Molecular weight enlargement : a molecular approach to continuous homogeneous catalysis

Citation for published version (APA):

Janssen, M. C. C. (2010). *Molecular weight enlargement : a molecular approach to continuous homogeneous catalysis*. [Phd Thesis 1 (Research TU/e / Graduation TU/e), Chemical Engineering and Chemistry]. Technische Universiteit Eindhoven. <https://doi.org/10.6100/IR675414>

DOI:

[10.6100/IR675414](https://doi.org/10.6100/IR675414)

Document status and date:

Published: 01/01/2010

Document Version:

Publisher's PDF, also known as Version of Record (includes final page, issue and volume numbers)

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.tue.nl/taverne

Take down policy

If you believe that this document breaches copyright please contact us at:

openaccess@tue.nl

providing details and we will investigate your claim.

Molecular Weight Enlargement –
a Molecular Approach to Continuous Homogeneous Catalysis

Molecular Weight Enlargement –
a Molecular Approach to Continuous Homogeneous Catalysis

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Technische Universiteit Eindhoven, op gezag van de
rector magnificus, prof.dr.ir. C.J. van Duijn, voor een
commissie aangewezen door het College voor
Promoties in het openbaar te verdedigen
op woensdag 30 juni 2010 om 16.00 uur

door

Michèle Catherine Christianne Janssen

geboren te Geleen

Dit proefschrift is goedgekeurd door de promotor:

prof.dr. D. Vogt

Copromotor:
dr. C. Müller

Copyright © Michèle Janssen, 2010

Molecular weight enlargement – a molecular approach to continuous homogeneous catalysis

Eindhoven University of Technology

A catalogue record is available from the Eindhoven University of Technology Library.

ISBN: 978-90-386-2266-8

Cover design: OpHonk Design and Evgeny A. Pidko

Printed at Wöhrmann Print Service, Zutphen

Dit proefschrift is goedgekeurd door de manuscriptcommissie:

prof. dr. D. Vogt (TU/e)

dr. C. Müller (TU/e)

prof. dr. E. W. Meijer (TU/e)

prof. dr. H. Hiemstra (UvA)

prof. dr. D. J. Cole-Hamilton (University of St. Andrews, Scotland)

Contents

Chapter 1. Molecular weight enlargement – a molecular approach to continuous homogeneous catalysis

1.1	Introduction	2
1.2	Historical perspective	4
1.3	Molecular weight enlargement (MWE) in combination with nanofiltration	5
1.4	Selected examples of repetitive batch catalyst precipitation	9
1.5	Selected examples of repetitive batch nanofiltration	11
1.6	Continuous flow nanofiltration	13
1.7	Conclusions and future perspectives	16
1.8	Scope of the thesis	17
1.9	References	18

Chapter 2. ‘Click’ dendritic phosphines: design, synthesis, application in Suzuki coupling and recycling by nanofiltration

2.1	Introduction	22
2.2	Synthesis of the molecular weight enlarged ligands	22
2.3	Pd-catalyzed Suzuki-Miyaura coupling	27
2.4	Catalyst recycling studies	30
2.5	Concluding remarks	32
2.6	Experimental part	33
2.7	References	40

Chapter 3. Continuous homogeneous catalysis: POSS-enlargement as the *non plus ultra*

3.1	Introduction	44
3.2	Synthesis and characterization of POSS-enlarged PPh_3	45
3.3	Rh-catalyzed hydroformylation of 1-octene	46
3.4	Concluding remarks	52
3.5	Experimental part	53
3.6	References	54

Chapter 4. POSS-enlarged ligands in the continuous hydroformylation: broadening the scope

4.1	Introduction	58
4.2	Synthesis of the POSS-enlarged ligands	59
4.3	Hydroformylation of 1-octene in a batch reactor	60
4.4	Kinetic considerations	63
4.5	Continuous hydroformylation of 1-octene	65
4.6	Concluding remarks	70
4.7	Experimental part	71
4.8	References	74

Chapter 5. Hydroformylation of styrene: in search for selectivity

5.1	Introduction	76
5.2	Synthesis of binaphthol-based ligands	77
5.3	Coordination chemistry towards Rh(I) and Ni(0)	79
5.4	Mechanistic considerations	82
5.5	Rh-catalyzed hydroformylation of styrene	83
5.6	Molecular weight enlargement with POSS	87
5.7	POSS-enlarged ligands in the hydroformylation of styrene	89
5.8	Concluding remarks	90
5.9	Experimental part	90
5.10	References	94

Chapter 6. Compartmentalized bidentate ligands in the Ni-catalyzed isomerization of 2M3BN: An initial study

6.1	Introduction	98
6.2	The Ni-catalyzed isomerization of 2M3BN	99
6.3	Catalyst recycling studies	100
6.4	Molecular weight enlarged ligands in the isomerization reaction	103
6.5	Towards the synthesis of bidentate 'click' dendrimers	104
6.6	Concluding remarks	108
6.7	Experimental part	109
6.8	References	110

Summary	111
----------------	-----

Samenvatting	115
---------------------	-----

Dankwoord	119
------------------	-----

Scientific publications	123
--------------------------------	-----

Curriculum vitae	125
-------------------------	-----

1

Molecular weight enlargement – a molecular approach to continuous homogeneous catalysis

Molecular weight enlargement (MWE) is an attractive method for homogeneous catalyst recycling. Applications of MWE in combination with either catalyst precipitation or nanofiltration have demonstrated their great potential as a method for process intensification in homogeneous catalysis. Selected, recent advances in MWE in combination with catalyst recovery are discussed, together with their implication for future developments. These examples demonstrate that this strategy is applicable in many different homogeneously catalyzed transformations.

Parts of the work described in this chapter have been published:

Michèle Janssen, Christian Müller, Dieter Vogt, *Dalton Transactions*, **2010**, accepted for publication.

1.1 | Introduction

Homogeneously catalyzed reactions play an increasingly important role in organic synthesis today, both in academia and in industry.^[1] Often, precious metals are used in combination with valuable ligands and since prices of precious metals are expected to increase further in the future, methods for their efficient recycling and reuse are of utmost importance. Another driving force is product purity, especially for pharmaceutical ingredients. Figure 1 shows the development of the precious metal prices from 1993 until present.^[2]

Figure 1 | Development of the precious metal prices.

