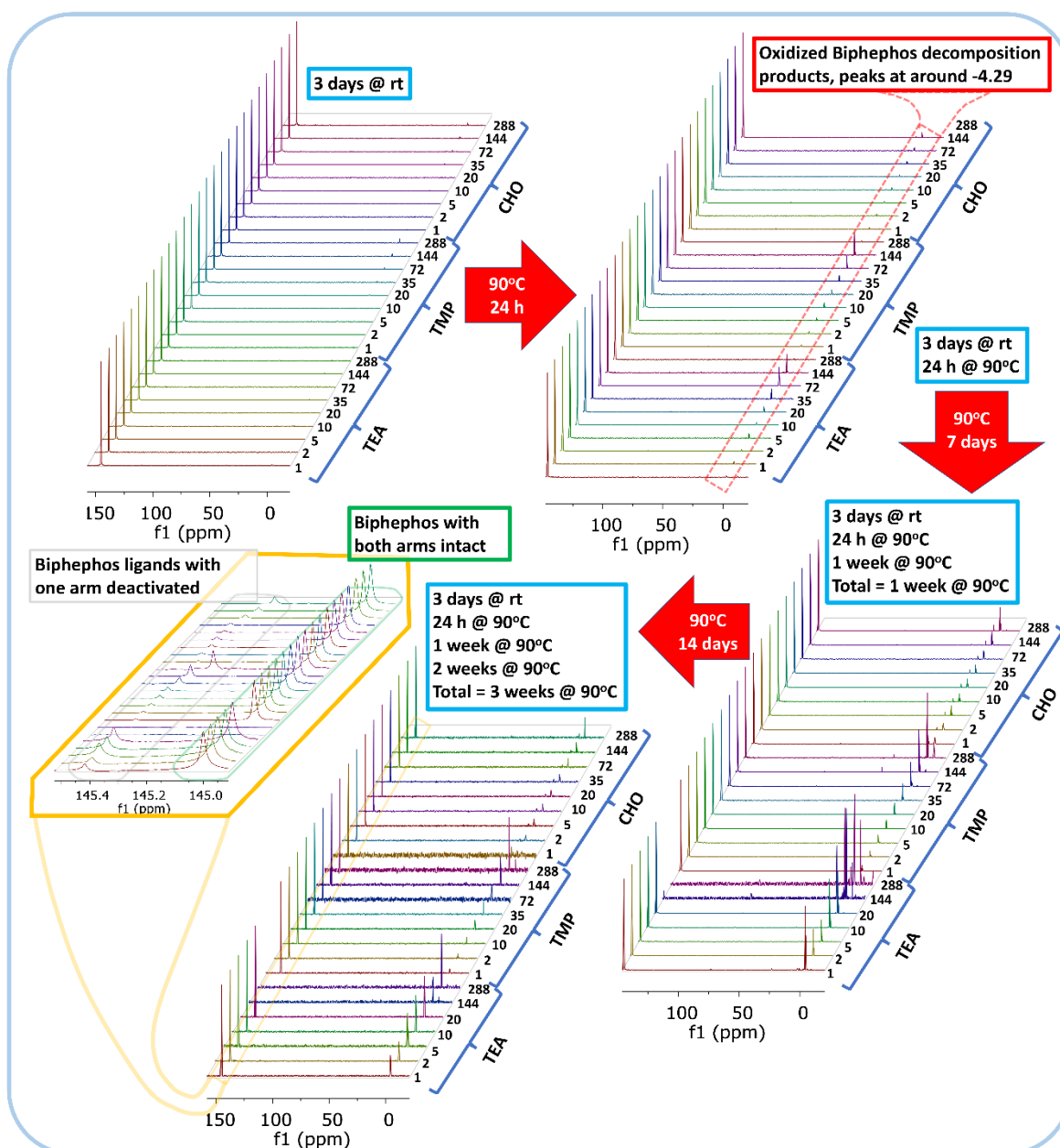


Figure 6-14: Different Biphephos : stabilizer ratios and the resulting stability of Biphephos. The solutions were made up into NMR tubes which were exposed to 90 °C for various lengths of time with intermittent ^{31}P -NMR analysis. The stabilizers are Et_3N (TEA), tetramethylpiperidine (TMP) or cyclohexene 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, 600 MHz. Samples were prepared with no care taken to exclude air or water.

When the Biphephos is intact, only one peak at around +145 ppm is visible. Upon decomposition of Biphephos, new peaks at different chemical shifts appear. Slightly upshift of +145 ppm (intact Biphephos) comes a peak that is thought to be the Biphephos with one arm deactivated. The relative integral between the two peaks at around +145 ppm can thus be used to get a quick estimation about the degree of decomposition. A more thorough analysis requires

the full integration of all the ^{31}P -NMR peaks. This was done on the data set presented in Figure 6-14, and the analysis is presented in Figure 6-15 below.

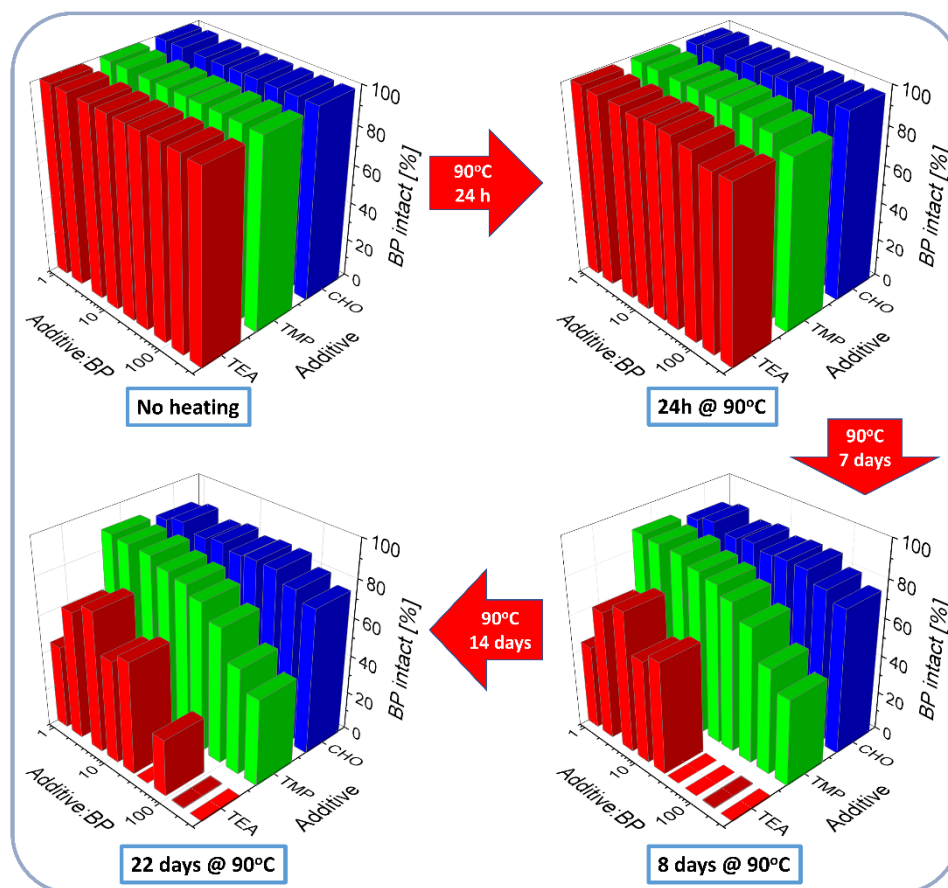


Figure 6-15: Quantitative view of the effect of different additives and their quantities upon the stability of Biphephos. Conditions: Same as in Figure 6-14.

It is noteworthy that some of the (Et_3N containing) NMR tubes lost liquid volume during this investigation as the solvents and additives are volatile at elevated temperatures, and the tightness of the NMR tube cap seal was only safeguarded by parafilm. The parafilm was noticeably brittle amongst those tubes that had visibly lost material. Especially the tubes, which had Et_3N as the additive suffered from reduced volumes. It is possible that volatile Et_3N (b.p. = 89°C) was too much for the parafilm over the course of the heat treatments, while the other two additives posed a lesser risk with their lower boiling points (TMP b.p. = 152°C and CHO b.p. = 129°C). It is therefore not possible to draw too strong conclusions.

The overall conclusions: The order of how Biphephos and $\text{Rh}(\text{acac})(\text{CO})_2$ are dissolved and added together is important to protect Biphephos from oxidation, as certain Rh-species (formed if Rh and Biphephos are co-dissolved) are likely to be responsible for catalysing the oxidation of Biphephos in the presence of O_2 . All three additives (TMP, CHO and Et_3N) can stabilise Biphephos dissolved in toluene against hydrolysis in comparison to an additive free solution

of Biphephos in toluene. Increasing concentrations of the amine-based additives resulted in slightly increasing amount of oxidation products, not necessarily the case for CHO. The presence of oxygen does not cause oxidation of the Biphephos without the presence of Rh, as determined from the ^{31}P -NMR experiments.

6.3.5. Pressure, De-Pressure (PDP) Experiments

Reflecting back to the “Autoclave Experiments with Additives” in section 6.3.3. , and the fact that they showed no trends in terms of stability with the inclusion of the additives, and comparing this with the results from ^{31}P -NMR studies of the additives, it was clear that there was still a parameter that was not under control. This parameter had no influence over the simplified system studied by ^{31}P -NMR analysis while it had a major impact upon the full catalytic system in the autoclave experiments. It was suspected that those autoclave experiments were not prepared under sufficiently inert conditions, despite using “standard Schlenk technique” during their preparation. Solvents and solutions were degassed by sonication under a stream of argon for at least 30 min, they were stored in Schlenk flasks and standard Schlenk technique was used for transferring desired volumes into the reactors. The reactors were always evacuated and filled with argon before any reaction mass was introduced. Although this was the standard technique used for preparation of the reactors, it is still highly possible that small amounts of oxygen could have contaminated the reactor systems during the preparations. To improve the inertness of the reaction system by other means than being more careful when using Schlenk-technique while transferring liquids, the application of a “pressurise/de-pressurise” (PDP) cycle of the reactors was investigated. The idea was to “wash out” any oxygen present inside the reactor system after it has been loaded with reaction mass. By applying high pressure, high purity gas to the reactor, the O_2 equilibrium between the liquid- and gas phase can be offset. When the pressure of the reactor system is then released, a large part of the O_2 will be washed out of the system together with the other gasses. For high efficiency a high purity gas is recommended, e.g. synthesis gas, N_2 or argon. This concept of using PDP-cycles is illustrated in Figure 6-16. There are commercially available products for solvent degassing that are utilising this principle of moving dissolved O_2 into a high purity scrubber gas, e.g. 3M Liqui-Cel Membrane contactor series of products.^[389]

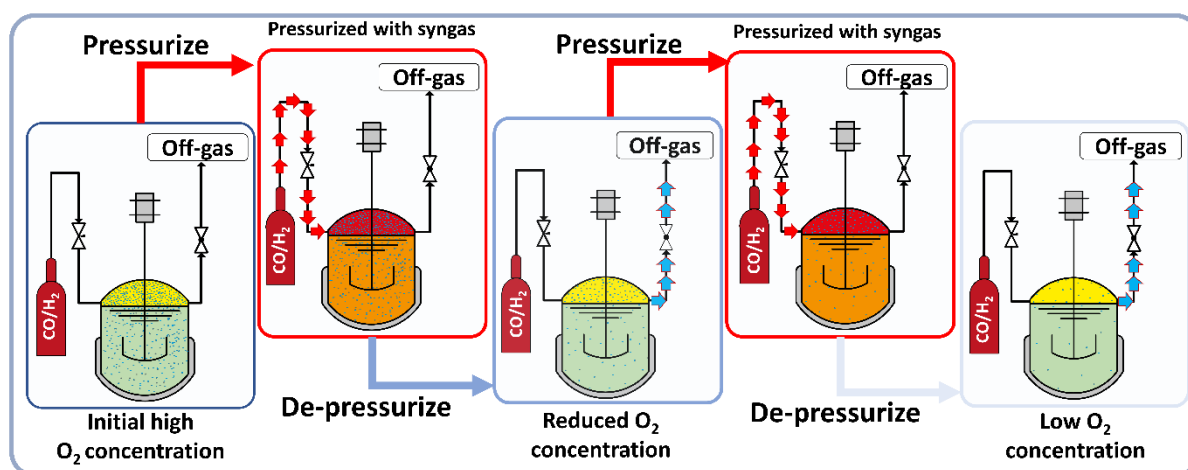


Figure 6-16: Schematic representation of the "pressure-de-pressure" concept.

Each cycle will help reduce the concentration of O_2 present within the autoclave reactor after it has been charged with all the reaction mass.

There are sources in the literature that describe the performance of purge/degassing^[67,132,136,153,163,380,390–397] after loading the reactor with all reaction mass and before starting to heat. The effect of applying PDP cycles was measured by the final l/b ratio of Rh/Biphephos-catalysed hydroformylation of 1-octene reaction mixtures after 1000 min (16.7 h) of reaction in batch autoclaves. 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 of these experiments are presented in Figure 6-17 below.

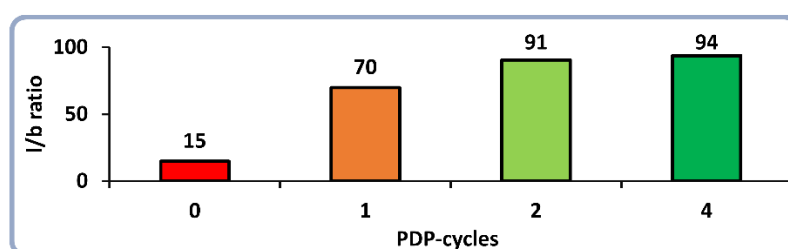


Figure 6-17: The effect of PDP-cycles upon the l/b ratio of the final reaction mixture at $t=1000$ min (16.7 h).

Reaction being the Rh/Biphephos-catalysed hydroformylation of 1-octene in batch autoclaves reactors. Solutions and reactors were prepared using standard Schlenk-technique. After loading the reactors with reaction mass, and before the onset of heating, the reactors were cycled through various number of "pressure de-pressure" (PDP) cycles using synthesis gas. 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, 0.0111 mmol); Biphephos (43.8 mg, 0.0557 mmol); TMP (0.0557 mmol); 1-octene (10.5 ml, 67.4 mmol); CO/H₂ = 1:1; P = 20 bar; solvent = toluene 41 ml; 2 h preformation (80 °C, 18 bar).

There was a significant improvement in the l/b ratio to the end of the run at $t = 1000$ min (16.7 h) by applying an increasing number of PDP cycles. This method of measuring the effectiveness of applying PDP cycles is indirect as it is being assumed that the l/b ratio is connected to the state of the Biphephos only; whether it is being intact or decomposed. The

conclusions from these PDP-cycle experiments must be that a Rh/Biphephos hydroformylation process is very sensitive towards the presence of oxygen contamination in the reaction system and feed. Apart from using standard Schlenk technique to prepare the reactors with previously degassed solvents, catalyst- and substrate-solutions, the application of at least one, better two PDP-cycles will significantly improve the long-term stability and selectivity of the system.

Comparing the methodologies applied in preparing phosphite-based catalytic systems:

The findings about suitable measures that are recommended to be included in the preparation of phosphite-based catalytic systems can be put in comparison to the various preparation methodologies that have been described in various publications that concern phosphite-based systems. A collection of such publications and what preparation steps they included is presented in Table 10 below.

Table 10: Reports on phosphite-based catalytic systems and measures taken during the reaction preparation.

Ligand	Year	Type	Cat. sol. prep method	Purified substrate	Final inert gas flush / PDP-cycles	Stabilisers	Ref.
Monodentate phosphite	1983	Batch	Unknown	Percolation over alumina	No	No	[398]
Monodentate phosphite	1985	Batch	Unknown	No	Yes, one cycle	No	[399]
Monodentate phosphite	1985	Cont.	Unknown	No	Yes	No	
Monodentate phosphite	1986	Batch	Unknown	No	No	Tertiary amines	[179]
Biphephos	1987	Batch	Simultaneous solvation of Rh and ligand	No	Yes, one cycle	No	[132]
Biphephos	1987	Cont.	Simultaneous solvation of Rh and ligand	No	Yes	No	
Biphephos	1988	Batch	Simultaneous solvation of Rh and ligand	No	Yes, one cycle	No	[162]
Biphephos	1988	Cont.	Unknown	No	Yes	Amberlyst-A-21	
Polymer bound phosphite	1992	Batch	Unknown	No	No	No	[166]
Heterogenised bulky phosphite	1993	Batch	Unknown	No	No	No	[167]
Biphephos	1993	Batch	Simultaneous solvation of Rh and ligand	No	Yes	No	[394]
Biphephos	1994	Cont.	Unknown	No	Yes	epoxides	[161]
Biphephos	1996	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[35]
Biphephos type	1999	Batch	Separate solvation of Rh and ligand	Freshly distilled	No	No	[395]
Phosphane-phosphite	1999	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[400]
Biphephos	2003	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[135]
Biphephos	2003	Batch	Unknown	Freshly distilled	No	No	[141]
POSSphites	2004	Batch	Separate solvation of Rh and ligand	Percolation over alumina	No	No	[396]

Biphephos	2005	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[281]
Biphephos	2005	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[137]
Biphephos	2005	Batch	Separate solvation of Rh and ligand	No	Yes	No	[136]
POSSphites	2005	Batch	Separate solvation of Rh and ligand	No	No	No	[397]
JanaPhos	2009	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[168]
Biphephos	2009	Batch	Simultaneous solvation of Rh and ligand	No	No	TMP derivatives	[165]
Biphephos	2011	Cont.	Rh dissolved separately	No	Yes	No	[271]
Biphephos	2011	Batch	Unknown	No	No	No	[401]
Sulfonated calix[4]arene	2011	Batch	Separate solvation of Rh and ligand	No	yes, one cycle	No	[185]
JanaPhos	2011	Cont.	Simultaneous solvation of Rh and ligand	Freshly distilled	No	No	[169]
Bulky phosphite	2013	Batch	Simultaneous solvation of Rh and ligand	Percolation over alumina	Yes	No	[391]
Biphephos	2013	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[175]
Bulky phosphite	2014	Batch	Unknown	Percolation over alumina	No	No	[171]
Biphephos	2014	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[402]
Biphephos	2014	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[403]
Biphephos	2015	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[134]
Biphephos	2015	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[404]
Biphephos	2015	Cont.	Rh dissolved separately	No	No	Tinuvin	[405]
Biphephos	2016	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[172]
Biphephos	2016	Cont.	Unknown	No	No	No	[173]
Biphephos	2017	Batch	Simultaneous solvation of Rh and ligand	No	Yes	No	[393]
Biphephos	2017	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[406]
Biphephos	2018	Batch	Rh dissolved separately	Percolation over alumina + vacuum distilled	No	No	[407]
Biphephos	2018	Batch	Simultaneous solvation of Rh and ligand	No	No	No	[408]
Biphephos	2019	Batch	Unknown	No	Yes	No	[409]
Biphephos	2023	Batch	Unknown	Freshly distilled	Yes, 3 cycles	No	[410]
Biphephos	2023	Batch	Simultaneous solvation of Rh and ligand	Freshly distilled	Purged 10 min	No	[411]
Bulky phosphite	2023	Batch	Both simultaneous solvation and separate solvation	No alkenes included in experiments	No ¹	No	[412]

1. To have fully oxygen free conditions were not decisive for these experiments as there was no hydroformylation performed.