Homogeneous catalysts generally exhibit both high activity and selectivity, but are difficult to recycle and reuse, in contrast to heterogeneous catalysts.^[3] Usually, homogeneous catalysts deactivate or decompose during product work-up. This intrinsic difficulty of recycling makes process intensification by means of continuous catalysis an exciting, though complex undertaking.^[4]

A range of approaches have been studied over the years, all with their own strengths and weaknesses, leading to the conclusion that one ultimate solution does not exist. This is inherently due to the vast variety of applications, each with its own specific requirements and conditions. Hence, there is a great need for the development of complementary generic methods - a toolbox for practical application. These methods can roughly be divided in biphasic catalysis^[5] and immobilization on insoluble (heterogenization) and soluble supports (molecular weight enlargement, MWE).^[4,6-8]

Many examples of biphasic catalysis as a means of process intensification have appeared in literature. The first industrial example of this concept was realized in the Shell Higher Olefin Process (SHOP), of which the first step is a nickel catalyzed oligomerization of ethylene to prepare linear α -olefins on a large scale. This reaction is performed in a glycol solvent, such as 1,4-butanediol. The product α -olefin layer is immiscible in the catalyst-containing glycol layer and is decanted.^[9]

Another well-known example is the aqueous phase Rh-catalyzed hydroformylation of propene and butene in the so-called Ruhrchemie/Rhône Poulenc Process. The water-soluble catalyst (TPPTS/Rh) is immobilized in the aqueous phase and the product, *n*-butanal, forms the organic phase, which can easily be removed by decantation. It is important to note, however, that this approach is limited to lower alkenes with sufficient solubility in the aqueous phase (commercially up to butenes).^[5,10]

MWE catalysts can, in principle, be recovered by means of precipitation, nanofiltration, or ultracentrifugation, but especially nanofiltration has recently received substantial attention and has proven to be one the most useful alternatives.^[7,8,11,12]

Apart from the economical point of view to recycle homogeneous catalysts, these recycling strategies lead to cleaner reaction products, which is especially interesting for the pharmaceutical industry, where precious metal levels in the end-products typically have to be < 10 ppm.^[13]

Although MWE of homogeneous catalysts has proven to be a versatile method to make homogeneous catalysts recyclable, the catalytic system has to fulfill a couple of requirements: (relatively) straightforward synthesis, high activity, high total turnover number, and high retention. It is clear that the synthesis of MWE catalysts is often more tedious than that of its unsupported analogues. This can be justified by the fact that the MWE catalyst can be recovered and reused, in contrast to its unsupported analogue, but therefore the other requirements are a necessity. In essence this means that catalysts that either show a low retention or a low total turnover number have to be discarded for a practical application of MWE, unless they possess other special properties, such as increased selectivity.

This introduction chapter will focus on molecular weight enlarged, molecularly defined systems that are applied in combination with a recovery and recycling strategy and are published in recent years. Several reviews cover contributions in a related field of research, but do not fit within the scope of this chapter, because no catalyst recycling is involved or the catalytic systems are not defined on the molecular level. Examples covered are the application of dendrimers

in homogeneous catalysis^[14-20] and the application of catalytic metal nanoparticles,^[21] respectively.

1.2| Historical perspective

While ultra/nanofiltration in applied homogeneous catalysis is still in its infancy, it is applied in biocatalysis for about three decades already. Wandrey showed as early as in the 1970s the possibility of continuous operation of enzymes in a membrane reactor. One of the first examples was the hydrolysis of *N*-acetyl-L-methionine catalyzed by acylase as is shown in Figure 2.^[22-25]

Figure 2 | Acylase catalyzed hydrolysis of *N*-acetyl-L-methionine.

In 1987 Whitesides and co-workers extended the work of Wandrey also to batch-wise ultra/nanofiltration and used commercially available cellulose acetate dialysis membranes. In this way, enzymes that were used in organic transformations were compartmentalized, combining the advantages of soluble and immobilized enzymes. A variety of enzymes, like dehydrogenases, acylases, lyases, aldolases and lipases, were applied in the studies, indicative for the versatility of the method. Some examples are shown in Figure 3.^[26]

Figure 3 | Organic transformations catalyzed by lipase and acylase I.

1.3 | Molecular weight enlargement (MWE) in combination with nanofiltration

MWE is generally achieved by attaching a ligand or a homogeneous catalyst as a whole to a soluble molecular weight enlargement unit. This unit can be a soluble polymer, dendrimer, dendron, hyper branched polymer, dendronized polymer or, since recently, polyhedral oligomeric silsesquioxane (POSS) (Figure 4). All have been used in the last years as soluble supports for homogeneous catalysts, but all have their own combination of advantages and disadvantages.^[27]

Figure 4 | Molecular weight enlargement units used for MWE of homogeneous catalysts.

For practical application, the price of soluble supports is of great importance. Obviously, polymers are attractive in this respect, because they can be synthesized in one step. In contrast, dendrimer synthesis is tedious and therefore expensive, but dendrimers typically are very well-defined and monodisperse, which leads to a localized functionalization of the catalyst. Furthermore, they can either be functionalized in the core or at the periphery of the dendrimer. Cheaper alternatives for dendrimers are hyperbranched polymers. These are, like polymers, synthesized in one single reaction step, but their drawback is a higher polydispersity and the fact that their functionalities are spread over the whole macromolecule. Another alternative for dendrimers are dendrons that are easier to prepare than dendrimers, but still very well-defined. Also polyhedral oligomeric silsesquioxanes (POSS) are prepared in a single synthetic step and therefore relatively cheap.

Not all of these supports are suitable for nanofiltration. Generally speaking, rigid, three dimensional supports show a better retention (entry 5 and 6, Table 1).^[27] This makes especially the cubic structure of POSS cages and the rod-like shape of dendronized polymers extremely interesting candidates as soluble supports for homogeneous catalysts, when nanofiltration is the means of process intensification.^[7]

For the same reason, soluble polymers are less ideal for nanofiltration (entry 1, Table 1). Although the molecular weight of the polymer supported catalyst is higher than the molecular weight cut-off of the membrane, the (linear) polymer can stretch itself and pass through the membrane, like spaghetti through a kitchen sieve.

The same holds for dendrimers that can show 'backfolding' of the dendron's arms, but to a lesser extent than in case of linear polymers.^[3] Apart from these retention problems, sometimes negative dendritic effects are observed, *e.g.* van Koten reported on such an effect in the Kharasch addition reaction. A fast deactivation for the carbosilane dendrimer supported NCN pincer catalyst was observed by comparison with a mononuclear analogue. This deactivation is expected to be caused by irreversible formation of inactive Ni(III) sites on the periphery of these dendrimers. The use of dendrimers in which the distance between the Ni sites was increased, led to significant improved catalytic efficiency.^[29]

Table 1 | Overview of MWE methods used in homogeneous catalysis.

Entry	Support	Easy to synthesize	Retention	Price	Ref.
1	Polymer	++	-	++	30
2	Dendrimer	--	+	--	11,14-16,18-20,31,32
3	Dendron	±	+	±	33,34
4	Hyperbranched polymer	+	±	+	35
5	Dendronized polymer	-	++	±	36,37
6	POSS	+	++	+	38-46

1.3.1 | Synthesis of the MWE catalyst

In almost every example of MWE catalyst design the adopted strategy is typically very uniform: an existing, well-performing ligand system is chosen and decorated with a functional group. On the other hand a suitable support is selected with a 'complementary' functional group. Great care has to be taken in selecting an appropriate support, it has to fulfill requirements such as thermal and kinetic

stability and in the ideal case it should be available at low cost (*vide supra*). Both the soluble support and the ligand are combined to a MWE ligand system, preferably in a high yielding and clean reaction step that tolerates other functional groups that are typically present in a ligand (Figure 5). Until now, *e.g.* azide-alkyne cycloaddition reactions and condensation reactions have been used.^[33] In the last step the metal precursor is introduced.

Figure 5 | Synthesis of a MWE ligand.