No single publication did include all the four (recommended) preparation steps/elements and there is overall a great inconsistency in the methodologies applied. Nevertheless, the fact that publications did not include such measures does of course not necessarily mean that the reaction systems were compromised. However, it is still surprising how inconsistent the various preparation methodologies have been up until now, and that is especially true for Biphephos, which is seemingly rather sensitive towards unfavourable environments and treatment.

6.3.6. Stability of Biphephos in Different Solvents

Biphephos clearly benefits from the presence of a weakly basic environment, as the presence of acids has a directly dire consequence upon its longevity. Toluene was used as the solvent during the studies where additives were used to improve the stability. Toluene itself is a neutral molecule in terms of its ability to donate or accept protons. Instead of using toluene and additives, another route to take could be to make use of a solvent that is inherently weakly basic. Two solvents that have this property are dimethylformamide (DMF) and acetonitrile (ACN), see Figure 6-18 below.

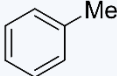
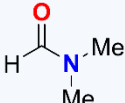
Structure:			
Boiling point [°C] :	111	81.3 – 82.1	152 - 154
Hazards			
Environment	EHB3	EHB1	EHB1
Concern	CMR (Reprotoxic)	Availability	CMR (Reprotoxic)

Figure 6-18: A comparison of the three different solvents (toluene, ACN and DMF).^[413]

Both DMF and ACN are polar, aprotic solvents that are weakly basic because they contain a nitrogen atom with an electron lone pair that can readily accept acidic protons. Both DMF and ACN have previously been used as solvents in Rh/Biphephos-catalysed hydroformylation of long chain alkenes showing good catalytic results.^[384] There was no attention paid to study the relative stability of Biphephos in the solvents. To fill this gap, solutions of Biphephos in either toluene, DMF or ACN were brought into NMR tubes that were then intermittently analysed by ³¹P-NMR between being subjected to heating cycles of 70°C at various lengths of time. The slightly lower temperature of 70°C was chosen due to the low boiling point of ACN. The results from this study are presented in Figure 6-19 below.

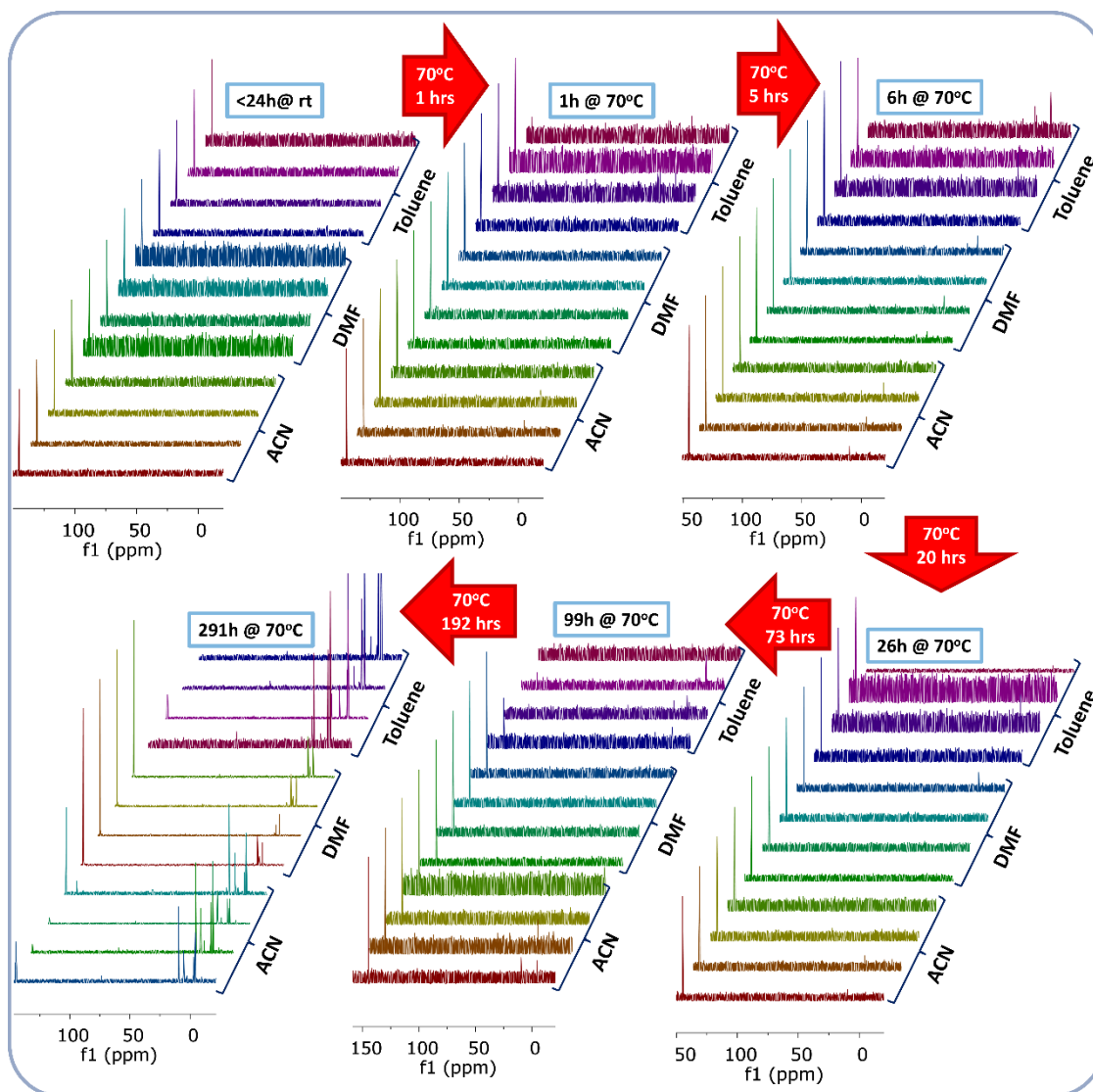


Figure 6-19: The relative stabilising effect of toluene, DMF and ACN towards hydrolysis of Biphephos. Conditions: Biphephos solutions were made up using either toluene, DMF or ACN, no Rh and no additional stabiliser present. ^{31}P -NMR measured in toluene- d_8 , 600 MHz.

The first round of ^{31}P -NMR analyses was done directly after preparation of the solutions, before exposing to elevated temperatures. Here only the single peak of Biphephos at 145 ppm is visible and no signs of any hydrolysis products. After the first heating cycle at 70°C for 1 h, one Biphephos/toluene-solution was completely hydrolysed and the three others showing clear signal peaks of decomposition. ACN also showed small signs of decomposition product signals, while in DMF it was at large intact. After another 5 h of heating, also the Biphephos/DMF solutions showed decomposition signal peaks. The state of the solutions remained relatively unchanged after another 20 h of heating. The autocatalytic decomposition in toluene happens much slower at 70°C as compared to 90°C. Nevertheless, after exposing the Biphephos/toluene solutions to 70°C for an accumulated time of 99 h, all of them were completely hydrolysed.

Meanwhile, the Biphephos/ACN solutions had mostly unhydrolyzed Biphephos and the Biphephos/DMF solutions seemed to be relatively intact. After the last heating cycle at 70°C that lasted for 192 h, all the Biphephos/ACN solutions were completely hydrolysed while all the Biphephos/DMF solutions remained mostly intact.

In conclusion from these experiments, the decomposition of Biphephos dissolved in toluene happens much slower at 70°C compared to 90°C. ACN has a slightly stabilising effect, while DMF was signifi

tly better at stabilising Biphephos against decomposition. Although DMF is better at stabilising Biphephos than ACN, it is important to also recognise that DMF has a considerably higher boiling point (152-154°C) than ACN (82°C). Furthermore, consulting any of the available “solvent selection guides” it becomes clear that DMF has extended warnings due to its substantially greater human health hazards.^[413–417]

6.4. Conclusions and Outlook

The stability of Biphephos is very sensitive to the conditions in which it is present. The methodology applied when preparing the catalyst solution containing Biphephos and Rh(acac)(CO)₂ does matter. It was shown that it is important to dissolve the two solids separately and mix the solutions together in order to not risk extensive oxidation of the Biphephos. A suggestion to why this happened is that the initial high concentration of Rh species can catalyse the hydrolysis of Biphephos, the exact nature of the Rh-species capable of catalysing the oxidation in this situation is not yet known. A solution containing Biphephos without the presence of stabilisers is highly unstable at elevated temperatures and the Biphephos will soon decompose by hydrolysis. The presence of any of the three stabilisers investigated in this work (CHO, TEA or TMP) resulted in significantly more stable systems regarding hydrolysis. It was also observed that an increasing concentration of the amine-based additives (TEA and TMP) resulted in slightly increasing decomposition by oxidation of the Biphephos. The best Biphephos/toluene/additive system was achieved with TMP and CHO as additives at lower concentration, where after 3 weeks of continuous heating at 90°C most of the Biphephos was still intact. The ³¹P-NMR experiments were all prepared under non-inert conditions highlighting that O₂ alone will not oxidise Biphephos. Applying a “pressure de-pressure” cycles with high purity (synthesis) gas to a fully charged reactor before the start of a reaction gave significantly more stable reaction system. The PDP-cycle was used to “wash out” any remaining oxygen remaining inside the reactor contaminating the reaction system. This was confirmed by an increased l/b ratio at the end of the reaction. A summary of suitable actions

that can be taken in order to safeguard against phosphite decomposition are listed in Table 11 below.

Table 11: List of measures against phosphite decomposition when applied in hydroformylation systems

Degas and store liquids under argon
Use standard Schlenk technique
Dissolve Rh and ligand separately before combining
Remove peroxides in alkene substrate, e.g. by percolation over alumina or distillation
Use suitable stabilizers at suitable concentration
Apply PDP cycles after everything has been loaded into the reactor before start of reaction

Up until this moment, no report has stated that it has incorporated all these measures, but many have managed to include a few. Further ^{31}P -NMR experiments showed that weakly basic solvents such as ACN and DMF have a stabilising effect on Biphephos as compared to toluene.

Suggestions for future developments: Where things stand now, there are different paths that are recommended to be further investigated in order to establish a stable continuously operated Rh/Biphephos hydroformylation system with integrated ceramic nanofiltration membrane unit for catalyst recycling.

Using more polar solvent system: More polar solvents should be explored to see if a higher flux across the ceramic membrane can be realised for a Rh/Biphephos-catalysed hydroformylation reaction system. Also, the rejection of Biphephos by the ceramic nanofiltration membranes might improve with more polar solvents as the relative affinity between the different components of the system will change, see Figure 2-36. Recommended polar solvents to try are those that are non-protic (no acidic protons), and specifically those that are slightly basic (DMF and ACN) which will provide an intrinsically stabilising environment for Biphephos. Nevertheless, it is likely that any ACN or DMF solvent based reaction system would still require the presence of stabilisers to provide a suitable environment for Biphephos.

Complementary stabilisation: Since epoxides and amines will provide stabilisation through slightly different mechanisms, it is possible that a combination of different stabilisers could provide enhanced stability to a Biphephos system.

Larger MW stabilisers: In this work, the stabilisers that were investigated were either medium large (Tinuvin® 770 MW = 480.73) and resulted in a significant drop in the flux across the

membrane, or the additives were relatively small (TEA, TMP and CHO MW = 98.15 – 141.25) and were not rejected at all by the membrane. An alternative would be to use stabilising solutes that are large enough to be efficiently rejected by the membrane without causing the membrane pores to be clogged. In Figure 6-20 below is presented commercially available solutes containing functional groups which are likely to provide a stabilising effect against acid catalysed decomposition reactions of phosphites.

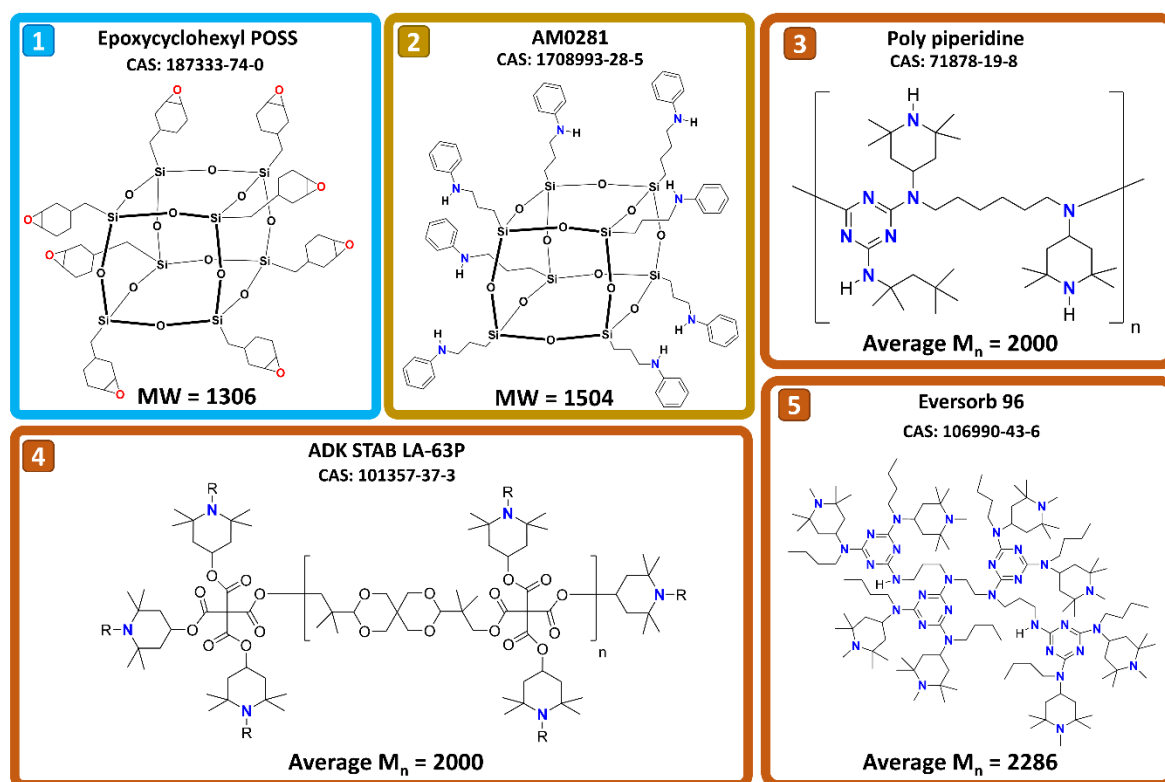


Figure 6-20: Commercially available large MW compounds with potential as phosphite stabilisers.

(1) Epoxycyclohexyl POSS,^[365] (2) AM0281,^[365] (3) Poly piperidine,^[418] (4) ADK STAB LA-63P,^[419] and (5) Eversorb 96.^[420]

Although all the molecules in Figure 6-20 are very large, they are also decorated with highly polar functional groups, which can potentially result in very strong interactions between these solutes and the membrane. This in turn could then lead to lower rejection and/or blockage of pores. It is not guaranteed that they will be rejected merely based on their large size, and so it is recommended that their rejection by nanofiltration membranes is initially studied in a simplified system only containing the solute and an appropriate (polar) solvent.

POSS-modification of Biphephos: No POSS-modified phosphite ligand was synthesised within this chapter or thesis, but it is worth discussing a few points related to this. Biphephos is a highly active and selective phosphite ligand that could benefit greatly from a POSS-modification now that its long-term stability under reaction conditions can be controlled. The first question when thinking about a potential POSS-Biphephos ligand is where on the ligand

it is most suitable to attach the POSS cage. Biphephos can be viewed as being made up of two different molecular entities as is shown in Figure 6-21 below.

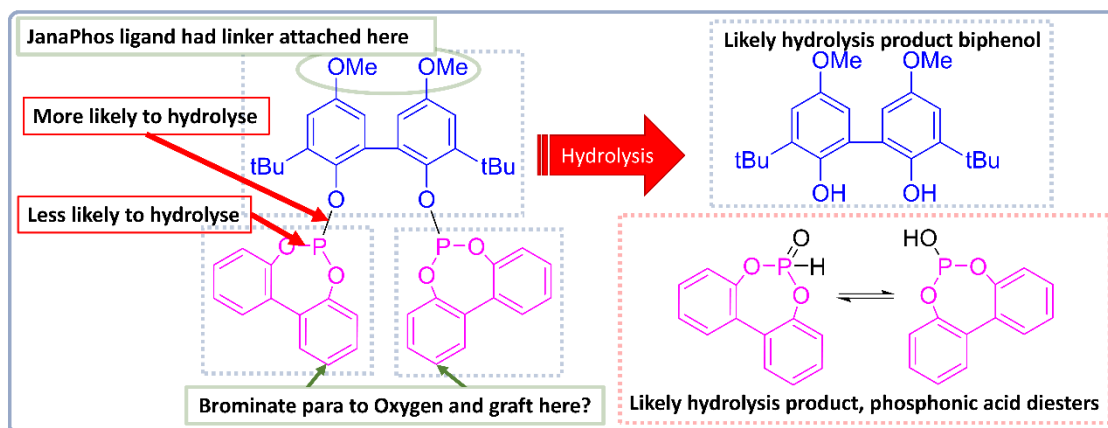


Figure 6-21: Considering potential approaches for MWE of Biphephos.

If Biphephos is hydrolysed it will most likely result in the two fragments presented in the figure above. Thus, it would make most sense to have the phosphonic acid diester fragment as small as possible as it could then be washed out of the membrane reactor. The biphenol hydrolysis-product is likely not going to cause many issues for the continuous stability of the system. Hence, it is best to attach a potential POSS cage to the upper segment, which was also done in the synthesis of JanaPhos.^[168]

6.5. Experimental

6.5.1. Materials

Chemicals used in the reaction were purchased from abcr, Acros Chemicals, deuteron, Fisher Chemicals, Merck, Sigma Aldrich, Umicore or VWR. Solvents used in the reactions were not dried but degassed in an ultrasonic bath while bubbling argon for 45 minutes. 1-octene used in Rh-catalysed hydroformylation was run through a plug of aluminium oxide to remove peroxides.

6.5.2. Setup

See section E. for detailed information about the setup (autoclave and ceramic membrane loop reactor).

6.5.3. Analytical methods

NMR: Measured using Bruker AV Avance III HD (400MHz or 600 MHz). The relative uncertainty for reported molar ratios is estimated at $\pm 5\%$ for ^1H -NMR and $\pm 10\%$ for ^{31}P -NMR.

GC-FID: Measured on an Agilent Technologies 7890A GC System. Quantitative analysis of reaction mixtures was performed via GC-FID using dodecane as an internal standard. Response factors were determined using five-point calibration curves ($R^2 > 0.999$). Based on the precision of the autosampler and the reproducibility of sample preparation, the relative standard deviation (RSD) for conversions and yields is estimated at $\pm 2.5\%$. For instance, a reported conversion of 95% carries a trustiness region of approximately ± 2.4 percentage points. This level of uncertainty is considered standard for the evaluation of kinetic trends in homogeneous catalysis. See section E. on page X for details about the GC methodology.

ICP-OES: The results of the samples for retention were determined with an ICP-OES of type iris intrepid ICP from Thermos Elemental with a radial and axial evaluation. The full amount of permeate and retentate were concentrated on a rotary evaporator prior to sample preparation for the ICP-OES measurement. For membrane retention values (e.g., reported as 99%), the uncertainty was minimized by concentrating permeate samples to ensure metal content remained significantly above the Limit of Quantification (LOQ). Based on the propagation of a conservative 5% relative standard deviation (RSD) for ICP-OES sample preparation and analysis, the absolute uncertainty for a 99% retention value is estimated to be approximately $\pm 0.1\%$. See section E. on page X for details about ICP sample preparation methodology.

6.5.4. Rh-catalysed hydroformylation of 1-octene in batch autoclave reactors

Batch autoclave experiments

All batch autoclave experiments were conducted in overhead stirred autoclaves described in E.4. page XI, where also the procedure for preparing the reactors is described. All autoclave experiments used a ratio of Rh:L:S = 1:5:6000.

Added to the pot: catalyst solution was introduced first followed by any additives and then the extra toluene. Added to the dropping funnel: 1-octene. After adding everything to the reactors, preformation was performed (700 rpm, 80°C at 18 bar $H_2:CO = 1:1$) for 1-2 hours. Final adjustment to the desired reaction set-points were then made, 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. Samples were withdrawn from the reactors at regular intervals using the sample device. A few seconds before each sample, the pipes of the sample device were flushed by discarding a small volume of reaction mass through it. Collected samples were analysed by GC-FID using the method of internal standard (IS = dodecane). The set-points of each experiment (T, p, rpm) were kept static.

Temperature variable- and the first two Et₃N and CHO additive experiments:

One single reactor (reactor 1) was used during these experiments. The catalyst solution was prepared by weighing out both Rh(acac)(CO)₂ (2.87 mg, 0.0111 mmol) and Biphephos (43.8 mg, 0.0557 mmol) dry into a single Schlenk-flask fitted with a stirrer bar to which toluene (20 ml) was added, the solution was left to stir for about 20 min or until everything had dissolved (it is highly likely that there were still undissolved debris present at the point when the catalyst solution was filled into syringe). The catalyst solution was removed from the Schlenk-flask into a 20 ml syringe, another 20 ml syringe was filled with 21 ml toluene, a “10 ml syringe” was filled with 10.5 ml 1-octene (44.6 mmol).

CHO/Et₃N/TMP additive experiments:

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. Both Rh(acac)(CO)₂ (8.754 mg, 0.0339 mmol) and Biphephos (133.59 mg, 0.1698 mmol) dry into a single Schlenk-flask fitted with a stirrer bar to which toluene (70.15 ml) was added, the solution was left to stir for about 20 min or until everything had dissolved (it is highly likely that there were still undissolved debris present at the point when the catalyst solution was filled into syringe). For each autoclave reaction, catalyst solution (23 ml) was removed from the Schlenk-flask into a 20 ml syringe, another 20 ml syringe was filled with 18 ml toluene and a “10 ml syringe” was filled with 10.5 ml 1-octene (44.6 mmol).

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 (8.754 mg, 0.0339 mmol) and Biphephos (133.59 mg, 0.1698 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 60.15 ml toluene. The solutions were left to stir for about 20 min or until everything had dissolved, (this time it is was highly likely that all material was 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. For each autoclave reaction, catalyst solution (23 ml) was removed from the Schlenk-flask into a 20 ml syringe, another 20 ml syringe was filled with 18 ml toluene and a “10 ml syringe” was filled with 10.5 ml 1-octene (44.6 mmol). The correct amount of additive for each reaction was measured out into 1 ml syringe, for the lower quantities diluted stock solutions of additive in toluene were

made up. 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. A PDP-cycle was performed according to the description in E.6. The PDP-cycle was then repeated the number of times the experiment requested. At the end of the PDP-cycle the usual procedure of pre-formation was done before the onset of the reaction.

6.5.5. Rh-catalysed hydroformylation of 1-octene in a continuous flow loop reactor experiments:

The ceramic membrane loop reactor used in these experiments is described in E.5. The reactor was also prepared according to the procedure described in E.5. Reactions were designed to have ratio Rh:L:S = 1:5:6000. A catalyst solution was prepared by weighing out both Rh(acac)(CO)₂ (14.8 mg, 0.057 mmol) and Biphephos (226.6 mg, 0.288 mmol) dry into a single Schlenk-flask fitted with a stirrer bar to which toluene (14 ml) was added. After stirring this solution for about 30 min it was introduced into the dropping funnel of the reactor from the upper valve under a steady counterflow of argon. The reactor was then heated to the reaction temperature (90°C), when this had been reached the reactor was pressurised with synthesis gas (H₂:CO = 1:1). The membrane was always free to permeate, and the permeated volume was made up by fresh substrate solution (1.6 M 1-octene in toluene) via the HPLC-pump which was operating on feedback from the level sensor of the reactor. When the reactor had reached a steady state of permeation after reaching the set reaction temperature and pressure, the valve to the dropping funnel was opened so that the catalyst solution entered the substrate solution inside the reactor and the reaction was considered to have started (t = 0). Samples were taken from the permeate stream at regular intervals, which were analysed by GC-FID using the method of internal standard (dodecane). The permeate was collected into a bottle standing on a balance, and the substrate was kept inside another bottle also standing on a balance. The change in mass over time of permeate and substrate was thus recorded. At the end of an experiment the total volume of all the solutions were measured separately (mass and volume). These solutions were the pre-catalyst addition permeate and the post-catalyst addition permeate. These were then concentrated down on a rotary evaporator and again measured for mass and volume. The two permeate solutions as well as un-altered sample from the end of the reaction reactor solution were then submitted for ICP analysis (P and Rh).

6.5.6. Studying the stability of Biphephos using ³¹P-NMR

A total of 6 different sets of ³¹P-NMR experiment series were investigated. All of the sets contained Biphephos, but they then differed in what other solutes and solvents were present as

well as the method of how the solutions were being prepared. Once the Biphephos solutions were prepared, the general procedure was to add 0.3 ml of that solution to an NMR tube together with 0.3 ml toluene-d₈. (obs. for phosphites, must not use CDCl₃, as this will always contain a certain amount of HCl from the solvent's decomposition). The NMR tube was then sealed with a cap and extra layers of parafilm. The samples were then submitted for analysis by ³¹P-NMR with inverse gated decoupling of protons. Throughout an investigation the NMRs were subjugated to heating cycles at defined temperature and time with intermittent ³¹P-NMR analysis. Heating of the NMR tubes was achieved by using a hot-plate heating sand-bath, with the thermocouple of the hot-plate being stuck into the sand bath. NMR tubes were then easily placed and removed into the hot sand-bath.

Premature hydrolysis of Biphephos experiment 1:

A total of 30 NMR samples were prepared containing Rh:Biphephos = 1:5 and one out of three additives (TMP, Et₃N or CHO) in different ratios Biphephos:additive = 1:0.01, 1:0.1, 1:0.35, 1:1, 1:3.5, 1:35, 1:70, 1:175, 1:350 and 1:700. The samples were prepared accordingly:

Rh(acac)(CO)₂ (17.69 mg, 0.0685 mmol) and Biphephos (471.8 mg, 0.600 mmol) were weighed out into a single round bottom flask containing a stirrer bar, no care was taken to inertness. Toluene (35 ml) was added to the solids in the round bottom flask to dissolve them while stirring for about 1 h until (almost) everything had dissolved. A series of 30 test tubes (3 x 10) with screw caps were prepared with 1 ml each of the Biphephos/Rh solution so that each test tube contained Biphephos (13.48 mg, 0.0171 mmol). The three different additives were then added to the test tubes according to the table below and vigorously shaken.

Test tube	Add:BP	Add	V TMP	V TMP M=0.1	V CHO	V CHO M=0.1	V Et ₃ N	V Et ₃ N M=0.1
[-]	[-]	[mmol]	[μL]	[μL]	[μL]	[μL]	[μL]	[μL]
1	700	12	2024	X	1242	X	1672	X
2	350	6	1012	X	621	X	836	X
3	175	3	506	X	310	X	418	X
4	70	1.2	202	X	124	X	167	X
5	35	0.6	101	X	62	X	84	X
6	3.5	0.06	X	600	X	600	X	600
7	1	0.0171	X	171	X	171	X	171
8	0.35	0.006	X	60	X	60	X	60
9	0.1	0.00171	X	17.1	X	17	X	17
10	0.01	0.000171	X	1.71	X	1.7	X	1.7

These solutions were then used for preparing the NMR samples according to standard procedure previously described above. The NMRs were never subjugated to any heating cycle

as large quantities of hydrolysis products were detected already during the first ^{31}P -NMR analysis.

Premature Hydrolysis of Biphephos Experiment 2:

A total of 27 NMR samples were prepared, all containing Rh:Biphephos = 1:5 and one out of three additives (TMP, Et₃N or CHO) in different ratios Biphephos:additive = 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. 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 x 9) with screw caps were prepared with 2 ml each of the Biphephos/Rh solution so that each test tube contained Biphephos (12.58 mg, 0.01599 mmol). The three different additives were then added to the test tubes according to the table below and vigorously shaken.

Test tube	Add:BP	Add	V TMP	V CHO	V Et ₃ N
[-]	[-]	[mmol]	[μL]	[μL]	[μL]
1	288	4.605	777.2	476.8	641.9
2	144	2.303	388.6	238.4	320.9
3	72	1.151	194.3	119.2	160.5
4	35	0.560	94.4	57.9	78.0
5	20	0.320	54.0	33.1	44.6
6	10	0.160	27.0	16.6	22.3
7	5	0.080	13.5	8.3	11.1
8	2	0.032	5.4	3.3	4.5
9	1	0.016	2.7	1.7	2.2

These solutions were then used for preparing the NMR samples according to standard procedure previously described above. After the NMR tubes had been analysed by ^{31}P -NMR they were subjugated to heating at 90°C for 14 h and then again analysed by ^{31}P -NMR.

Rh-free additive-containing solutions:

A total of 27 NMR samples were prepared, all containing Biphephos and one out of three additives (TMP, Et₃N or CHO) in different ratios Biphephos:additive = 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, 0.7197 mmol) was weighed out into a round bottom flask containing a stirrer-bar, no care was taken to inertness. 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 x 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 additives were then added to the test tubes so that the relevant ratio of Biphephos:additive was established. These solutions were then used for preparing the NMR samples according to standard procedure.

Correct order of preparing a Rh(acac)(CO)₂ and Biphephos solution:

A total of 4 NMR samples were prepared, all containing Rh:Biphephos = 1:5, one of which had no additive and the other three had one out of the three additives TMP, Et₃N or CHO present in a ratio Biphephos:additive = 1:5. The samples were prepared accordingly:

Biphephos (134.80 mg, 0.171 mmol) and Rh(acac)(CO)₂ (8.84 mg, 0.034 mmol) were weighed out separately and added to two separate round bottom flasks containing stirrer-bars. 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 13.48 mg Biphephos (0.017 mmol). Additives were then added to 3 of the test tubes according to the table.

Test tube	Add:BP	Add	V CHO	V TMP	V Et ₃ N
[-]	[-]	[mmol]	[μL]	[μL]	[μL]
1	5	0.086	8.9	-	-
2	5	0.086	-	14.5	-
3	5	0.086	-	-	11.9
4	-	-	-	-	-

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

Effect of Biphephos:additive ratio:

A total of 27 NMR samples were prepared, all containing Rh:Biphephos = 1:5 and one out of three additives (TMP, Et₃N or CHO) in different ratios Biphephos:additive = 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. Toluene (45 ml) was added to each of the 2 round bottom flasks to dissolve all the solids, they were left stirring for about 1 h. The Rh(acac)(CO)₂ solution was then added dropwise to the Biphephos solution. A series of 27 test tubes (3 x 9) with screw caps were

prepared with 2 ml each of the Biphephos/Rh solution so that each test tube contained Biphephos (12,58 mg, 0.016 mmol). The three different additives were then added to the test tubes according to the table below and vigorously shaken.

Test tube	Add:BP	Add	V TMP	V CHO	V Et ₃ N
[-]	[-]	[mmol]	[μ L]	[μ L]	[μ L]
1	288	4.6	780	480	640
2	144	2.3	390	240	320
3	72	1.2	190	120	160
4	35	0.56	94	58	78
5	20	0.32	54	33	44
6	10	0.16	27	17	22
7	5	0.080	14	8.3	11
8	2	0.032	5.4	3.3	4.5
9	1	0.016	2.7	1.7	2.2

These solutions were then used for preparing the NMR samples according to standard procedure previously described above. After the NMR tubes had been prepared, they waited 3 days at room temperature before they were first analysed by ³¹P-NMR. After this they were subjugated to heating cycles with intermittent ³¹P-NMR analysis accordingly: 90°C for 24 h; 90°C for 7 days; 90°C for 14 days.

Stability of Biphephos in Different Solvents:

Three different round bottom flasks were prepared each with one stirrer bar and Biphephos (134.8 mg, 0.1714 mmol). To each flask was added Toluene, DMF or ACN (10 ml) to give clear solutions. From each solution was prepared four NMR tubes taking 0.3 ml solution and 0.3 ml toluene-d₈. The NMR tubes were capped and sealed with parafilm, analysed by ³¹P-NMR between being subjected to heating at 70°C.

Chapter 7: Synthesis, Characterisation and Application of H-S-POSS

7.1. Abstract

The commercially available compound octaphenyl-POSS was sulfonated using chlorosulfonic acid. The resulting material was highly insoluble in all common laboratory solvents, but its Na-salt showed limited solubility in water. The sulfonated-POSS (H-S-POSS) acid was further characterised by NMR, ATR-IR, SEM, DLS, and theta-potential. It was then investigated as a catalyst in the ketalisation of glycerol with butanone. The H-S-POSS proved to have excellent catalytic properties and performed almost as well as para-toluenesulfonic acid (PTSA), which is the homogeneous derivative version of H-S-POSS and considerably more active than Amberlyst-36. Recycling experiments using centrifugation-sedimentation-decantation showed no loss of activity over 10 recycling runs for the H-S-POSS catalyst having the lowest degree of sulfonation.

7.2. Introduction

This chapter is concerning the application of POSS as a MWE-unit for a Brønsted catalyst. The synthesis of H-S-POSS has already been reported in several sources, but it has so far never been explored as an acid catalyst for any reaction. The synthesis of H-S-POSS is a one-pot reaction that can yield completely sulfonated products, although some reports state that the sulfonation can be unpredictable as to what degree the sulfonation will reach. There are Brønsted acids based on sulfonated polyorganosiloxanes (SPOS), which is not POSS, but a closely related material as it constitutes a silicon oxide meshwork with organic phenyl rest groups that have been sulfonated.^[242] These sulfonated polyorganosiloxanes catalysts have proved to have higher thermal stability than the typical cation exchange resin Amberlyst 15 but the same activity.^[241] Hence it was anticipated that H-S-POSS would be an at least as active catalyst as those aforementioned ones.

7.3. Results and Discussion

Three attempts at synthesising a fully sulfonated S-POSS product were made using different conditions. The three attempts resulted in products that had different overall degrees of sulfonation. The three S-POSS products were purified and characterised using a variety of techniques. Their catalytic activity was then investigated in the model reaction, ketalisation of glycerol with butanone, by sampling over time under controlled conditions. The equilibrium

yield at different reactant ratios was explored and a suitable ratio for further kinetic experiments was then identified. The H-S-POSS catalysts were proven to be highly insoluble and recycling attempts were conducted where the catalysts were separated after a reaction by means of centrifugation. Only slight loss in activity was measured after 10 recycling rounds.

7.3.1. Synthesis of H-S-POSS

H-S-POSS was synthesised by direct chlorosulfonation of octaphenyl-POSS by adding chlorosulfonic acid in excess at 0°C, then leaving to react over night at room temperature and finally adding water for hydrolysis. The synthetic protocol that was used was based on that of Kafi et al.^[421] The overall reaction is presented in Figure 7-1 below.