1.3.2 | Ceramic versus polymeric membranes

In order to lead to practical solutions for the recycling problem of homogeneous catalysts, not only the catalyst has to fulfill certain requirements, this also counts for the membrane. It is important to note that the field of membrane research is on the move, and that new membranes with lower molecular weight cut-off's (MWCO) and smaller pore-size distributions are developed, both ceramic and polymeric.^[7] Nowadays, both types of membrane are commercially available, and both with specific characteristics, like MWCO, membrane material, and pore-size distributions (ceramic for example at Inopor, Germany and polymeric at MET, UK) (Figure 6).^[47,48] However, both have their own strengths and weaknesses and therefore a well-considered choice between them has to be made for each application.

Figure 6 | Ceramic membranes by Inopor.^[47]

To achieve good catalytic performance, the pore size of the membrane should guarantee high retention of the catalyst and, at the same time, smooth transport of the reactants and products. Interactions of the catalyst and/or reactants/products with the membrane surface have to be considered, *e.g.* OH-groups on the surface of ceramic membranes.

Last but not least, the membrane should be thermally, chemically, and mechanically stable under the catalytic reaction conditions applied. In general, ceramic membranes are stable in organic solvents, even at elevated temperature and pressure, whereas polymeric membranes may swell, leading to changes in *e.g.* pore size.

In membrane separation, a gradient has to be applied, in order to transport reactants and products, while the MWE catalyst is retained due to its size. The most commonly used gradients are a pressure gradient, which is often used in continuous flow systems (Figure 7b and c), or a concentration gradient, which is used in repetitive batch nanofiltration setups (Figure 7a), in literature often referred to as ‘cat-in-a-cup’ or ‘tea-bag’ setup. Temperature gradients or differences in electrical potential are less commonly used in catalysis.^[28,49]

However, pressure gradients, as often applied in continuous flow systems, can induce a polarization layer on the membrane, in this way hindering efficient nanofiltration of the reactants and products. This drawback can be minimized by applying a turbulent flow along the membrane.^[7,28]

Figure 7 | Examples of cat-in-a-cup (a), dead-end filtration reactor (b), and continuous flow membrane reactor (c).

1.4 | Selected examples of repetitive batch catalyst precipitation

Catalyst precipitation is an attractive alternative for MWE catalyst separation, since it usually does not need any advanced and dedicated equipment. Furthermore, because of the pronounced difference in size of MWE catalyst as compared to the substrate molecules, one is often able to precipitate the catalyst while the substrate/product stays in solution. Hence, interesting examples of this principle have appeared in literature in recent years. Astruc and co-workers attached a Buchwald-type ligand to a star-shaped support (Figure 8) and applied this hexaphosphine ligand in the Pd-catalyzed Suzuki-Miyaura coupling of chloro-arenes. The MWE catalyst proved to be as efficient as its non-supported analogue, and could be recovered by precipitation with pentane after each cycle for at least 4 times and total turnover numbers of 16,000 were reached.^[50]

Figure 8 | Hexaphosphine ligand by Astruc *et al.* and the Pd-catalyzed Suzuki coupling.

Fan and co-workers applied the repetitive batch precipitation method in asymmetric hydrogenation reactions. Dendronized poly(BINAP) (Figure 9) was synthesized and applied in the Ru-catalyzed asymmetric hydrogenation of aryl ketones and 2-arylacrylic acids. This is one of the few examples in which dendronized polymers are used as support in homogeneous catalysis. The dendronized poly(Ru-BINAP) exhibits high catalytic activities and selectivities (*ee*'s up to 92% for the aryl ketones and up to 83% for the arylacrylic acids) in this

reaction, comparable with unsupported Ru-BINAP and Ru(BINAP)-cored dendrimers. Dendronized poly(Ru-BINAP) could be recovered for at least 4 times by precipitation with methanol, without decrease in conversion or *ee*.^[36]

Figure 9 | Dendronized poly(BINAP) by Fan *et al.* and the Ru-catalyzed asymmetric hydrogenation of aryl ketones and 2-arylacrylic acids.

Dendron-enlarged Ir-BINAP catalysts were applied in the asymmetric hydrogenation of quinolines (Figure 10). The catalyst containing a third generation dendron could be recycled and recovered for 6 times by precipitation with hexane, and still performed with high yields (80% in the 6th run) and no change in *ee* (*ee* = 85%). Apart from the interesting recyclability properties, the dendronized ligands exhibit higher activities (TON up to 3450 for the dendronized catalyst vs. 500 for BINAP) and enantioselectivities (89% vs. 71% for BINAP) than the parent Ir/BINAP catalyst. This is an example in which MWE changes the characteristics of the catalyst in a positive way.^[34]

Figure 10 | Dendronized BINAP by Fan *et al.* and the Ir-catalyzed asymmetric hydrogenation of quinolines.

1.5 | Selected examples of repetitive batch nanofiltration

Whereas continuous flow nanofiltration often requires dedicated membrane reactor technology, Rothenberg *et al.* showed that the ‘cat-in-a-cup’ or ‘tea bag’ principle is a simple but practical solution for MWE catalyst separation (see also Figure 7). It was applied in the ruthenium-catalyzed asymmetric transfer hydrogenation of acetophenone and a dendron-enlarged analogue of Noyori’s Ts-DPEN in combination with $[\{\text{RuCl}_2(\text{cymene})\}_2]$ was used (Figure 11). Less than 0.3% of the Ru leached into the outer solution, as determined by ICP-MS analysis. The leached Ru was not causing the observed activity, as was shown in an experiment in which the membrane cup was removed from the reaction medium. In the period that the membrane cup was not present only a slight increase in conversion was observed.^[33]

Figure 11 | Fréchet-type dendron-enlarged Ts-DPEN and the Ru-catalyzed transfer hydrogenation reaction.

Oxazolines have emerged as an interesting ligand class, because of their modular nature and have proven efficacy in many asymmetric catalytic reactions. Therefore, Gade and co-workers have chosen to immobilize bis- and trisoxazolines (BOX and trisox) on carbosilane dendrimers. The Cu-catalyzed Henry reaction of 2-nitrobenzaldehyde and nitromethane, as well as the Cu-catalyzed α -hydrazination of a β -keto ester were studied as bench mark reactions. In both reactions, the BOX ligands showed superior behavior, both with respect to activity (58% for trisox vs. 87% for BOX) and selectivity (53% for trisox vs. 87% for Box in the Henry reaction). Recycling experiments with the supported BOX ligands (Figure 12) by means of nanofiltration with a polymeric membrane (benzoylated dialysis tubing) proved to be efficient for 7 runs, both with respect to activity and enantioselectivity.^[50]

Figure 12 | Cu-BOX catalyst immobilized on a carbosilane dendrimer and the Cu-catalyzed α -hydrazination and Henry reaction.

1.6 | Continuous flow nanofiltration

The ultimate achievement in continuous homogeneous catalysis probably is continuous flow membrane filtration. Apart from the catalyst recycling, this technology can have numerous advantages. From an economic point of view, an integrated process like a continuous flow membrane reactor can be beneficial in terms of lower total investment costs and lower energy consumption. With respect to the chemistry, the continuous removal of product can decrease possible product inhibition and side reactions, leading to higher reaction rates and a cleaner product stream.

However, continuous flow membrane filtration also has some serious drawbacks. Combining (homogeneous) catalytic reactions with a nanofiltration step, makes the reaction setup considerably more complex and hence expensive, as compared to the batch reactors that are commonly in use in homogeneous catalysis. Also modeling and prediction of the outcome of reactions gets more difficult, which is of course in coherence with the design of the reactor.^[51]

Although cross-flow nanofiltration has a great potential for innovative applications, no industrial applications in organic solvents are known until now. This might be due to the limited availability of solvent resistant polymeric

membranes and the difficulty to produce larger ceramic membranes with reliable narrow pore-size distribution.

1.6.1 | Selected examples of continuous homogeneous catalysis with nanofiltration

Until now, only a limited number of examples of continuous flow membrane filtration of MWE catalysts on laboratory scale have appeared in literature. Pd-catalyzed allylic substitution reactions have been studied in a continuous flow reactor by Vogt and co-workers. Nanometer-sized multiple PCP-pincer ligand systems (Figure 13) were used in the Pd-catalyzed allylic amination of cinnamyl acetate with morpholine and the allylic alkylation of cinnamyl acetate with dimethyl malonate. In both reactions, the multiple PCP-pincer ligands exhibit a high selectivity towards the linear *trans* product.

Figure 13 | Multiple PCP-pincer ligands by Vogt *et al.* and the Pd-catalyzed allylic substitution reaction.

The kinetic parameters were carefully investigated before applying the multiple pincer ligands in the continuous nanofiltration reactor setup. For both

reactions a rapid decrease in activity was observed, which might be caused by introduction of oxygen into the system, leading to catalyst deactivation.^[52]

Another reaction that has been applied in continuous nanofiltration setups is the metathesis reaction. Two distinctly different types of complexes are well-known to catalyze metathesis reactions. The Schrock type catalysts, based on early transition metals are highly active, but their great sensitivity towards polar groups makes them less suitable for nanofiltration. The Grubbs type metathesis catalysts based on ruthenium are more stable and therefore more widely studied in literature examples. Grubbs type catalysts, i.e. Grubbs II and Grubbs-Hoveyda, typically consist of an *N*-heterocyclic carbene ligand and a benzylidene ligand. The active catalyst is generated by liberation of the benzylidene ligand from the precatalyst. The MWE tag should therefore be attached to the NHC ligand, i.e. the ligand that stays on the metal center during catalysis, in order to achieve high catalyst retention. Furthermore, the MWE tag should be electron donating to increase the catalytic activity. The Ru complex shown in Figure 14, which has a molecular mass of 1080 g/mol, was synthesized and compared with mesityl Grubbs-Hoveyda. Both catalysts showed almost quantitative yield in the RCM of diethyl diallyl malonate at 40°C at 0.1% catalyst loading in a batch reaction. The continuous flow membrane process showed a rapid catalyst deactivation. However, the reason for deactivation might be the increasing ethene concentration, since the Ru retention is 97.6%. Despite the rapid catalyst deactivation, a total turnover number 866 mol/mol catalyst was reached.^[53]

Figure 14 | MWE RCM catalyst by Plenio *et al.* the Ru-catalyzed metathesis of diethyl diallyl malonate.

1.7 | Conclusions and future perspectives

Molecular weight enlargement (MWE) of homogeneous catalysts is a promising method towards continuous homogeneous catalysis. Interesting examples of MWE in combination with nanofiltration appeared in literature covering a variety of homogeneously catalyzed reactions, such as hydroformylation, metathesis, and cross-coupling reactions. For all of these reactions advantages and disadvantages of either the type of support, the kind of membrane or the method of attaching the ligand to the support led to different strategies within the framework of MWE. The support has to be stable under the catalytic conditions applied and chemically inert. Preferably, it is a rigid, three dimensional structure, which enhances its retention by the nanofiltration membrane. Nowadays, both polymeric and ceramic membranes are commercially available and have been applied successfully in nanofiltration of MWE catalysts. Still, every application requires a dedicated choice between the two for an optimal efficiency.

Besides repetitive batch nanofiltration, interesting results have been obtained in repetitive batch catalyst precipitation. Since MWE catalysts often possess very different solubility properties compared to the reactants and products, this feature can be used. Different kinds of reactions have been investigated applying this strategy, such as (asymmetric) hydrogenation and cross-coupling reactions. The fact that for this method no dedicated laboratory equipment is needed, makes repetitive batch precipitation a viable technique.

Both repetitive batch and continuous flow setups have been discussed. Whereas continuous homogeneous catalysis is the ultimate goal for many research groups, it requires dedicated setups and expertise to achieve it. Often budget restrictions do not allow for a lab-scale continuous flow membrane reactor, and the potential of the MWE catalyst is demonstrated in a repetitive batch fashion, often made of commercially available parts and compatible with conventional laboratory equipment.

Molecular weight enlargement of homogeneous catalysts, especially in combination with nanofiltration, is a very promising technique for catalyst recovery and reuse. Encouraging results have been obtained for various catalytic transformations, but still a lot of development is needed for industrial application.

Homogeneous catalyst recycling is a very diverse field of research. Contributions in the field of membrane preparation, reactor engineering, as well as synthesis of the MWE catalysts need to be combined, in order to be successful.

For the MWE catalyst preparation, we believe that MWE units that are either commercially available or synthesized in a single reaction step will find more application. So far, Polyhedral Oligomeric Silsesquioxanes (POSS) are underestimated as means for MWE. Besides their easy preparation, they possess a rigid three dimensional structure that makes them particularly suitable for nanofiltration. They might have a great potential for process intensification in many different homogeneously catalyzed transformations.

1.8 | Scope of the thesis

The recyclability properties of homogeneous catalysts need to be improved for application in catalytic processes in industry. In this thesis, various new methods of molecular weight enlargement (MWE) as well as new materials that can serve as molecular weight enlargement units, in combination with either repetitive batch or continuous flow nanofiltration have been investigated and these MWE systems have been applied in several homogeneously catalyzed reactions.

In chapter 2 a new synthetic route towards stable MWE monodentate phosphine ligands via 'click' chemistry is described. These ligands are applied in the Pd-catalyzed Suzuki-Miyaura coupling of aryl halides and phenyl boronic acid. The supported systems show very similar activities compared to the unsupported analogues. Moreover, recycling experiments by means of repetitive batch nanofiltration demonstrate that these systems can be recovered and reused efficiently.

In chapter 3, PPh_3 , a widely used ligand in homogeneous catalysis in general and in the hydroformylation of *n*-alkenes in particular has been decorated with a POSS moiety for MWE and has been applied in the Rh-catalyzed hydroformylation of 1-octene, accordingly. Recycling experiments in the continuous flow nanofiltration reactor show unprecedented turnover numbers as well as high catalyst stability and retention.

However, PPh_3 is not one of the best performing ligands in the Rh-catalyzed hydroformylation of 1-octene, neither in terms of activity nor in terms of selectivity. Therefore, the strategy introduced in chapter 3 is extended to POSS-enlarged bidentate ligands, such as DPEPOSS and XantPOSS that are known to exhibit higher l/b ratios than PPh_3POSS . Bulky, monodentate phosphite ligands are known for their high activity in the Rh-catalyzed hydroformylation of 1-octene, and a POSS-enlarged bulky monophosphite analogue is prepared and applied in the continuous

hydroformylation of 1-octene in the continuous flow membrane reactor. This will be discussed in chapter 4.