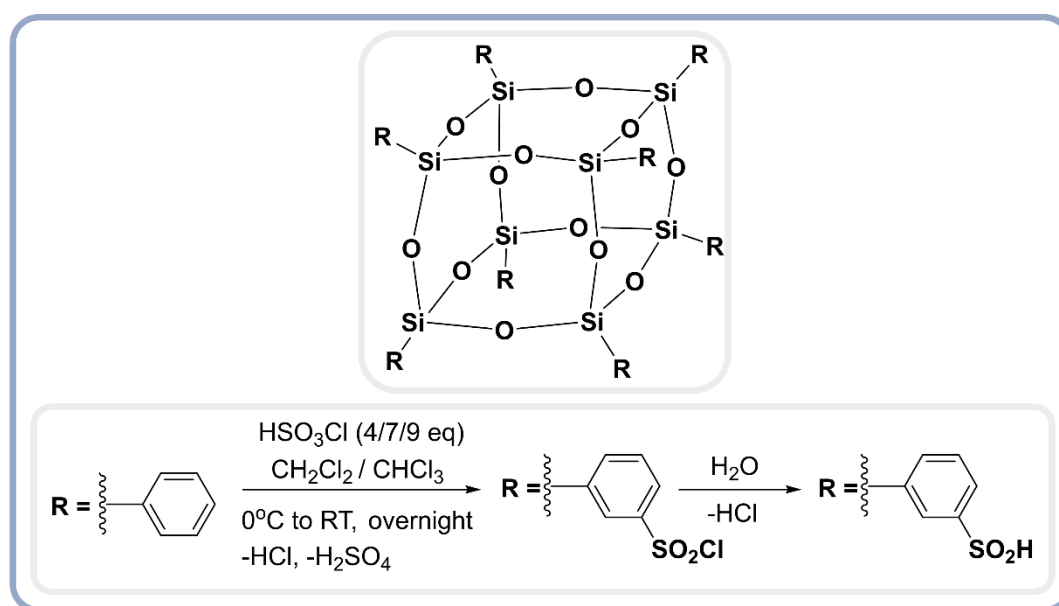


Figure 7-1: Synthesis of H-S-POSS by chlorosulfonation of octaphenyl-POSS and subsequent hydrolysis.

The synthesis was attempted three times where small changes in parameters were made between them, which are presented in Table 12 below. The first two experiments, resulted in overnight premature precipitation of (product) material while the third experiment stayed fully dissolved until water was being added the next day. Each of the three different products has been labelled a specific name (H-S-POSS-1, -2 or -3).

Table 12: The three H-S-POSS batches presented with the associated conditions, degree of sulfonation and yield.

H-S-POSS	Solvent	V(solvent) / m(OP-POSS)	Eq. of HSO ₃ Cl (per Ph)	Est. Sulf. Deg.	Yield
[-]	[-]	[ml/g]	[-]	[-]	[%]
1	CH ₂ Cl ₂	9	3.9	0.195	30
2	CHCl ₃	20	7.2	0.285	62
3	CHCl ₃	10	8.7	0.660	81

The equivalence is based on the total number of phenyl groups. The yield was calculated by taking the overall sulfonation degree into consideration.

The absence of any acidic contamination material in the collected crude H-S-POSS product had to be safeguarded as they were to be investigated for their acidic catalytic properties. The crude products were therefore first neutralised with NaOH (Na₂CO₃ was used in the first attempt) and then re-acidified by stirring in concentrated HCl and finally left under high vacuum. During the chlorosulfonation stage, up to eight phenyl groups of each octaphenyl-POSS substrate could have been sulfonated. The collected products therefore contained a varying degree of sulfonation (ratio between sulfonic acid groups to total number of phenyl groups). The overall degree of sulfonation for each product batch was estimated based on the H-S-POSS ion-exchange-capacity (IEC) of a sample from that batch. During all three synthetic attempts an initially clear, homogeneous and slightly yellow reaction mixture resulted after all chlorosulfonic acid had been added. Large premature precipitation of a white solid occurred over night in the first two experiments. The product from these two initial experiments showed significantly lower IEC than the third, which stayed in solution also until the next day. Prior reports stated that the degree of sulfonation can be controlled by the excess of chlorosulfonic acid used, where 6 – 11 equivalents of chlorosulfonic acid to phenyl groups would give about 40% complete sulfonation.^[422] In contrast, others have reported significantly higher degree of sulfonation when using the same equivalents of chlorosulfonic acid.^[246] And yet again, others have reported as high as 94% sulfonation when only using 1.5 eq. of chlorosulfonic acid to phenyl groups.^[247] Hence there is large ambiguity about what the important factors are that determine the degree of sulfonation of octaphenyl-POSS. But in all protocols the temperature has always been kept close to 0°C while adding the chlorosulfonic acid dropwise. A previous study on sulfonation of phenyl-silanes observed large amounts of aromatic ring cleavage.^[423] The lower degree of sulfonation of the first two products is attributed to their premature precipitating out of the reaction mixture. This effectively made their still unreacted phenyl groups inaccessible to the chlorosulfonic acid. The reason for the premature precipitation is thought to be that too much of any formed intermediate chlorosulfonic-POSS was being

hydrolysed too soon. The result is the formation of H-S-POSS entities that possess very large hydrogen bonding capacity between each other causing their solubility in chloroform to be significantly reduced as compared to unhydrolyzed Cl-S-POSS intermediates. On top of this comes also intermolecular π - π stacking from any phenyl groups. Hence, using a higher equivalence of the chlorosulfonic acid would help to speed up the chlorosulfonation step and increase the number of Cl-S-POSS moieties (increased solubility), while also reduce the chance of any formed Cl-S-POSS being hydrolysed as there would be an increased concentration of freely available unreacted ClSO_3H present in solution ready to neutralise any water that is present. Despite this, the product that was collected from experiment 3 had an overall degree of sulfonation of 66% after having reacted at room temperature for 12 h. Hence, the rate of the sulfonation reaction at room temperature was not very high. In order to reach higher degrees of sulfonations it is important to maintain full solubility of all the POSS material throughout the first stage (hence use a large excess of chlorosulfonic acid and/or use dryer reagents and solvent, but longer reaction time and a slightly increased reaction temperatures are suggested to be tested).

All three H-S-POSS products were obtained as very fine grey/white powders. They were practically insoluble in any of the following solvents: water, ethanol, DMSO, THF, DCM, chloroform – measured at room temperature, 20°C. And so, their characterisation by NMR had to be done on their associated Na-salts, which improved solubility in water for H-S-POSS-1 to 2g/L, and for H-S-POSS-2 and -3 to approximately 5 g/L at 20°C. The yields of the products were not great for any of the experiments, especially bad for H-S-POSS-1 (30%). The reason for this is mainly due to underestimating the water solubility of the Na-derivatives during their washing with water. General losses were thus incurred during the neutralisation of the crude H-S-POSS to the Na-S-POSS, and during the reacidification steps. Albeit, those steps were necessary as to guarantee no remaining chlorosulfonic or sulfonic acid being present in the final products. An attempt was made to immobilise the H-S-POSS onto silica. Silica, with a particle size of 40-60 μm was added to an aqueous suspension of H-S-POSS-3 (10 wt% based on silica). The water was then evaporated under reduced pressure.

7.3.2. Characterisation of S-POSS

Ion exchange capacity and degree of sulfonation: To determine the IEC of the different H-S-POSS products a reverse acid-base-titration was carried out. The IEC is then correlated to the degree of sulfonation according to the plot presented in Figure 7-2 below.

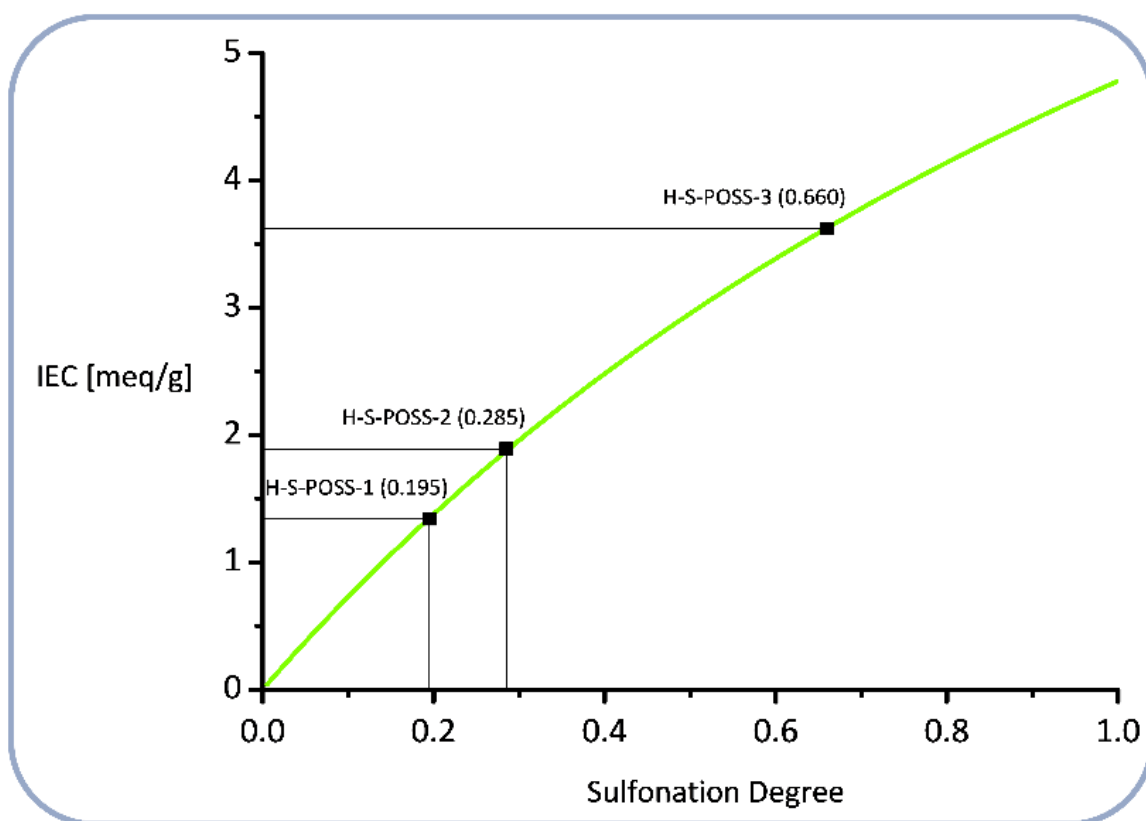


Figure 7-2: The theoretical IEC as a function of the sulfonation degree (green line) of H-S-POSS. The experimentally determined IEC values are marked out and the corresponding sulfonation degrees were retrieved from the plot.

IEC was determined for both the crude product and the product obtained after the neutralisation-reacidification step. The results are presented in Table 13 below.

Table 13: The ion exchange capacity (IEC) of the different H-S-POSS products.

H-S-POSS	IEC [meq/g]		Est. Sulfonation Degree
	Crude	Reacidified	
1	-	1.34	0.20
2	2.99	1.89	0.29
3	4.03	3.62	0.66
3 (on silica)	0.50	-	-

As can be seen, the crude products had significantly greater IEC than after they had been neutralised and reacidified. The crude products contained contaminating sulfuric or chlorosulfonic acid that becomes neutralised and removed during the reacidification. But it is also possible that the reacidification process was not complete, so unprotonated sulfonate groups remained after the reacidification step. This could be a possibility as when the relatively highly water-soluble Na-S-POSS is protonated, its solubility decreases and starts precipitating and trapping still unprotonated sulfonate groups inside precipitated particles. The silica-

absorbed H-S-POSS-3 (10 wt%) had an IEC of 0.50 meq/g, which can at a first glance be considered a bit high. But silica is on its own slightly acidic which therefore explains this result.

NMR Spectroscopy: The H-S-POSS had very limited solubility for all three products and so their associated sodium salts were used to make up solutions which were analysed by ^1H , ^{13}C and ^{29}Si -NMR. The ^1H -NMR spectra of Na-S-POSS-1, -2 and -3 are presented in Figure 7-3 below.

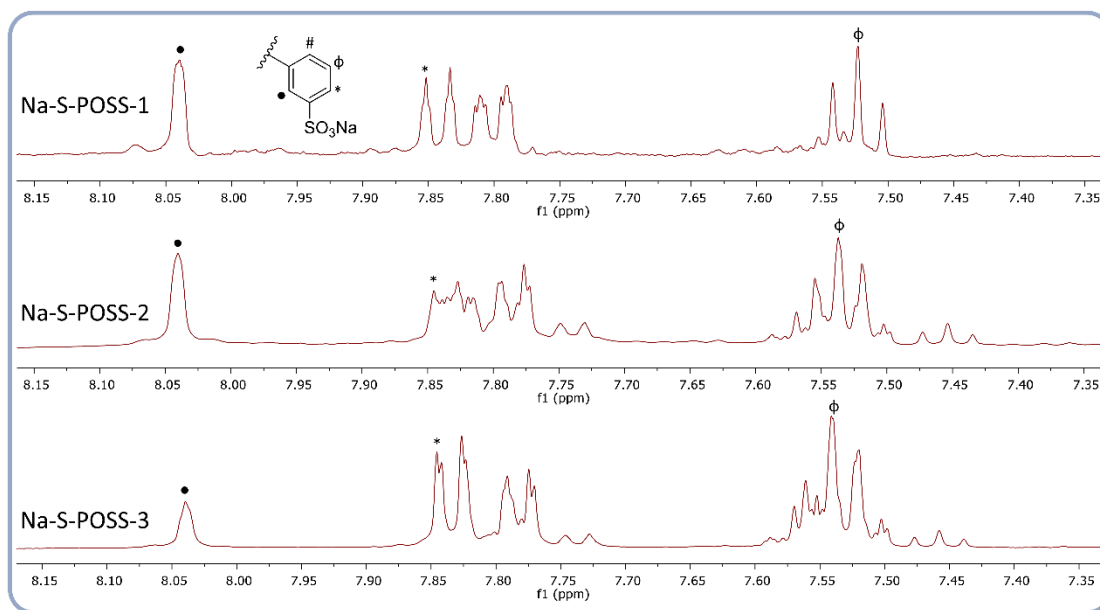


Figure 7-3: The ^1H -NMR of the sodium salts of S-POSS (Na-S-POSS-1, -2 and -3) dissolved in D_2O , 400 MHz.

The assignment of the spectra was less than trivial as each sample contained a mixture of S-POSS molecules with a variety of different degrees of sulfonation. Certain key peaks could be identified such as the singlet at 8.04 which represent the proton at the *ortho*-position to both POSS and the sulfonate group.^{[421], [422]}

ATR-IR Spectroscopy: The starting material octaphenyl-POSS (OP-POSS) and the product H-S-POSS-1 were analysed by ATR-FTIR-spectroscopy in their solid state. The spectra that were obtained are presented in Figure 7-4 below.

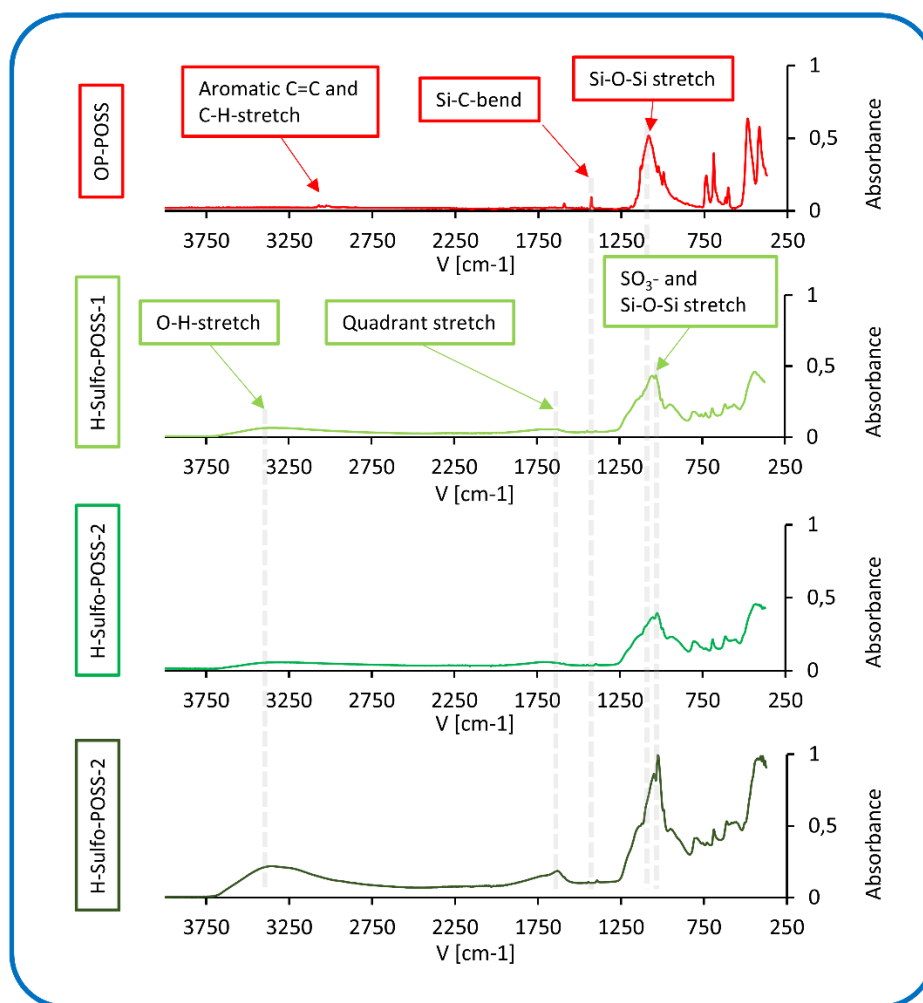


Figure 7-4: The ATR-FTIR spectra of octaphenyl-POSS (OP-POSS) and the three H-S-POSS catalysts. Bruker Alpha FT-IR spectrometer.

The IR spectrum of the starting material (OP-POSS) shows some distinguishable bands that were identified to belong to aromatic C=C and C-H stretch vibrations (around 3025 cm^{-1}), Si-C-bending vibrations (at 1425 cm^{-1}) and Si-O-Si stretching vibrations (at 1086 and $750\text{--}800\text{ cm}^{-1}$). After the aromatic electrophilic sulfonation a few very distinguishable bands associated with the $\text{-SO}_3\text{H}$ group (1050 , 1120 and 1170 cm^{-1}) appeared.^[424] Also, the broad band at 3370 cm^{-1} can be attributed to O-H stretching absorption bands, indicating strong H-bonding by its broad shape. The band at around 1650 cm^{-1} is attributed to the meta-substitution of the phenyl rings of octaphenyl-POSS.^[422] The spectra have not been scaled and can only be interpreted qualitatively and not quantitatively.