Tuning the regioselectivity in the hydroformylation of styrene is discussed in chapter 5. A new class of binaphthol-based ligands is developed and applied in the Rh-catalyzed hydroformylation of styrene. High activities as well as high regioselectivities towards the linear product have been obtained. Modification of the best performing ligands with a POSS moiety and consecutive application the POSS-enlarged ligands in combination with Rh in the hydroformylation of styrene will be discussed.

In chapter 6, the application of bidentate ligands in the nickel-catalyzed isomerization of 2M3BN was studied in combination with catalyst compartmentalization of the catalyst. In order to maximize retention POSS-enlarged ligands are applied, and the synthesis of bidentate ligands that are connected to the soluble support via 'click' chemistry is discussed.

1.9 | References

- [1] B. Cornils, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, Wiley-VCH, 2nd ed., **2002**.
- [2] <http://www.platinum.matthey.com/pgm-prices/price-charts/>
- [3] H. P. Dijkstra, G. P. M. van Klink, and G. van Koten, *Acc. Chem. Res.*, **2002**, 35, 798.
- [4] D. J. Cole-Hamilton, *Science*, **2003**, 299, 1702.
- [5] B. Cornils, W. A. Herrmann, I. T. Horvath, W. Leitner, S. Mecking, H. Olivier-Bourbigou, D. Vogt, *Multiphase Homogeneous Catalysis*, Wiley-VCH, 1 ed., **2005**.
- [6] D. Cole-Hamilton and R. Tooze, *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design*, Springer, **2006**.
- [7] C. Müller, M. G. Nijkamp, D. Vogt, *Eur. J. Inorg. Chem.*, **2005**, 4011.
- [8] C. Müller, D. Vogt, in *Handbook of Green Chemistry: Green Catalysis*, 1 edn., **2009**, pp. 127-152.
- [9] G. W. Parshall, S. D. Ittel, *Homogeneous Catalysis*, 2nd ed., **1992**.
- [10] K. Kunna, C. Müller, J. Loos, D. Vogt, *Angew. Chem., Int. Ed.*, **2006**, 45, 7289.
- [11] D. Astruc, F. Chardac, *Chem. Rev.*, **2001**, 101, 2991.
- [12] G. P. M. van Klink, H. P. Dijkstra, G. van Koten, *C.R. Chim.*, **2003**, 6, 1079.
- [13] C. E. Garrett, K. Prasad, *Adv. Synth. Catal.*, **2004**, 346, 889.
- [14] R. Andres, E. de Jesus, J. C. Flores, *New J.Chem.*, **2007**, 31, 1161.
- [15] E. de Jesus, J. C. Flores, *Ind. Eng. Chem. Res.*, **2008**, 47, 7968.
- [16] J. K. Kassube, L. H. Gade, *Top. Organomet. Chem.*, **2006**, 20, 61.

- [17] D. Mery, D. Astruc, *Coord. Chem. Rev.*, **2006**, 250, 1965.
- [18] G. E. Oosterom, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Angew. Chem., Int. Ed.*, **2001**, 40, 1828.
- [19] J. N. H. Reek, D. de Groot, G. E. Oosterom, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Rev. Mol. Biotechnol.*, **2002**, 90, 159.
- [20] J. N. H. Reek, D. de Groot, G. E. Oosterom, P. C. J. Kamer, P. W. N. M. van Leeuwen, *C.R. Chim.*, **2003**, 6, 1061.
- [21] J. M. Campelo, D. Luna, R. Luque, J. M. Marinas, A. A. Romero, *ChemSusChem*, **2009**, 2, 18.
- [22] E. Flaschel, C. Wandrey, M. R. Kula, *Adv. Biochem. Eng./Biotechnol.*, **1983**, 26, 73.
- [23] A. F. Bueckmann, M. R. Kula, R. Wichmann, C. Wandrey, *J. Appl. Biochem.*, **1981**, 3, 301.
- [24] R. Wichmann, C. Wandrey, A. F. Bueckmann, M. R. Kula, *Biotechnol. Bioeng.*, **1981**, 23, 2789.
- [25] C. Wandrey, E. Flaschel, K. Schuegerl, *Chem. Ing. Tech.*, **1977**, 49, 257.
- [26] M. D. Bednarski, H. K. Chenault, E. S. Simon, G. M. Whitesides, *J. Am. Chem. Soc.*, **1987**, 109, 1283.
- [27] P. Vandezande, L. E. M. Gevers, I. F. J. Vankelecom, *Chem. Soc. Rev.*, **2008**, 37, 365.
- [28] R. W. Baker, *Membrane Technology and Applications*, Wiley, **2000**.
- [29] A. W. Kleij, R. A. Gossage, R. J. M. Klein Gebbink, N. Brinkmann, E. J. Reijerse, U. Kragl, M. Lutz, A. L. Spek, G. Van Koten, *J. Am. Chem. Soc.*, **2000**, 122, 12112.
- [30] D. E. Bergbreiter, J. Tian, C. Hongfa, *Chem. Rev.*, **2009**, 109, 530.
- [31] R. J. M. K. Gebbink, C. A. Kruithof, G. P. M. van Klink, G. van Koten, *Rev. Mol. Biotechnol.*, **2002**, 90, 183.
- [32] R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Rev.*, **2002**, 102, 3717.
- [33] A. V. Gaikwad, V. Boffa, J. E. ten Elshof, G. Rothenberg, *Angew. Chem., Int. Ed.*, **2008**, 47, 5407.
- [34] Z. J. Wang, G. J. Deng, Y. Li, Y. M. He, W. J. Tang, Q. H. Fan, *Org. Lett.*, **2007**, 9, 1243.
- [35] R. van de Coevering, R. J. M. Klein Gebbink, G. van Koten, *Prog. Polym. Sci.*, **2005**, 30, 474.
- [36] G. J. Deng, B. Yi, Y. Y. Huang, W. J. Tang, Y. M. He, Q. H. Fan, *Adv. Synth. Catal.*, **2004**, 346, 1440.
- [37] B. M. J. M. Suijkerbuijk, L. Shu, R. J. M. K. Gebbink, A. D. Schlueter, G. van Koten, *Organometallics*, **2003**, 22, 4175.
- [38] N. R. Vautravers, P. Andre, D. J. Cole-Hamilton, *Dalton Trans.*, **2009**, 3413.
- [39] N. R. Vautravers, D. J. Cole-Hamilton, *Dalton Trans.*, **2009**, 2130.
- [40] N. R. Vautravers, D. J. Cole-Hamilton, *Chem. Commun.*, **2009**, 92.
- [41] K. J. Haxton, D. J. Cole-Hamilton, R. E. Morris, *Dalton Trans.*, **2007**, 3415.
- [42] K. J. Haxton, D. J. Cole-Hamilton, R. E. Morris, *Dalton Trans.*, **2004**, 1665.
- [43] B. F. Stengel, J. Ridland, M. Hearshaw, D. J. Cole-Hamilton, R. Tooze, R. E. Morris, 2003-GB3829, 19 pp. 18-3-2004. WO. 4-9-2003.