Scanning electron microscopy: A field emission scanning electron microscopy (FESEM) was used for taking high resolution pictures of the H-S-POSS-1 and silica absorbed H-S-POSS-3. Pictures are presented in Figure 7-5 to Figure 7-8 below.

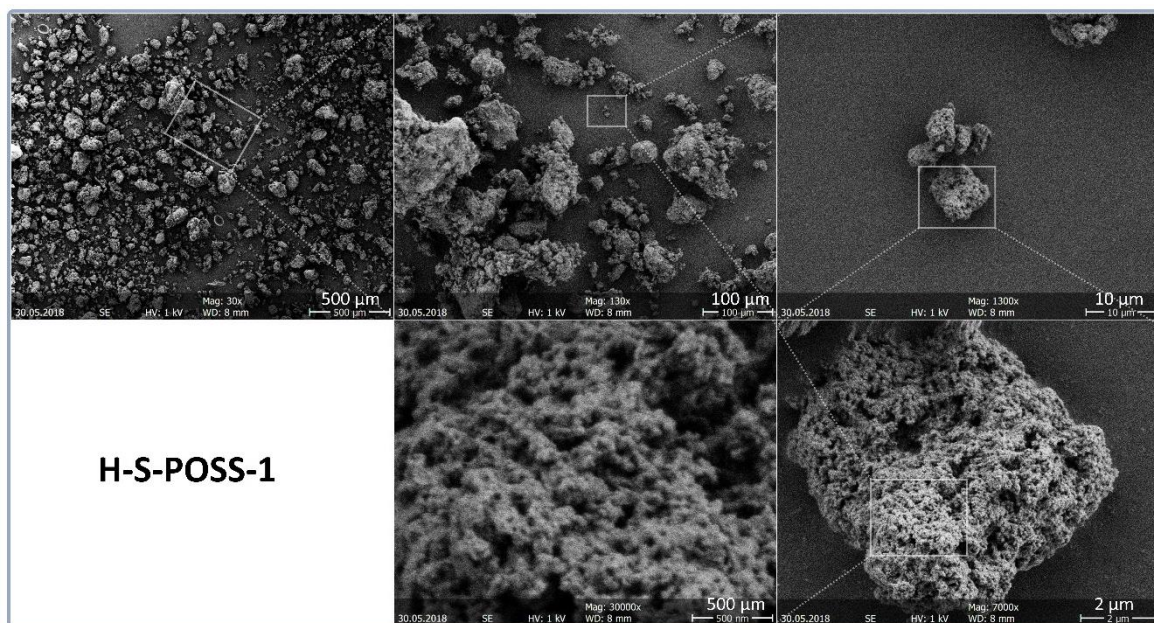


Figure 7-5: Scanning electron microscopy (SEM) pictures of H-S-POSS-1.

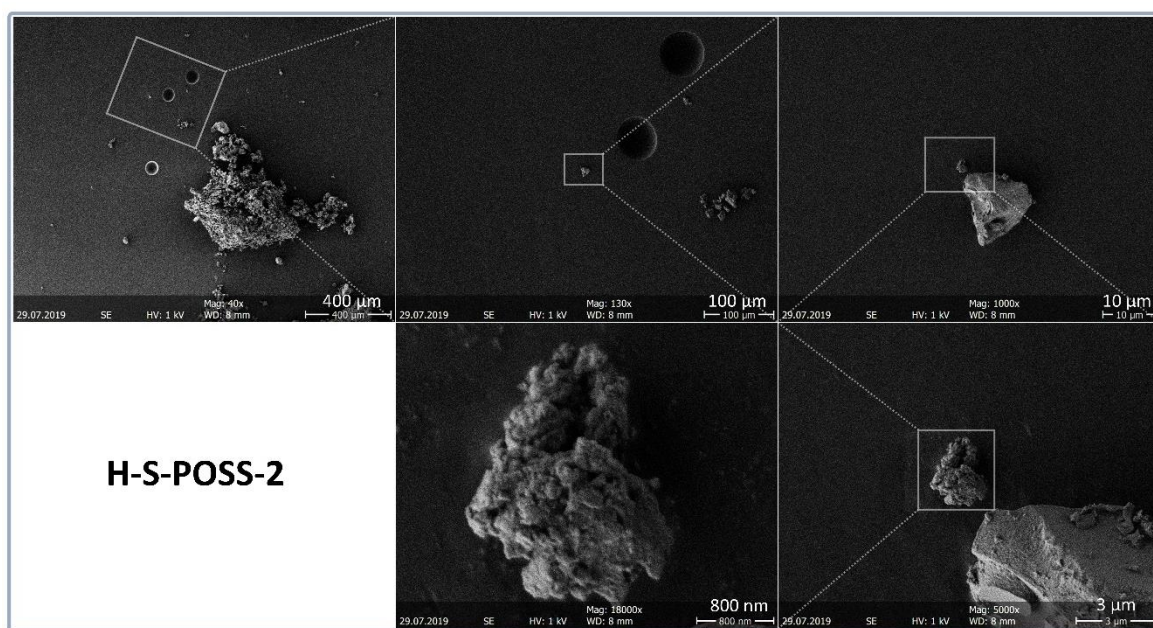


Figure 7-6: Scanning electron microscopy (SEM) pictures of H-S-POSS-2.

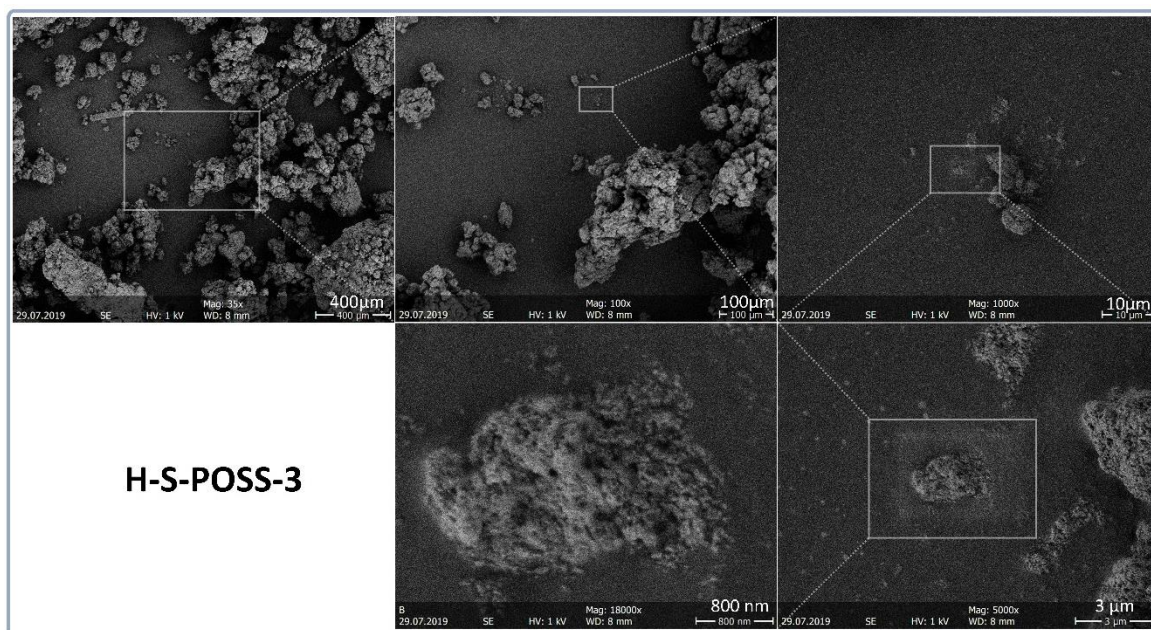


Figure 7-7: Scanning electron microscopy (SEM) pictures of H-S-POSS-3.

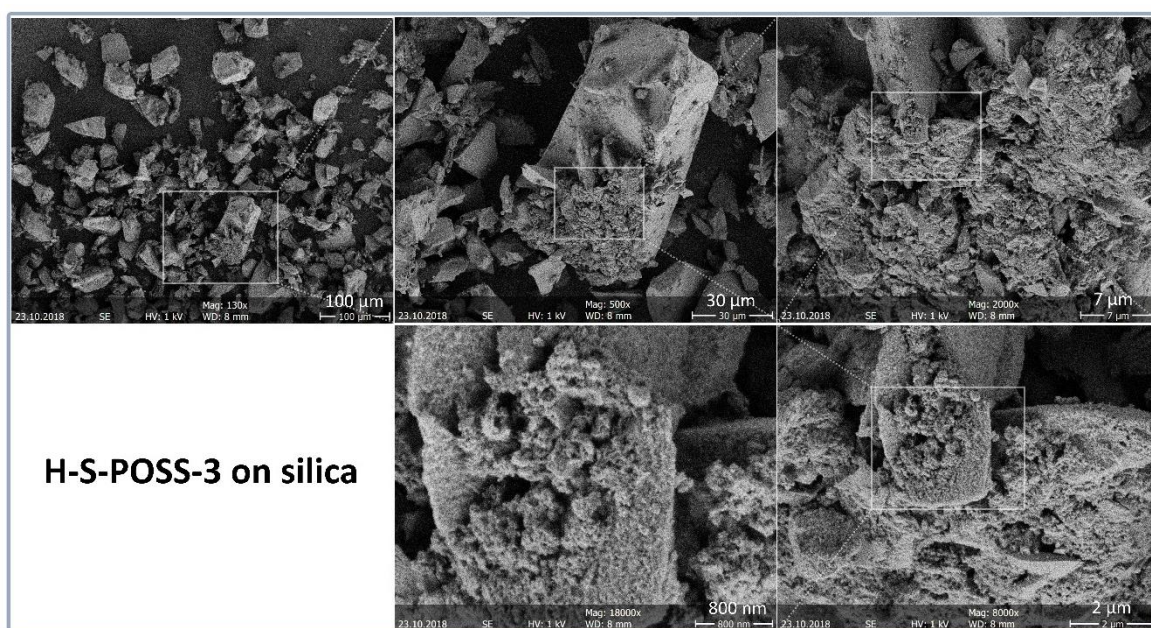


Figure 7-8: Scanning electron microscopy (SEM) pictures of H-S-POSS-3 deposited onto silica.

The H-S-POSS-1 compound forms particles of varying sizes from as small as 9 μm up to approximately 250 μm, where the larger particles look like an assembly of smaller particles. At the maximum zoom on the particles, the surface looks highly uneven and rough, almost porous. A similar scenario is observed with the H-S-POSS-2 material. The H-S-POSS-3 material shows significant amounts of very fine debris scattered at the 2 μm and 800 nm zoom. After the deposition of the H-S-POSS-3 onto silica, no large free H-S-POSS particles were visible anymore. The silica particles are coated with the H-S-POSS which only becomes clear

after zooming in. The coating is uneven in thickness between the various silica particles giving some particles a higher catalyst loading than others.

Dynamic light scattering and ζ -potential: H-S-POSS-1 was characterised with these two techniques. A suspension of H-S-POSS-1 in water was measured with DLS, the results indicated that the suspension contained particles of a size 760 ± 150 nm. That is considerably smaller than any of the free particles observed in the SEM pictures, but still significantly larger than the size of the smallest observed particles in the SEM of H-S-POSS-3. The ζ -potential of H-S-POSS-1 was determined to be -17.7 ± 1.8 mV. This falls into the range where the material is expected to form delicate dispersion, without having particles coagulating to form large ones.

7.3.3. Analysis Method for the Ketalisation of Glycerol with Butanone

After the synthesis and characterisation of S-POSS, it was time to investigate their catalytic properties as acid catalysts. Ketalisation of glycerol with butanone was chosen as the model reaction. To be able to monitor the course of a reaction an appropriate method for analytics had to be established. First the product compound from the reaction was isolated from a reaction mixture containing a large excess of butanone and H-S-POSS-1 as the catalyst. Initially gas chromatography was explored but was soon realised to have some major hurdles. Next ^1H -NMR was identified to be a highly suitable method for monitoring the progress of a reaction. In all cases, as soon as a sample had been withdrawn from the reaction mixture, they were quenched by being mixed with an excess of pyridine.

Gas chromatography: For the gas chromatography analysis, the method of internal standard was used where n-dodecane was the internal standard added in a known amount to a sample. The reactants and the product (glycerol, butanone and ketal) were all individually calibrated against n-dodecane so that quantification of each mole fraction in every sample could be analysed. A typical gas chromatogram is presented in Figure 7-9 below.

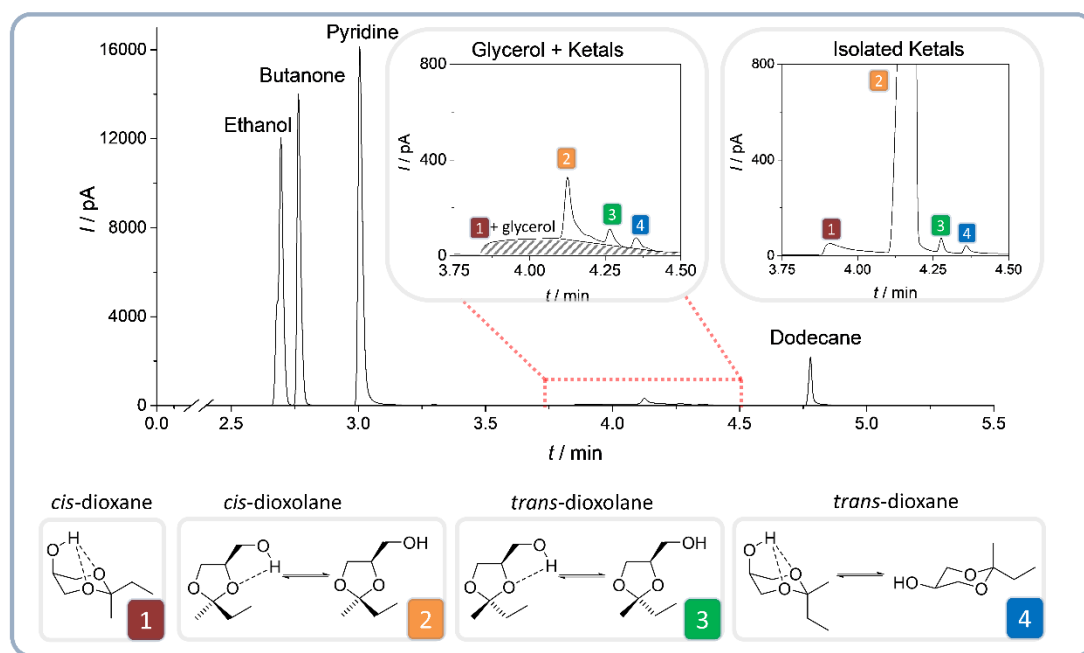


Figure 7-9: A gas chromatogram of a typical reaction mixture from the ketalisation of glycerol with butanone. The chromatogram contains four different ketal isomers (1 – 4), glycerol (reactant, hatched), butanone (reactant), ethanol (solvent), pyridine (quenching) and dodecane (internal standard). Above is also presented a gas chromatogram of isolated ketals.

The four different isomers of the ketal can be clearly observed in the chromatogram with one significantly larger peak 2 (*cis*-dioxolane) than the other three. Their m/z was confirmed to be

that of the ketal using complementary GC-MS. It is known that between the five- and six-membered ketals (1,3-dioxolane or 1,3-dioxane), the five ring structures are more stable than the six membered isomers. It is also known that the *cis*-isomer will have a shorter retention time than the *trans*-isomer.^[250] It is also known that the *cis*-isomer of various 5-hydroxy-2-X-1,3-dioxanes (X represents various substituents) have exclusively intramolecularly bonded hydroxyl groups, supporting that peak 1 is likely to be the *cis*-dioxane.^[425] The chromatogram also highlights a major issue with this method of analysis, which is peak overlap. The glycerol peak overlaps with all the four different ketal peaks due to its very pronounced tailing through the column that is a result of its high density of hydroxyl groups. The first ketal peak is completely lost inside the glycerol peak and so a different method of analysis was investigated.

¹H-NMR: An alternative method for quantifying the reaction mixture composition is to use ¹H-NMR spectroscopy. A spectrum of a typical reaction mixture containing glycerol, butanone, ethanol and the product ketals is displayed in Figure 7-10 below.

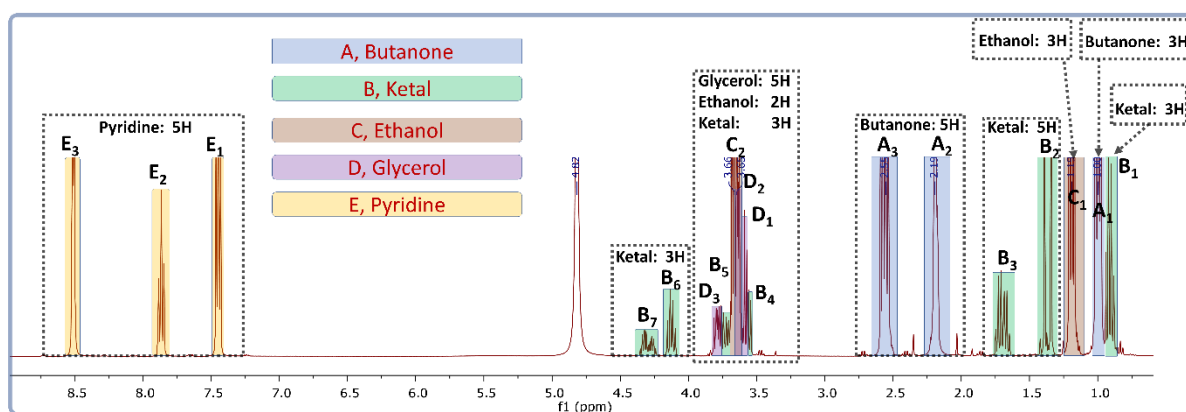


Figure 7-10: ¹H-NMR spectrum of a typical reaction mixture from the ketalisation of glycerol by 2-butanone, (CDCl₃, 600 MHz). The different peaks have been coloured and labelled according to the reaction mixture component that it is associated with.