- [44] L. Ropartz, R. E. Morris, D. F. Foster, D. J. Cole-Hamilton, *J. Mol. Catal. A: Chem.*, **2002**, 182-183, 99.
- [45] L. Ropartz, D. F. Foster, R. E. Morris, A. M. Z. Slawin, D. J. Cole-Hamilton, *Dalton Trans.*, **2002**, 1997.
- [46] L. Ropartz, R. E. Morris, D. J. Cole-Hamilton, D. F. Foster, *Chem. Commun.*, **2001**, 361.
- [47] <http://www.inopor.com>
- [48] <http://membrane-extraction-technology.com>
- [49] M. Gaab, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Eur. J.*, **2009**, 15, 5450.
- [50] J. Lemo, K. Heuzé, D. Astruc, *Chem. Commun.*, **2007**, 4351.
- [51] I. F. J. Vankelecom, *Chem. Rev.*, **2002**, 102, 3779.
- [52] N. J. Ronde, D. Totev, C. Müller, M. Lutz, A. L. Spek, D. Vogt, *ChemSusChem*, **2009**, 2, 558.
- [53] D. Schoeps, K. Buhr, M. Dijkstra, K. Ebert, H. Plenio, *Chem. Eur. J.*, **2009**, 15, 2960.

2

'Click' dendritic phosphines: design, synthesis, application in Suzuki coupling and recycling by nanofiltration

A new synthetic route towards stable molecular-weight enlarged monodentate phosphine ligands via 'click' chemistry was developed. These ligands were applied in the Pd-catalyzed Suzuki-Miyaura coupling of aryl halides and phenyl boronic acid. The supported systems show very similar activities compared to the unsupported analogues. Moreover, recycling experiments by means of nanofiltration using ceramic nanofiltration membranes demonstrate that these systems can be recovered and reused efficiently.

Parts of the work described in this chapter have been published:

Michèle Janssen, Christian Müller, Dieter Vogt, *Adv. Synth. Catal.* **2009**, 351, 313-318

2.1 | Introduction

Homogeneously catalyzed reactions play an increasingly important role in organic synthesis.^[1] However, a major drawback of homogeneous catalysts over heterogeneous systems is the difficulty of their recovery and recycling.^[2] A range of approaches have been studied over the years, all with their own strengths and weaknesses, leading to the conclusion that one ultimate solution does not exist. This is inherently due to the vast variety of applications, each with its own specific requirements and conditions. Hence, there is a great need for the development of complementary generic methods – a toolbox for practical application. These methods can be roughly divided in biphasic catalysis ^[3-5] and immobilization on insoluble (heterogenization) and soluble supports (molecular weight enlargement, MWE).^[6-8]

MWE catalysts can in principle be recovered by means of precipitation, ultracentrifugation or nanofiltration.^[9-16] Although there are numerous examples of catalyst recovery especially via precipitation, the field of nanofiltration in homogeneous catalysis is still rather unexploited, because advanced membrane reactor technology is usually needed.^[7,17-20] Recently, Rothenberg *et al.* demonstrated, however, that this is not necessarily required and that a Ru-based transfer hydrogenation catalyst can efficiently be recovered with a relatively simple setup.^[21]

We report here on the synthesis of multiple phosphine ligands attached to a dendritic support via ‘click’ chemistry. Their application in the Pd-catalyzed Suzuki coupling and their facile recovery and reuse by means of nanofiltration has been investigated.

2.2 | Synthesis of the molecular weight enlarged ligands

In order to attach a ligand to a soluble support, both ligand and support need to be decorated with an anchoring group. In this respect, we started to focus on ‘click’ chemistry, since it is an elegant way to attach ligands to a support. The triazole-forming Huisgen 1,3-dipolar cycloaddition reaction between an organic azide and an alkyne occurs at elevated temperatures and usually results in a mixture of the 1,4- and 1,5-regioisomer (Scheme 1).^[22,23]

Scheme 1 | The triazole-forming Huisgen 1,3-dipolar cycloaddition reaction between an organic azide and an alkyne towards the 1,4- and the 1,5-regioisomer.

Sharpless and co-workers discovered that the Huisgen reaction can be catalyzed by a copper(I) salt or a copper(II) salt in the presence of a reducing agent (*e.g.* $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ with sodium ascorbate). In this way, the reaction occurs at ambient temperature and yields selectively the 1,4-regioisomer. Sharpless *et al.* coined the term ‘click’ reaction for modular reactions that have a wide scope, give high yields, and generate only inoffensive by-products. Chemical transformations that fulfill these requirements are *e.g.* cycloadditions of unsaturated species (1,3-dipolar cycloaddition reactions, Diels-Alder reactions), nucleophilic substitution chemistry (ring-opening reactions of strained heterocyclic electrophiles, such as epoxides and aziridines), carbonyl chemistry of the non-aldol-type (formation of ureas, thioureas, etc.) and additions to C-C multiple bonds (epoxidations, aziridinations, dihydroxylations, etc.).^[22]

Often, the copper-catalyzed azide-alkyne dipolar cycloaddition reaction is referred to as the ‘click’ reaction. This reaction exhibits several attractive features, such as high and often quantitative yields as well as a high functional group tolerance. These interesting characteristics have already been widely exploited in polymer and materials science,^[24,25] while examples in the field of catalysis are yet in its infancy.^[26-29]

Figure 1 | ‘Click’-reaction for the attachment of a ligand to a support.

In order to use the ‘click’ reaction to attach ligands to supports (Figure 1), a few practical points have to be considered. First, either the support or the ligand has to be decorated with the azide functionality. For safety reasons we chose to functionalize the ligand with an azide anchoring group, avoiding several azide moieties in one molecule. A large amount of the spring-loaded azide moieties in one molecule could lead to explosive elimination of N_2 . Second, azides and free phosphines would undergo a Staudinger reaction under formation of dinitrogen and an iminophosphorane.^[30] For this reason, the phosphine moiety has to be protected until the triazole ring is formed.

For a suitable support we chose tetrakis(4-ethynylphenyl)methane, since this results in a rigid, spherical molecule after ligand attachment. These structures are known to display better retention and less membrane fouling than linear shaped or flat macromolecules.^[31]

Support **4** was prepared according to a literature procedure.^[35] Commercially available tetraphenylmethane **1** was selectively brominated in the *para* position using bromine in the presence of iron filings.^[36] The tetra-(4-bromophenyl)-methane **2** was coupled with TMS-protected acetylene in a Sonogashira reaction. After deprotection, support **4** was obtained in 65% overall yield (Scheme 2).

Scheme 2 | Synthesis of support **4**.

Based on literature data, triphenylphosphine (**A**), dicyclohexylphenylphosphine (**B**) and 2-dicyclohexylphosphine biphenyl (**C**) were chosen for immobilization purposes. These ligands are among the best and most frequently used monodentate phosphines for the Pd-catalyzed Suzuki-Miyaura coupling reaction (Figure 2).^[32-34]

Figure 2 | Monodentate phosphines frequently used in Suzuki coupling.

The synthesis of the azide-functionalized ligands started with the deprotonation of diphenyl- or dicyclohexylphosphine with potassium or PhLi, respectively. The obtained phosphide was reacted with 4-fluorobenzonitrile in a nucleophilic aromatic substitution reaction yielding the cyano-functionalized phosphine **6** in high yield.^[37]

Compound **6** was then reduced to its corresponding benzyl amine and protected as its phosphine oxide **7**, necessary to prevent Staudinger reaction once the azide is formed. This was followed by a copper-mediated diazotransfer reaction to obtain the azide-functionalized phosphine oxides **8** and **9** in 64 and 71% overall yield, respectively (Scheme 3).^[38]

Scheme 3 | Synthesis of azide-functionalized phosphine oxides **8** and **9**.

The synthesis of the azido-functionalized phosphine oxide **14** was achieved by a slightly modified procedure. After a Suzuki coupling between 1-bromo-2-iodobenzene and 4-cyanophenyl boronic acid, **11** was obtained in 80% yield, which was lithiated and subsequently reacted with chlorodicyclohexylphosphine to yield compound **12**.^[39,40] Nitrile **12** was reduced to the corresponding benzyl amine and protected by reaction with H₂O₂. After the copper-mediated diazotransfer reaction, the azide-functionalized Buchwald phosphine oxide **14** was obtained in 60% overall yield (Scheme 4).

Scheme 4 | Synthesis of azide-functionalized Buchwald phosphine oxide **14**.

The azide-functionalized phosphine oxides were then attached to support **4** by means of a copper-mediated 1,3-dipolar cycloaddition reaction ('click' reaction). After deprotection of the phosphine with excess HSiCl_3 , the desired molecular weight enlarged ligands **L1-L3** were obtained in good yields (Scheme 5).^[41]

Scheme 5 | Synthesis of 'click' dendritic ligands **L1-L3**.

2.3 | Pd-catalyzed Suzuki-Miyaura coupling

In order to justify immobilization of homogeneous catalysts, they should be easy to prepare and should show high activity as well as high total turnover number (tTON). We chose to investigate the Suzuki reaction, since single monodentate phosphine ligands are frequently applied. Thus, ligands **L1-L3** were explored in the Pd-catalyzed coupling of phenyl boronic acid and aryl halides (Scheme 6).

Scheme 6 | Suzuki-Miyaura coupling between aryl halide and phenyl boronic acid.

First, the activities of the Pd-catalysts containing ligands **L1-L3** were compared with those of their original unsupported analogues **A-C** for three different aryl halides, that vary in terms of steric and electronic properties. The results are

summarized in Table 1. In the case of 4-chlorotoluene the observed activities were considered too low (**L2** = 27% conversion in 8h; **L3** = 78% conversion in 8h) for application in the repetitive batch experiments later on.

Table 1 | Comparison of ‘click’ dendritic ligands with their unsupported analogues.

Entry	Ligand	Aryl halide	Boronic acid	Time (h)	Yield (%)
1	A			7	94
2	A			7	71
3	A			7	98
4	L1			7	96
5	L1			7	77
6	L1			7	92
7	B			3	>99
8	B			3	>99
9	B			3	>99
10	L2			3	>99
11	L2			3	>99
12	L2			3	>99
13	C			2	>99
14	C			2	>99
15	C			2	>99
16	L3			2	>99
17	L3			2	>99
18	L3			2	>99

Reaction conditions: 1.0 mmol 4-bromotoluene, 1.5 mmol phenyl boronic acid, 3.0 mmol Na_2CO_3 , 0.01 mmol $\text{Pd}(\text{OAc})_2$, Pd:P = 1:1, solvent: THF (3mL)/water (2mL), $T = 60^\circ\text{C}$. Yields are GC yields.

The conversion followed in time is depicted in Figure 3 exemplarily for the catalyst system Pd/**L3** in comparison with Pd/**C**. Both, Table 1 and Figure 3 clearly demonstrate that the supported systems show essentially identical activities as the original unsupported ones, indicating that the four catalysts on a dendrimer act truly independently. Moreover, NMR studies on the MWE ligands before and after the catalysis experiments showed no degradation of the triazole ring.

Figure 3 | Comparison of activities of Pd/**L3** and its unsupported analogue **C**.

Subsequently, the total turnover numbers (tTON) of the three ‘click’ dendritic systems were determined. The results are depicted in Table 2. The tTON’s turned out to be high (~ 15,000) for all three MWE systems and, moreover, comparable with values reported in the literature.^[42]

Table 2 | Comparison of activities of ‘click’ dendritic ligands and their unsupported analogues.

Entry	Ligand	tTON
1	A	nd
2	L1	15500
3	B	nd
4	L2	12000
5	C	nd
6	L3	16000

Reaction conditions: 1.0 mmol 4-bromotoluene, 1.5 mmol phenyl boronic acid, 3.0 mmol Na₂CO₃, 0.01 mmol Pd(OAc)₂, Pd:P = 1:1, solvent: THF (3mL)/water (2mL), T = 60°C. Yields are GC yields.

2.4 | Catalyst recycling studies

Since the ‘click’ dendritic catalysts fulfilled the requirements discussed above, (straightforward synthesis, high tTON and high activity), we applied these systems in a nanofiltration setup. This in-house made setup consists of a commercially available ceramic membrane tube,^[43] which is capped with Teflon discs and fixed in a stainless steel holder (Figure 4). The molecular weight cut-off of the applied membrane is 450 Da. Since the molecular weight of our ‘click’ dendritic ligands is higher than 1600 Da, the membrane should in principle be able to retain the corresponding catalysts.

Figure 4 | Ceramic nanofiltration membrane setup.

Prior to use, the membrane tube was thoroughly evacuated, filled with N₂ and soaked in THF. Subsequently, the ‘click’ dendritic Pd-catalyst solution was injected into the membrane tube. The stainless steel holder was placed in a 50 mL Schlenk tube and a solution of aryl halide, phenyl boronic acid and Na₂CO₃ in 25 mL of THF and 15 mL of water was added. The Schlenk tube was then placed in a thermostatic shake bath at 60°C and the reaction was allowed to proceed for 16 h. At the end of the reaction, the complete reaction mixture was collected by syringe and replaced by a fresh substrate solution. Between these recycling runs no additional Pd was added. The results obtained with the systems Pd/**L1-L3** are shown in Table 3.

Table 3 | Recovery and reuse of Pd/**L1-L3** catalysts.

Run	Ligand	Pd added (mol %)	Yield (%)
1	L1	0.8	>99
2	L1	0	96
3	L1	0	97
4	L1	0	90
5	L1	0	55
1	L2	0.8	>99
2	L2	0	>99
3	L2	0	>99
4	L2	0	76
5	L2	0	66
1	L3	0.1	>99
2	L3	0	82
3	L3	0	78
4	L3	0	64
5	L3	0	72

Reaction conditions: 1.0 eq. 4-bromotoluene, 1.5 eq. phenyl boronic acid, 3.0 eq. Na_2CO_3 , Pd:Click dendrimer = 4:1, Pd precursor = $\text{Pd}(\text{OAc})_2$, solvent: THF (30 mL) + H_2O (20 mL), $T = 60^\circ\text{C}$. Time = 16 h. Yields are GC yields.

In case of Pd/**L1** and Pd/**L2**, the recycling runs were performed with a substrate to Pd ratio of 125:1. In both cases a clear drop in activity was observed after the third run. This could be due to either Pd leaching or catalyst deactivation, although the tTON of the catalysts was not yet reached. ICP-AES analysis of the product solutions revealed a Pd leaching of 0.8% per run for Pd/**L1** and 0.4% per run for Pd/**L2**, which seems too small to account for the large drop in activity.