By normalising the integrals of the peaks related to the different compounds in the reaction mixture relative to the product peak, which has a known number of protons, the relative molar ratio between each compound and the product can be directly calculated. The signal labelled as “B₂” in the graphic was chosen as it is the product peak with the highest number of associated protons. Yield can then be calculated based on the integral relationship between this “B₂” peak and peaks associated with either glycerol or butanone. Pros and cons exist for both options. The glycerol peaks are overlapped by other peaks of other compounds and butanone is known to be somewhat volatile and it can be difficult to quantify the amount that evaporated during a reaction or during a sample preparation. Both options were evaluated, and it was concluded that using the glycerol peaks gave more reliable results, although this approach does require

that the peak area associated with both ethanol and the ketal must be taken into consideration and calculated for.

7.3.4. Equilibrium Yield in the Ketalisation of Glycerol with Butanone

The ketalisation reaction of glycerol with butanone is an equilibrium reaction where the maximum achievable conversion and yield is strongly dependent on the ratio between glycerol and butanone that is being applied. To find a suitable ratio which gives a good conversion that allow reaction monitoring over time to be implemented, a set of six experiments were conducted, each having a different glycerol to butanone ratio. The experiment covered glycerol:butanone ratios from 1:0.5 up to 1:13. The equilibrium conversion for each of the six experiments is presented in Figure 7-11 below.

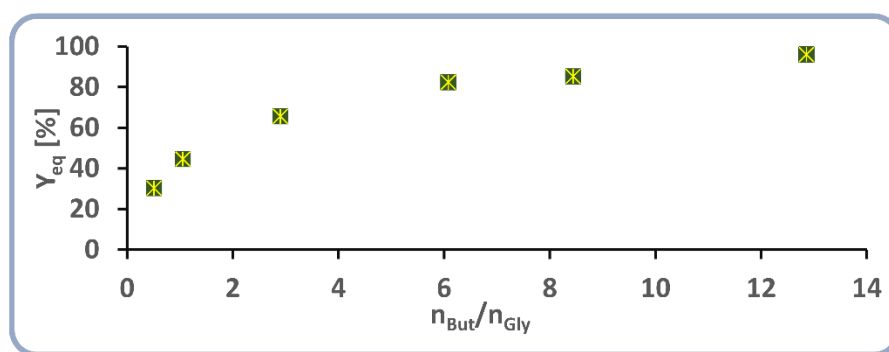


Figure 7-11: The equilibrium yield in the ketalisation of glycerol with butanone at different molar ratios. Conditions: 16 h, 25°C, ethanol (0.8 ml), glycerol (0.5 g, 5.4 mmol), butanone (according to ratio), catalyst: H-S-POSS-1 (1 mol%).

From the region around equimolar ratio between the two reactants the yield steeply increases with increasing excess of the butanone. At much higher excess ratios, the slope declines significantly. For the future experimental protocol, it is important to find a compromise between the excess of reagent and a high yield at equilibrium. As a compromise between these two opposing goals, it was decided that a glycerol/butanone ratio of 1:6 was suitable where a maximum yield of 82.3% at equilibrium is to be expected. Ethanol was also identified as a suitable solvent that allows the two reactants to become fully miscible, which is important when studying the kinetics of the reaction and mass transfer limitations between two phases must be avoided. In a process application it could be advisable to run the system neat, without solvent, as a solvent would be required to be removed after the reaction.

7.3.5. Catalytic Activity of H-S-POSS in a Ketalisation Reaction

With the set reaction protocol at hand the catalytic activity of the different acids was investigated. The three H-S-POSS catalysts were applied in the ketalisation of glycerol with

butanone, taking samples from the reaction mixture at regular intervals over time. H-S-POSS can be viewed as a molecular weight enlarged version of benzenesulfonic acid, where *para*-toluenesulfonic acid (PTSA) (Figure 7-12 left, below) is its closest widely available and utilised derivative. Conventional heterogenised versions of PTSA are the Amberlyst-type catalysts (Figure 7-12 right, below).

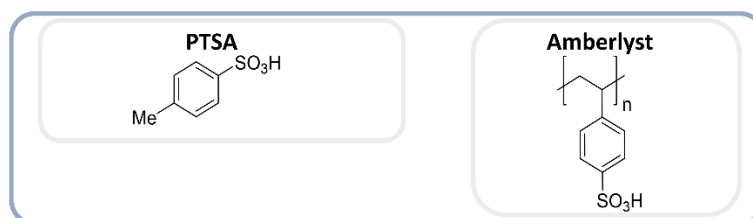


Figure 7-12: Structure of *para*-Toluene sulfonic acid (PTSA) and Amberlyst resin.

The catalytic activity of H-S-POSS was therefore compared to that of PTSA and Amberlyst-36, which acted as benchmark catalysts for the reaction. The catalysts were applied at a loading of 0.1 mol% acid protons relative to glycerol. The results from that set of experiments are presented in Figure 7-13 below.

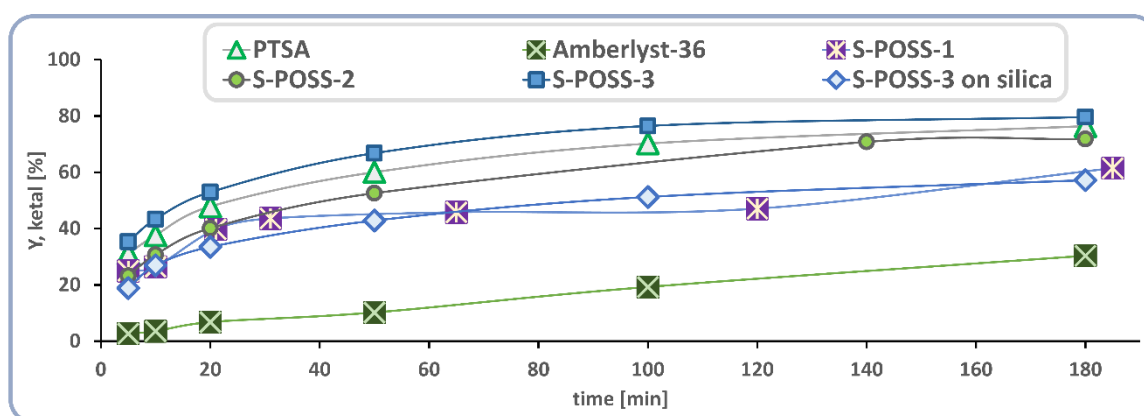


Figure 7-13: Yield over time plot for the ketalisation of glycerol with butanone.

Catalysts applied were PTSA, Amberlyst-36, H-S-POSS-1, -2 and -3 as well as H-S-POSS-3 on silica. Conditions: 25°C. Ethanol (1.7 g), glycerol (1 g, 10.8 mmol), butanone (4.7 g, 65.2 mmol, 6 equivalents per glycerol), catalyst loading of 0.1 mol%. Samples were quenched with pyridine (0.12 g per 0.6 g sample) and analysed by $^1\text{H-NMR}$.

The uncertainty for each molar ratio is estimated at $\pm 5\%$ for each data set, to take into consideration the quantification is done by $^1\text{H-NMR}$, errors from characterising the H-S-POSS true degree of sulfonation, reaction mixture preparation and that samples are withdrawn and then quenched (time sensitive). Hence, it is not necessarily true that the H-S-POSS-3 catalyst was more active than PTSA. But what is more certain to be true is that the higher degree of sulfonation H-S-POSS gave a more active catalyst as can be seen with the relative order in activity between H-S-POSS-1, -2 and -3. All four H-S-POSS catalysts were significantly more active than the Amberlyst-36, and only H-S-POSS-1 and H-S-POSS-3 on silica catalysts were

significantly less active than PTSA. The higher degree of sulfonation might result in better dispersion of the catalyst in the liquid reaction medium, meaning smaller particles/more soluble and thus more substrate-catalyst interaction.

7.3.6. Recycling H-S-POSS by Centrifugation

Because the H-S-POSS catalyst had very poor solubility in the reaction mixture (or any other solvent tested) it was hypothesised that these catalysts could be retained by merely using centrifugation. To investigate this, the H-S-POSS catalysts were applied in the ketalisation reaction for a specific amount of time, the reaction mixture was then centrifuged, product reaction mixture was decanted, and fresh substrate was added. The cycle was repeated 10 times to investigate if the yield of the ketal would change. The general outline of this approach is illustrated in Figure 7-14 below.

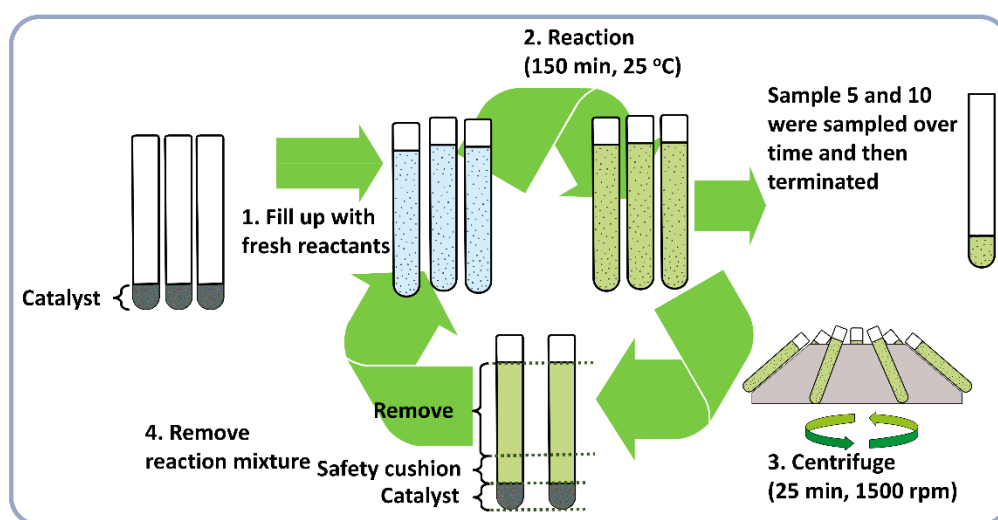


Figure 7-14: Catalyst recycling by centrifugation after each reaction.

The recycling experiments were conducted with the catalysts H-S-POSS-1, -2, -3 and H-S-POSS-3 on silica. The yield of ketal at the end of each reaction/centrifugation cycle for each catalyst is presented in Figure 7-15 below.

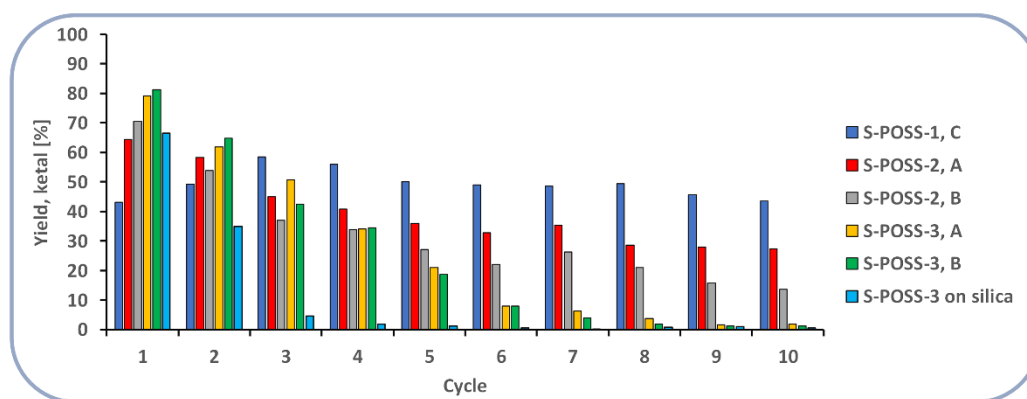


Figure 7-15: Yield per recycle run for the H-S-POSS catalysts using the centrifugation approach. Conditions: 25°C, 150 min, ethanol (1.7 g), glycerol (1 g, 10.8 mmol), butanone (4.7 g, 65.2 mmol, 6 equivalents per glycerol), H-S-POSS catalysts loaded at 0.1 mol%.

The H-S-POSS-3 catalyst gave initially the highest yield of the ketal but quickly lost its activity. H-S-POSS-2 showed an intermediate high initial activity while also showing a slightly reduced rate of activity loss between each cycle. The H-S-POSS-1 catalyst showed an intermediate initial activity, which it almost retained throughout 10 cycles. Clearly the degree of sulfonation of H-S-POSS has a significant impact upon how well suited the resulting catalyst is towards centrifugal applications. Although H-S-POSS-3 clearly did not fare well in this type of recycling application due to its much higher solubility, better retention is likely possible with the application of membranes. The H-S-POSS-1 catalyst was further investigated in the centrifuge recycling setup by applying sample over time experiments after 0, 5 and 10 cycles as was also illustrated in Figure 7-14 above. This recycling experiment setup started off with three reaction vessels run in parallel, when a time resolved experiment had to be conducted that reaction vessel was terminated from further recycling runs as sampling removes significant portions of catalyst from the reaction mixture. The results from those experiments are presented in Figure 7-16 below.

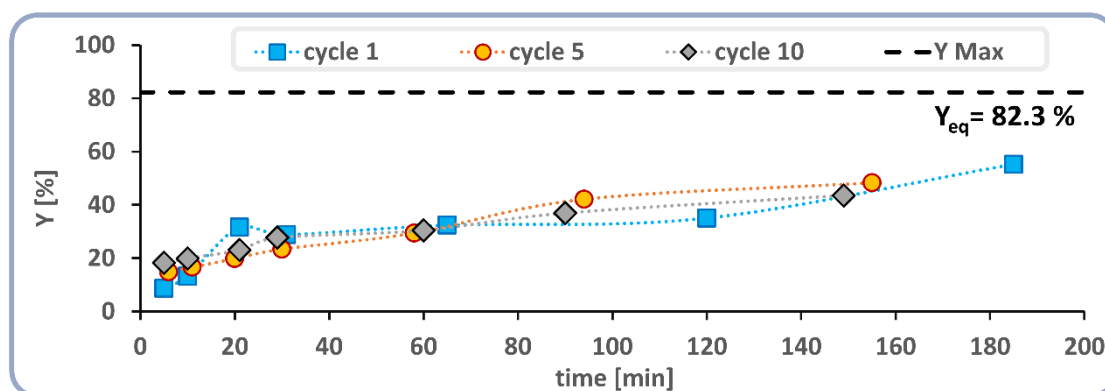


Figure 7-16: Yield over time plot for the H-S-POSS-1 catalyst after 1, 5 and 10 reaction cycles. Reaction being the ketalisation of glycerol with butanone. Conditions: 25°C, 150 min, ethanol (1.7 g), glycerol (1 g, 10.8 mmol), butanone (4.7 g, 65.2 mmol, 6 equivalents per glycerol), H-S-POSS-1 catalysts loaded at 0.1 mol%.

From these yield over time experiments it is not possible to tell if the activity of the catalyst decreased or not after subjecting the catalyst to either 5 or 10 recycling cycles. This is suggesting that the majority of the H-S-POSS catalyst was successfully retained through centrifugation and that there was a minimum washout of any catalyst between recycling runs. Hence, centrifugation in a laboratory setting is an efficient and simple method of retrieving the H-S-POSS-1 catalyst after a reaction. In industrial processes, other ways of catalyst separation might be more cost effective, but none of this will be further studied in this work.

7.4. Conclusions and Outlook

Three different H-S-POSS compounds were synthesised, each batch with a slightly higher degree of sulfonation. The first batch (H-S-POSS-1) was characterised with DLS and theta-potential, while all three batches were characterised by NMR, IR and SEM. The IEC was measured for all H-S-POSS catalysts in order to determine their degree of sulfonation. The solubility of the H-S-POSS form was close to non-existing in all the solvents that were investigated. The Na-S-POSS was on the other hand slightly soluble in water and other polar solvents, which then allowed them to be analysed by NMR. The H-S-POSS compounds were investigated for their catalytic activity in the ketalisation of glycerol with butanone. The H-S-POSS catalysts had a higher activity with increasing degree of sulfonation. This is explained by that the H-S-POSS with a higher degree of sulfonation are more likely to form smaller particles in suspension when the charge density is increased. The H-S-POSS-2 and -3 catalysts had similar activity to PTSA while H-S-POSS-1 was significantly less active, albeit still considerably more active than Amberlyst-36. An attempt at immobilising the H-S-POSS-3 catalyst on silica was performed. SEM pictures showed that the silica grains became covered with H-S-POSS material. Although the deposition was not homogeneously distributed. Centrifugation was explored as a way of recycling the H-S-POSS catalysts after a reaction. Only H-S-POSS-1 showed stable activity over 10 centrifugation-recycling runs. This can be explained by the lower charge density of the H-S-POSS-1 compared to the H-S-POSS-2 and -3. The lower charge density then favoured the existence of slightly larger particles which are easier to sediment than smaller ones. The poor solubility of lower degree sulfonated H-S-POSS material can thus be made into an advantage when applied as catalysts as this allows them to be treated more akin to heterogeneous catalysts when it comes to their separation and recycling.

7.5. Experimental

7.5.1. Materials

Chemicals used in the reaction were purchased from Acros Chemicals, deuteron, Fisher Chemicals, Merck, Sigma Aldrich or VWR. Solvents used in the synthesis were dried, DCM was dried over molecular sieves and chloroform was distilled from phosphorus pentoxide.

7.5.2. Procedure and analytical methods

NMR: Measured using Bruker AV Avance III HD (400MHz or 600 MHz). The relative uncertainty for reported molar ratios is estimated at ± 5 -10% for ^1H -NMR, this takes into consideration that the quantification is done by ^1H -NMR, errors from characterising the H-S-POSS true degree of sulfonation, reaction mixture preparation and that samples are withdrawn

and then quenched (time sensitive). A sample (0.6 g) was taken from the reaction mixture and quenched by pyridine (0.15 g). For analysis, 100 μL of the quenched sample was diluted with 500 μL of D_2O .

GC-FID: Measured on a Hewlett Packard HP 6890 Series GC System using a HP 5 column. Quantitative analysis of reaction mixtures was performed via GC-FID using dodecane as an internal standard to account for injection volume variances and detector drift. GC-samples were prepared accordingly: A sample of the reaction mixture (0.6 g) was quenched with pyridine (0.2 g). Then, isopropanol (0.4 g) was added as a solvent and n-dodecane (0.025g) as an internal standard. The samples were measured using a Hewlett Packard HP 6890 Series GC System, fitted with a HP 5 column.

ATR-IR: Measurements were conducted using a Bruker Alpha FT-IR spectrometer. Measurements were performed with help from Marko Milovanovic at the chair of Prof. Dr. Tiller.

Ion Exchange Capacity and Sulfonation Degree: The H-S-POSS' IEC was determined by reverse acid-base-titration. A sample of S-POSS (100 mg) was stirred in NaOH (aq) (0.05M, 10 mL) for 30 min. Then, the remaining amount of hydroxide was determined by titration against aqueous HCl (0.01 M) using phenolphthalein indicator.

SEM: FESEM Images were recorded on a Hitachi H-S4500 FEG microscope at the “Zentrum für Elektronenmikroskopie und Materialforschung” at the chair of Prof. Dr. Tiller by Volker Brandt.

DLS and ζ -Potential: Measurements were conducted on an aqueous dispersion of H-S-POSS-1 using a Malvern Zetasizer Nano ZS. Measurements performed with help of Björn Holtzapfel at the chair of Prof. Dr. Rehage.

7.5.3. Synthesis of H-S-POSS

Three attempts at sulfonating octaphenyl-POSS in order to synthesise H-S-POSS were made. In all three attempts the sulfonation was done by using chlorosulfonic acid.

First attempt at synthesis of H-S-POSS-1:

Octaphenyl-POSS (5 g, 4.8 mmol) was dried in vacuo for 5 h inside a Schlenk flask fitted with a stirrer bar. Argon was then filled to the flask and dichloromethane (35 ml) (dried with 3 Å molecular sieves) was added to make up a suspension. The freely stirring suspension was cooled to 0°C. Chlorosulfonic acid (10 ml, 150 mmol, 3.9 eq. to phenyl groups) was added

dropwise over the course of 45 min using a dropping funnel. The suspension turned through the course of the addition of the chlorosulfonic acid into a clear solution. After all had been added, additional dichloromethane (10 ml) was added, causing a white solid to precipitate. The mixture was allowed to warm to room temperature and was stirred overnight. The next day the precipitate had to be manually broken up. Dichloromethane and excess chlorosulfonic acid were removed under vacuum, first at ambient temperature and later at 90°C. The remaining solid was suspended in water (200 ml) and Na₂CO₃ was added until the mixture reached a pH of 7. After filtration, the solid was stirred in HCl_{aq} (conc., 15 ml), then filtered and washed with water until the filtrate reached a pH of 7. The H-S-POSS-1 was obtained as a white powder (1.675g, 30 % yield).

¹H-NMR (S-POSS-1 sodium salt, 400 MHz, D₂O) δ = 7.97 (s, 1H), 7.77 (d, J=7.3 Hz, 1H), 7.73 (dd, J=8.0, 1.6 Hz, 1H), 7.46 (t, J=7.6 Hz, 1H) ppm.

Second and Third Attempt at H-S-POSS-2 and -3:

The reaction protocols for the second and third attempts were identical with exception of the quantity of certain chemicals. That is why they are presented together. Octaphenyl-POSS (4 g, 3.9 mmol) was dried in vacuo for 6 h inside a Schlenk-flask fitted with a stirrer bar. Argon was then applied to the flask and chloroform (freshly distilled from phosphorus pentoxide) was added to make up a suspension of the octaphenyl-POSS. (amount of chloroform in 2nd attempt: 80 ml, 3rd attempt: 40 ml). The suspension was cooled to 0°C before chlorosulfonic acid (2nd attempt: 15 ml, 226 mmol, 7.2 eq. 3rd attempt: 18 ml, 271 mmol, 8.7 eq.) was added dropwise over the course of 30 min using a dropping funnel. The suspension turned into a clear solution during the addition of the chlorosulfonic acid. The reaction mixture was slowly warmed to room temperature and was stirred overnight. In the second attempt, a small amount of white solid had precipitated out by the next day while the third attempt stayed as a clear solution. The mixture was cooled to 0°C before water (10 ml) was added dropwise which caused precipitation of a white solid. The slurry was diluted with chloroform (40 ml). The solid was separated by filtration and washed with water (50 ml). The white solid was dried in vacuo at 50°C for 6 h. The solids IEC was determined by reverse titration. The crude H-S-POSS product was then stirred in aqueous NaOH (1 eq. based on IEC) in order to neutralize any remaining sulfuric acid and transform the H-S-POSS into the corresponding Na-S-POSS (water soluble). The Na-S-POSS was then reacidified by stirring in concentrated aqueous HCl for two days, excess HCl and water was removed by evaporation under reduced pressure. H-S-POSS-2 and -3 were

obtained as fine, white powders. H-S-POSS-2: 3.065 g, 62% yield; H-S-POSS-3: 4.738 g, 81% yield).

^1H -NMR (Na-S-POSS-2, 400 MHz, D_2O) δ = 8.08 (s, 1H), 7.87 (m, 1H), 7.83 (dd, J =8.1, 1.3 Hz, 1H), 7.58 (m, 1H).

^{13}C -NMR (Na-S-POSS-2, 101 MHz, D_2O) δ = 142.17, 141.59, 137.02, 136.94, 131.59, 130.32, 128.98, 128.41, 126.63, 125.31 ppm.

^1H -NMR (Na-S-POSS-3, 400 MHz, D_2O) δ = 8.09 (s, 1H), 7.88 (dd, J =7.5, 1.3 Hz, 1H), 7.83 (dd, J =8.0, 1.4 Hz, 1H), 7.60 (m, 1H) ppm.

^{13}C -NMR (Na-S-POSS-3, 101 MHz, D_2O) δ = 141.65, 137.00, 136.37, 131.60, 130.33, 128.98, 128.47, 126.79, 125.31 ppm.

Adsorption of H-S-POSS-3 Onto Silica

H-S-POSS-3 (0.307 g) was suspended in water (400 ml). While vigorously stirring the suspension, silica (2.366 g, particle size: 40 to 63 μm) was slowly added. The suspension was stirred for 24 h before the water was removed by evaporation under reduced pressure.

7.5.4. Characterisation and analytics

Determine IEC and degree of sulfonation

The ICE of any H-S-POSS material was determined by reverse acid-base titration. A sample of H-S-POSS (100 mg) was stirred in NaOH_{aq} (0.05 M, 10 ml) for 30 min. The remaining amount of hydroxide was determined by titration against aqueous HCl (0.01 M) using phenolphthalein as indicator.

Analysis by GC-FID:

GC samples were prepared as follows: A sample from the reaction mixture (0.6 g) was quenched by being thoroughly mixed with pyridine (0.2 g). Isopropanol (0.4 g) was then added as a solvent and *n*-dodecane (0.025 g) was added as internal standard. The samples were measured on a Hewlett Packard HP 6890 Series GC System using a HP 5 column.

Analysis by NMR:

NMR samples were prepared as follows: A sample from the reaction mixture (0.6 g) was quenched by being thoroughly mixed with pyridine (0.15 g). The NMR tube was then prepared with 100 μl of quenched sample and 500 μl of D_2O . The relative uncertainty for reported molar ratios is estimated at $\pm 5\%$ for ^1H -NMR.

ATR-IR:

ATR-IR measurements were conducted on solid samples of octaphenyl-POSS and H-S-POSS-1 using a Bruker Alpha FT-IR spectrometer.

Scanning Electron Microscopy (SEM):

SEM images of H-S-POSS-1 as well as of the silica absorbed H-S-POSS-3 were recorded on a Hitachi H-S4500 FEG microscope.

7.5.5. Ketalisation of Glycerol with Butanone

Isolation of the Ketal Product:

The ketal product was isolated from a reaction mixture to allow for its calibration on a GC-FID. The reaction was conducted as follows: H-S-POSS-1 (0.129 g) was added to a mixture of glycerol (5 ml) and butanone (30 ml). The mixture stirred for 2.5 h to achieve a higher conversion of the glycerol. Water was being actively removed using MgSO_4 . After filtration, the excess butanone was removed by evaporation under reduced pressure. The remaining ketal was characterized by NMR.

^1H NMR (600 MHz, CDCl_3) δ = 4.17 (m, 1H), 3.97 (m, 1H), 3.71 (m, 2H), 3.53 (m, 1H), 1.86 (br s, 1H), 1.62 (m, 2H), 1.28 (2 s, 3H), 0.88 (m, 3H) ppm.

^{13}C NMR (151 MHz, CDCl_3) δ = 111.55, 111.24, 76.52, 75.84, 65.81, 65.76, 63.08, 62.88, 32.52, 31.61, 24.16, 23.07, 8.49, 8.20 ppm.

Investigation of the Equilibrium Yield:

Six experiments using different molar ratios between glycerol and butanone were performed to investigate their thermodynamic equilibrium yield. In each experiment glycerol (0.5 g, 5.4 mmol) was first diluted with ethanol (0.8 ml). Butanone (0.5, 1, 3, 6, 8, 13 molar equivalents to glycerol) was then added to the mixture. Finally, the H-S-POSS-1 catalyst was added, and the reaction mixture was allowed to stir at room temperature overnight. Yield was determined by NMR.

Investigating the catalytic activity:

All the experiments of this type were performed on the same scale, sampled over time and the only variable was the amount of catalyst being added. In a reaction vessel was added glycerol (1.0 g, 10.9 mmol) that was diluted with ethanol (1.7 g). Butanone (4.7 g, 65.2 mmol, 6 eq.) was then added and the whole reaction vessel was placed in a water bath. The water bath temperature was controlled by a thermostat with a precision of 0.2°C. The reaction vessel was left in the bath for 20 min to reach the desired temperature. The catalyst was then added ($t = 0$)

and samples (a 0.2 ml) were from then on taken at regular intervals from the reaction mixture. The samples were quickly quenched by an excess of pyridine (0.15 g per 0.60 g sample) to stop them from reacting any further. NMR samples were then prepared according to procedure.

Recycling strategy, centrifugation:

Nine reaction vessels were prepared with a reaction mixture composed exactly as described in section 0. Three vessels for each H-S-POSS catalyst (1, 2 and 3). The catalyst was added at $t = 0$ and the reaction mixture was stirred at 25°C for 150 min. The stirrer bar was then removed, and the glass tube reaction vessel was centrifuged for 25 min at 15000 rpm using a Hettich Universal 16 centrifuge. Carefully the vessels were removed from the centrifuge and the upper three quarters of the reaction mixture was removed from the vessel using a syringe and analysed by NMR. The bottom quarter was left untouched to be sure that no catalyst sediment would be disturbed and by accident be removed from the vessel. Starting the next cycle, the removed liquid was replenished by fresh reaction mixture. In cycle 1, 5 and 10, the reaction was sampled over time. Because sampling removes catalyst from the reaction mixture it will have to be discarded from future cycles. Therefore, the whole experiment started with three reaction vessels. The first vessel was used up for sample over time experiment in cycle 1, the second and third vessels were used up in sampling over time experiments in cycle 5 and 10 respectively.

Chapter 8: Summary, Conclusions and Outlook

In this thesis was presented work on advancing the applicability of homogeneous catalyst in continuous processes. The central theme was to use POSS as an MWE-unit of certain ligands and catalysts in order to enhance their recyclability in conjunction with nanofiltration membrane technology. The focus was specifically on advancing the status of POSS-modified phosphine ligands, phosphite ligands and Brønsted acids.

8.1. Regarding MWE of Phosphine Ligands

Since phosphine ligands were identified to be relatively easy to maintain stable during application in continuous processes, focus in this thesis was directly at synthesising new POSS-modified phosphine ligands. This included a set of TPP-POSS ligands with variable number of POSS cages as well as POSS-modified Xantphos-type ligands. The TPP-POSS ligands contained 1, 2, or 3 POSS cages whose relative activity in the Rh-catalysed hydroformylation of 1-octene was difficult to rationalise. Their ^{31}P -NMR chemical shift moved increasingly downfield with each additional ethyl-tethered POSS cage. Overall, grafting POSS cages so close to the binding site of the ligand does come at a risk of significantly changing the catalytic properties of the resulting metal-ligand complexes. There were also signs that the presence of the (iBu)₇POSS cages helped the solubility of CO in the reaction mixture. The rejection of the TPP-POSS ligands by a ceramic nanofiltration membrane increased with increasing number of POSS cages but was lower than what had previously been reported for the TPP-POSS-3 ligands. This difference in rejection was possibly due to differences in pore size distribution of the different membranes that were used and produced in different batches. Two different designs for POSS-modified Xantphos-type ligands were attempted; both designed with the POSS cages attached in the rear of the ligand backbone. The first design approach contained two POSS cages, grafted at the 2,7-position of the backbone. The synthesis ran into issues with a planned hydrosilylation reaction that behaved unpredictably and the decisive parameters that determine a successful reaction were never fully realised. Furthermore, the full synthesis included 5 steps which is rather lengthy and arguably the synthesis of the full ligand could be challenging to justify. The other POSS-Xantphos-type ligand was a late stage one-pot synthesis that produced the so-called NixantPOSS ligand starting from Nixantphos. The NixantPOSS ligand had a POSS cage grafted at the amine in the rear of its backbone. The ligand proved to be highly active and selective in the Rh-catalysed hydroformylation of 1-octene in batch autoclave setup. The application of NixantPOSS in a continuous flow nanofiltration membrane reactor gave ambiguous catalytic results. The ligand was rejected by the membrane at 99%, which can be

compared to 90% rejection for Xantphos in toluene or 70% rejection of Xantphos during continuous flow hydroformylation of 1-octene. Also comparable to the lower rejections that the TPP-POSS ligands had, which was measured with the same type of membrane, but produced in a different batch. NixantPOSS possessed a very high solubility in nonpolar solvents due to the presence of the *i*Bu-groups of the POSS cage; 185 mmol/L_{toluene}, compared to Nixantphos; 7.7 mmol/L_{toluene} at 20°C.

8.2. Regarding MWE of Phosphite Ligands

The bottles-neck for further applications of phosphite ligands in continuous processes was identified to be a lack of know-how surrounding the long-term stability of such ligands and their associated systems. Hence, the work within this thesis surrounding the phosphite ligands comprised fundamental investigations about the parameters that are most significant in determining the long-term stability of phosphite ligands under typical reaction conditions. Biphephos was used as a model diphosphite ligand due to its excellent *l/b* ratio in Rh-catalysed hydroformylation of alkenes when intact, and complete lack of selectivity when it has been decomposed. It was realised through continuous flow-, batch autoclave- and ³¹P-NMR experiments that the autocatalytic decomposition can be almost eradicated when applying a set of measures. This resulted in dissolving the Rh-precursor and the Biphephos ligand separately before mixing, applying suitable stabilisers and rigorously excluding oxygen before the start of a reaction.

8.3. Regarding MWE of a Brønsted Acid

The last focal point was to apply POSS as an MWE-unit for Brønsted acids. A sulfonated octaphenyl-POSS compound called H-S-POSS was targeted as the synthesis of this had already been reported by several authors. But up until now this material had up until now never been investigated for its application as an acid catalyst. The synthesis was in theory a simple one-pot reaction, but the reality was that uncontrolled premature precipitation of material happened during the various batches of synthesis. In total, three different batches were synthesised, each containing a different degree of sulfonation (19.5, 28.5 and 66%). These materials were investigated for their catalytic properties in the ketalisation of glycerol with butanone and compared to the catalytic activity of PTSA and Amberlyst-36, all loaded at 0.1 mol% of H⁺. All the H-S-POSS catalysts were significantly more active than the Amberlyst-36 catalyst, the H-S-POSS catalyst with 28.5 and 66% degree of sulfonation were comparably active to PTSA. All the H-S-POSS catalysts had very low solubility in all common laboratory solvents and so a recycling strategy based on centrifugation was investigated. Only the H-S-POSS-1 at 19.5%

sulfonation maintained good stability through 10 batch recycles. It is believed that the higher degree of sulfonation supports the formation of increasingly smaller particles which become increasingly difficult to sediment through centrifugation.

8.4. Overall Conclusions

The central objective of this thesis was to advance the field of process intensification in homogeneous catalysis by enhancing the recyclability of transition-metal-complexes and Brønsted acids. By integrating molecular weight enlargement (MWE) using polyhedral oligomeric silsesquioxane (POSS) with organic solvent nanofiltration (OSN), this work has demonstrated that industrial hurdles such as catalyst leaching and thermal deactivation can be systematically addressed.

A primary conclusion of this research is that the successful application of MWE strategies is strictly dependent on a fundamental understanding of ligand stability. The investigation into the phosphite ligand **Biphephos** revealed its extreme sensitivity to moisture, oxygen, and preparation methodology. It was demonstrated that Biphephos undergoes autocatalytic decomposition via hydrolysis into phosphonic acids unless stabilized by additives like cyclohexene oxide (CHO) or hindered amines (TMP). Furthermore, the discovery that the order of mixing Rh and Biphephos directly impacts oxidation highlights that operational protocols are as critical as the chemical design. Consequently, grafting POSS to such sensitive frameworks should only be pursued once these stabilization measures—specifically the use of acid scavengers and "pressure de-pressure" (PDP) cycles—are fully implemented.

In contrast, the modification of more robust **phosphine-type ligands** (TPP and Xantphos) and **Brønsted acids** proved to be a more direct route to intensification. The synthesis of **NixantPOSS** represents a significant milestone, achieving a 94% isolated yield in a simple one-pot reaction. This modification not only facilitated a 99% rejection rate by ceramic nanofiltration membranes during continuous hydroformylation but also resulted in a 25-fold increase in solubility in toluene (185 mmol/L) at room temperature (20°C) compared to unmodified Nixantphos. This drastic improvement in physical properties allows for higher catalyst loadings and more concentrated process streams, directly contributing to process intensification.

The study of **TPP-POSS** derivatives (bearing 1, 2, or 3 POSS cages) provided critical insights into the positioning of MWE units. It was concluded that grafting POSS cages too close to the phosphorus atom can negatively impact catalytic activity, whereas modification at the rear of

the ligand backbone (as seen in NixantPOSS) preserves high performance, showing only an 18% reduction in TOF.

Finally, the development of sulfonated octaphenyl-POSS (**H-S-POSS**) extended the utility of POSS beyond transition metal catalysis into the realm of acid-catalyzed transformations. While these catalysts showed activity comparable to PTSA in the ketalization of glycerol, their unique insolubility in common solvents enabled a novel recycling strategy based on centrifugation and sedimentation.

In summary, this thesis confirms that POSS is an exceptionally versatile MWE unit that can be tailored to enhance either solubility or insolubility depending on the catalytic requirement. To economically justify these modifications in an industrial context, future efforts should prioritize synthetic schemes with minimal steps and non-toxic reagents, ensuring that the benefits of high catalyst rejection and improved solubility outweigh the costs of ligand modification.

Chapter 9: References

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E. General Materials and Methods

E.1. Preparation of Inert NMR

In order to prepare an NMR sample under inert conditions a special Schlenk-flask designed for this purpose was used. The design of this NMR-preparation vessel is shown in Figure 0-1 below.

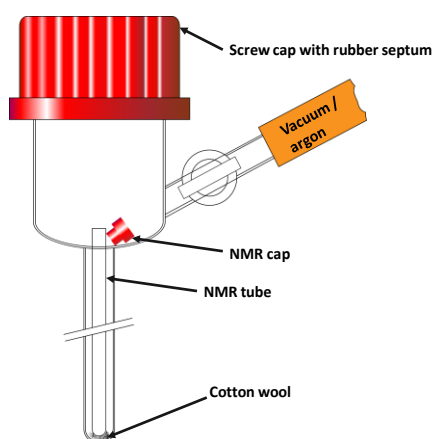


Figure 0-1: Inert NMR-preparation Schlenk-flask setup

Degassed solutions can then be transferred into the NMR tube using standard Schlenk-technique. The NMR tube has previously been prepared with an inert atmosphere of argon. The cap is fastened to the NMR tube with the use of a tweezer under a steady flow of argon over the opening of the NMR tube.

E.2. ICP-OES

An Iris Intrepid ICP (Thermo Elemental) was used to determine the rhodium and phosphorus content in the permeate and retentate. To do this, the permeate was concentrated on rotary evaporator. From this, 0.23 g of a sample was measured out in a Teflon cup and 2.5 mL nitric acid (65%) and 4 mL sulfuric acid (96%) was added.

The digestion process was conducted in a MWS μ Prep start-system microwave (MLS). Upon completion of the digestion process, the samples were treated with 2 mL double-distilled water and 1 mL of H_2O_2 (Fisher Scientific, Optima grade, phosphorus free). The prepared samples were rested for twelve hours before measurement.

E.3. Gas Chromatography Flame Ionizing Detector (GC-FID)

GC-FID samples were analysed on an Agilent Technologies 7890A GC fitted with an HP5 capillary column. The column was 30 meter long with an inner diameter of 0.25 mm and an outer diameter of 0.32 mm. Injection of samples was done by an autosampler of type G4531A.

Table 14: Parameters for method "Einstein_02".

Parameter	Value
Injected volume	1µl
Flow of N ₂	2,2 ml/min
Split ratio	15:1
Initial temperature	50 °C for 7 min
Temperature gradient	20 °C/min to 280
Target temperature	280 °C for 3 min
Runtime	21,5 min

E.4. High Pressure and Temperature Autoclave

All batch autoclave experiments were conducted in 100 ml stainless steel autoclaves with overhead stirrer. Each autoclave was fitted with a mass-flow controller for dosage of gas to maintain a desired set-point of pressure inside the autoclave through the course of a reaction. Temperature was controlled by DIN-controller controlling the power output to a heating jacket fitted around the pot of the autoclave. This allowed a specific set-point in temperature to be maintained. The power output was managed by the DIN-controller based on information from a thermocouple fitted around the jacket of the pot and one stuck inside the reactor liquid. The rpm of the stirrer was also controllable. Information about pressure, gas volume flow and temperature were recorded in a MATLAB proprietary software on a computer. The full schematics of the autoclave setup is presented in Figure 0-2 below.

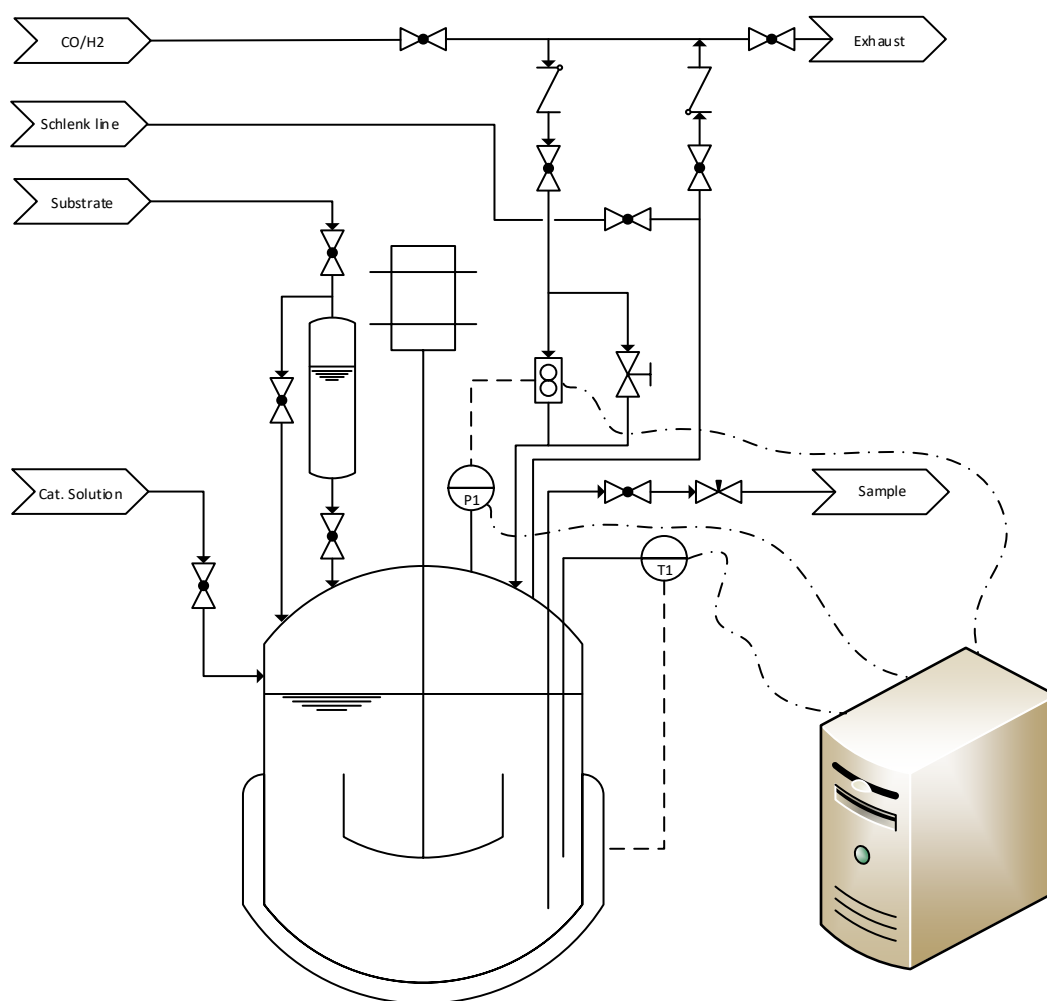


Figure 0-2: Schematic representation of the overhead-stirred high-pressure autoclave setup, featuring an integrated gas mass-flow controller (MFC) for pressure regulation.

Prior to using an autoclave, it was cleaned with acetone from top to bottom and the pot was drained using a 20 ml syringe. The reactors were then assembled, and vacuum was applied while the catalyst and substrate solutions were being prepared. The catalyst solution, substrate, any extra solvent and any additives were added to the reactor under a controlled steady stream of argon. Catalyst solution was added to the pot while substrate was added to the dropping funnel.

E.5. Ceramic Membrane Loop Reactor

The ceramic membrane loop reactor which was employed in parts of the work that is to be presented within this thesis is shown in Figure 0-3 below.

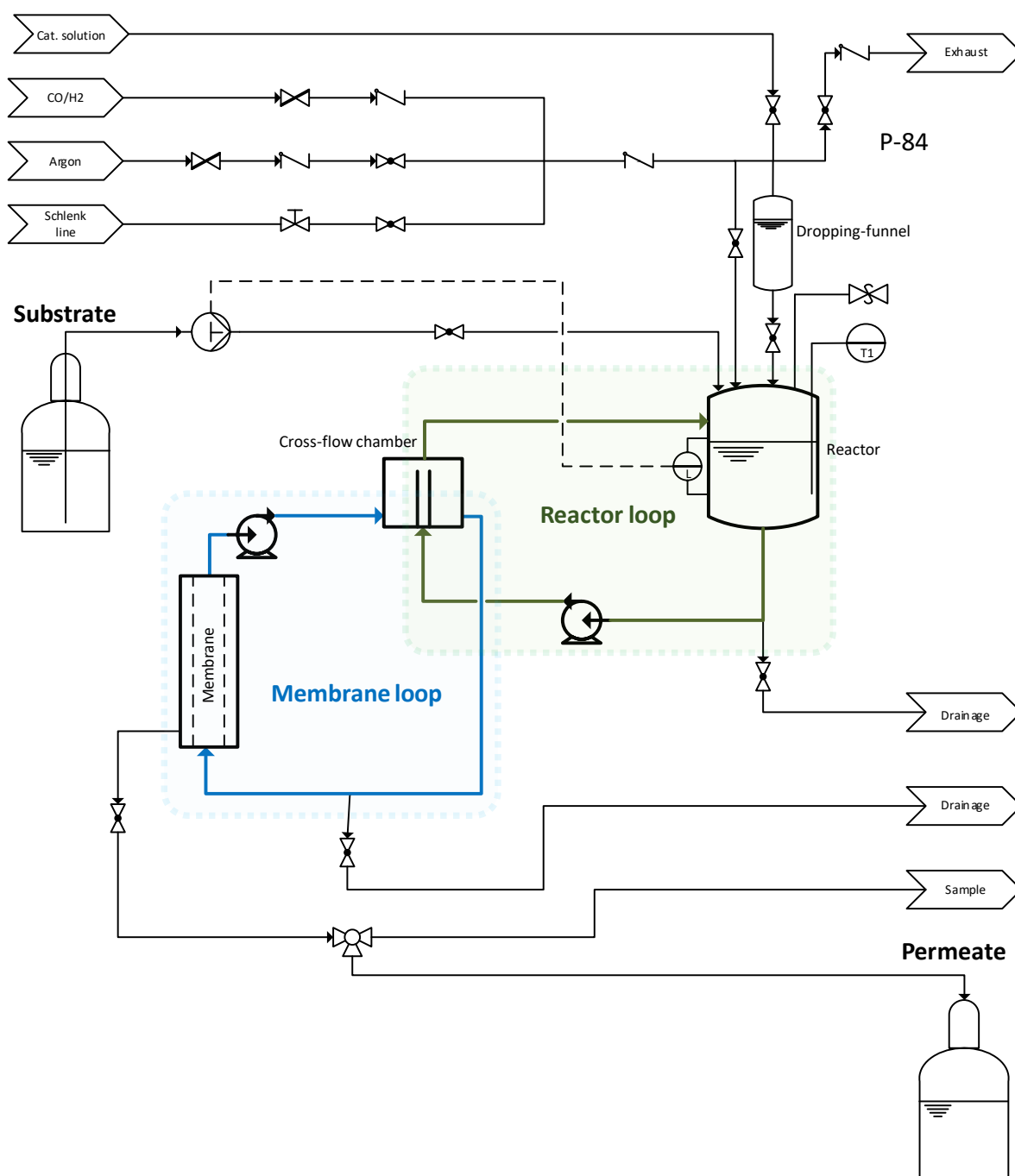


Figure 0-3: Schematic representation of the ceramic nanofiltration membrane loop reactor.

The reactor constitutes of two loops, one reactor loop and one membrane loop that are interconnected with each other via a cross-flow chamber. The substrate is introduced to the reactor by an HPLC-pump and runs on a feedback loop from a capacitive level sensor that is situated at a certain height inside the reactor vessel. On top of the reactor is a dropping funnel in which a catalyst solution can be placed before a reaction. This allows a reaction to be initiated at a defined time $t = 0$ under controlled conditions. The reaction mass is circulated through the

two loops by two centrifugal pumps. The intermixing of the reaction mass between the two loops is facilitated by the cross-flow chamber (CFC). The CFC is designed so that the incoming reactor loop stream will be de-bubbled/degassed before it is mixed with the membrane loop stream. This is to minimize the risk of gas bubbles damaging the membrane and the loss of gasses.^[304] The CFC has a pipe fitted in the bottom which guides the incoming reactor stream up towards the ceiling and out of direct reach of the membrane loop stream. A part of the liquid is then circulated towards the bottom of the CFC where it will mix with the membrane loop stream. The flow inside the membrane loop must become turbulent as it is passing along the active surface of the tubular membrane. This is to minimize the risk of concentration polarization happening at the membrane surface, which can lead to pores clogging and overall reduced membrane performance. The gas used in the reaction is supplied via a reducer (0 – 50 bar) and enters the reactor via the addition funnel. The overall design of the loop reactor fulfils a few criteria: Reaction and product separation are integrated. The reactor loop allows for efficient gas/liquid mixing and gas saturation of the reaction mixture. The cross-flow chamber allows for good mixing of the two streams of the two loops without introducing excessive amount of gas from the reactor loop into the membrane loop. The flow inside the membrane loop can be kept at a very high flow to make sure that turbulent flow is established along the membrane surface. The HPLC pump will feed fresh substrate solution to the reactor based on a feedback loop from the capacitive level sensor, which allows a constant volume to be maintained inside the reactor as reaction mixture is constantly permeating through the membrane. Because the ceramic membrane can tolerate high reaction temperatures, the whole reactor can therefore be kept under close to optimal reaction-conditions. This also simplifies the transfer of reaction mass from one “reactor” to “separator” as there is no need for heat exchangers. Fewer number of pumps, heat exchangers and pressure regulators of a (mini-)plant means a lower risk of a failure and an easier setup to operate.

E.6. Pressure De-Pressure Technique

The “Pressure-de-pressure” technique is designed to allow for further inertisation of a high-pressure reaction mixture just before starting the reaction. After filling the autoclave/reactor with the different solutions and substrates, and before starting the heating, the reactor is closed and then cycled through “pressure de-pressure” (PDP) cycles using a high purity gas (e.g. synthesis gas) that will “wash-out” any oxygen/air present within the reaction mixture with each completed PDP cycle. A typical PDP-cycle can be performed accordingly: 30 bar synthesis gas ($\text{H}_2/\text{CO} = 1:1$) is introduced to the reactor, stirring is applied (700 rpm) for 15

min. The reactor is then very slowly depressurised. The PDP-cycle can then be repeated as many times as is thought to be required, an asymptote in terms of beneficial inertisation is likely reached within 3-4 PDP cycles.

F. Supporting Information for Chapter 6: “Long-Term Stability of Biphephos”

F.1.1. Brown Precipitate Inside the Loop Reactor

It was discovered that the continuous flow reactor was internally covered in a brown precipitate containing large quantities of P and Rh, but also Si and different elements of the stainless-steel alloy that the reactor was built from, see Figure 0-4 below.

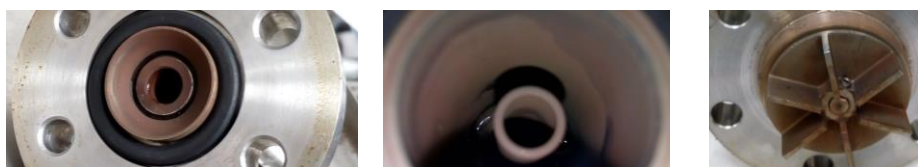


Figure 0-4: Brown precipitate on the interior of the loop reactor.

It is not possible to say when this precipitate was formed and how. Hence it is highly possible that both P and Rh had been leaching out from this brown precipitate and tainted the rejection results.

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I. Publications

- B. Bibouche, D. Peral, D. Stehl, V. Söderholm, R. Schomäcker, R. von Klitzing, D. Vogt, RSC Adv. **2018**, 8, 23332-23338
- V. Söderholm, J. Esteban, D. Vogt, Catal. Sci. Technol., **2021**, 11, 4529-4538
- V. Söderholm, M. Stajer, C. Savage, L. Splittgerber, D. Vogt, *Catal. Sci. Technol.*, **2025**, 15, 592-604

J. Posters and Lectures

Einstein workshop (Lecture): V. Söderholm, D. Vogt, Berlin **2016**, Compartmentalization of Homogeneous Catalysts using Polyhedral Oligomeric Silsesquioxanes (POSS) and Application in Continuous Processes

50. Jahrestreffen Deutscher Katalytiker (Poster): V. Söderholm, D. Vogt, Weimar **2017**, Polyoligomeric Silsesquioxane (POSS) enlarged Xantphos ligands for application in continuous flow nanofiltration membrane reactors.

DGMK International Conference on Synthesis Gas Chemistry (Poster): V. Söderholm, J. Dreimann, D. Vogt, Dresden **2017**, Synthesis of POSS-Modified Xantphos Ligands Towards Continuous Homogeneous Catalysis in a Nanofiltration Loop-Reactor

51. Jahrestreffen Deutscher Katalytiker (Poster): J. Dreimann, V. Söderholm, D. Vogt, Weimar **2018**, Organic Solvent Nanofiltration for compartmentalisation of ligand/catalyst

K. Supervised Thesis

Diekmann, Jonas (MT, 2018): Hydroformylation in mono- and multiphasic systems designed for efficient catalyst recycling.

Ellermann, Felix (MT, 2018): Operation of a continuous flow nanofiltration ceramic membrane loop reactor during rhodium catalysed hydroformylation of 1-octene.

Spiekermann, Maximilian (BT, 2018): Multiphasic hydroformylation reactions with and without polymer particles as phase transfer agents.

Nair, Sidharth (MT, 2018): Investigation of hydroformylation of higher olefins in absence of phase transfer agents.

Welsing, Andreas (MT, 2018): Steady state operation of a continuous flow ceramic nanofiltration membrane loop reactor during Rh/Biphephos catalysed hydroformylation of 1-octene.

Beckmann, Georg (BT, 2018): Late stage molecular weight enlargement of NiXantPhos for application in homogeneous catalysis and separation via nanofiltration.

Blömeke, Tobias (BT, 2018): Sulfonated octaphenyl-POSS: synthesis, characterisation and application as an acid catalyst in the ketalisation of glycerol with butanone.

Wegener, Hannes (BT, 2019): Synthese neuer UV-aktiver POSS-Verbindungen und deren Verwendung als Werkzeuge zur Beurteilung des Membranrückhalts

(BT: Bachelor Thesis; MT: Master Thesis)