The recycling runs for Pd/**L3** were performed with a Pd loading of only 0.1 mol%. The first run revealed a higher activity of the catalyst systems compared to the remaining ones, but the yield of 4-methylbiphenyl was essentially constant in the last four runs. ICP-AES analysis of the product solutions showed a Pd leaching of 0.8% per run. To discard the hypothesis that the leached Pd accounts for the observed activity, we performed an experiment in which the substrate solution was completely removed from the membrane tube containing the Pd/**L3** catalyst after 40 min. At this time the conversion had reached 56%. 16 hours later, no significant further increase in conversion (58%) was observed. The substrate solution was transferred back into the Schlenk tube containing the membrane tube. Interestingly, full conversion was reached after 2 h (Figure 5). From this experiment we can conclude that the catalytic reaction takes place inside the membrane tube and that the leached Pd accounts only for a very small amount of conversion (~2% in 16 h).

Moreover, the membrane tube can be stored for 16 h under argon without significant catalyst deactivation.

Figure 5 | Reaction profile for the formation of 4-methylbiphenyl.

2.5 | Concluding remarks

In conclusion, a new synthetic route towards stable dendritic monodentate phosphine ligands via ‘click’ chemistry was developed. These ligands were applied in the Pd-catalyzed Suzuki-Miyaura coupling of aryl halides and phenyl boronic acid. The supported systems show very similar activities as their original unsupported analogues. Recycling experiments by means of nanofiltration using ceramic nanofiltration membranes demonstrate that these systems can be recovered and reused efficiently.

2.6 | Experimental part

General considerations

Chemicals were purchased from Aldrich, Acros or Merck and used as received. All reactions were performed under argon atmosphere using standard Schlenk techniques. Solvents were taken HPLC-grade from an alumina filled argon flushed column. All manipulations were performed using standard Schlenk techniques.

NMR spectra were recorded on a Varian Mercury 200, Mercury 400 or Inova 500 spectrometer. Elemental analyses were measured on a Perkin-Elmer 2400 apparatus. IR spectra were recorded on an Avatar 360 FT-IR instrument in ATR mode.

Ceramic nanofiltration membranes were purchased from Inopor GmbH Germany and have a pore size of 0.9 nm and a molecular weight cut-off of 450 Da (www.inopor.com). Catalytic conversions were determined by GC on a PONA column (50 m x 0.20 mm) using pentadecane as an internal standard. Retention times were compared with authentic samples.

Synthesis of 4-(diphenylphosphino)benzonitrile

Diphenylphosphine (11.1 g, 59.7 mmol) was dissolved in 80 mL THF and potassium (2.5 g, 64 mmol) was added. The reaction mixture was heated at 40°C for 2h upon which the reaction mixture turned red. The excess of potassium was removed and the mixture was cooled to -10°C and 4-chlorobenzonitrile (7.37 g, 59.7 mmol) was added. The mixture was stirred at r.t. for overnight. All volatiles were removed *in vacuo* and the residue was washed with water. The product was recrystallized from EtOH. The desired product was obtained as a white solid in 69% yield (11.82 g, 41.19 mmol).

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.32-7.24 (m, 14H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 145.0, 135.6, 134.0, 133.4, 131.7, 129.4, 128.8, 118.6, 111.9.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -5.8 (s).

IR ν (cm^{-1}): 2221.48 (CN).

Synthesis of 4-(dicyclohexylphosphino)benzonitrile

Dicyclohexylphosphine (1g, 5.05 mmol) was dissolved in 20 mL of diethyl ether and 2.77 mL of phenyl lithium (2.0 M in dibutyl ether, 5.55 mmol) was added slowly at r.t. The lithium dicyclohexyl phosphide precipitated and was filtered off (in contact with air a strong yellow-green chemo luminescence was visible).

The obtained lithium phosphide was redissolved in THF and the mixture was cooled to -78°C. 4-Fluorobenzonitrile (591 mg, 5.05 mmol) was added in small portions and the mixture immediately turned dark purple. All volatiles were removed *in vacuo*; the

residue was redissolved in CH_2Cl_2 and washed with (degassed) brine. The phases were separated and the organic layer was dried over MgSO_4 and concentrated to dryness.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.76-7.37 (m, 4H), 1.83-1.53 (m, 11H), 1.43-0.82 (m, 11H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 144.7, 133.1, 132.0, 112.0, 118.6, 32.8, 30.3, 29.1, 27.5, 26.7.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 4.17(s)

IR ν (cm^{-1}): 2220 (CN).

Synthesis of 2-Dicyclohexylphosphino-4'-cyanobiphenyl (12)

At -100°C $n\text{-BuLi}$ (2.5M in hexanes, 2.71 mL, 6.78 mmol) was added dropwise to a solution of 2'-bromobiphenyl-4-carbonitrile (1.4 g, 5.43 mmol) in 35 mL of THF. The mixture was stirred for 1h. Then, Cy_2PCl (1.28 g, 5.50 mmol) was added dropwise to the mixture and the mixture was allowed to warm to r.t. overnight. All volatiles were removed *in vacuo*. The residue was redissolved in 60 mL of EtOAc and washed with 40 mL of water. The organic phase was dried over MgSO_4 and concentrated to dryness.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.65 (d, $J = 7.8$ Hz, 2H), 7.64-7.60 (m, 1H), 7.42-7.34 (m, 4H), 7.25-7.20 (m, 1H), 1.85-1.45 (m, 12H), 1.18-0.93(m, 10H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 148.8, 148.6, 147.8, 147.7, 133.9, 133.7, 133.2, 133.1, 131.5, 131.4, 131.2, 129.8, 129.7, 128.6, 127.4, 119.1, 110.5, 34.6, 34.4, 30.4, 30.3, 29.18, 29.1, 27.2, 27.1, 27.05, 27.0, 26.3.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -17.48 (s).

IR ν (cm^{-1}): 2222 (CN).

General synthesis for phosphinobenzylamine

The phosphinobenzonitrile (5.05 mmol) is dissolved in 40 mL of THF, cooled to 0°C and LiAlH_4 (765 mg, 20.2 mmol) was added in small portions. The mixture was stirred for 2h at 50°C . The reaction mixture was diluted with diethyl ether and then quenched by careful addition of water. The phases were separated; the organic phase was dried over MgSO_4 and concentrated to dryness.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.32-7.27 (m, 14H), 3.84 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 144.0, 137.0, 135.0, 134.0, 133.5, 128.6, 128.4, 127.2, 46.0.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -5.0 (s).

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.27 (dd, $^3J = 5.6$ Hz, $^3J = 2.6$ Hz, 2H), 7.00 (t, $^3J = 8.6$ Hz), 3.84 (s, 2H), 1.90-1.56 (m, 11H), 1.38-1.06 (m, 11H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 144.7, 133.1, 132.0, 112.0, 46.8, 32.8, 30.3, 29.1, 27.5, 26.7.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 2.84 (s).

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.55-7.60 (m, 1H), 7.49-7.46 (m, 1H), 7.39-7.30 (m, 2H), 7.25-7.16 (m, 4H), 3.96 (s, 2H), 1.85-1.55 (m, 12H), 1.20-0.85 (m, 10H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 150.51, 150.23, 141.47, 134.03, 133.83, 132.87, 132.84, 130.78, 130.74, 130.30, 130.24, 128.16, 126.39, 126.00, 46.31, 34.74, 34.6, 30.47, 30.3, 29.5, 29.16, 27.28, 27.22, 27.17, 27.14, 26.39.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -17.4 (s).

General synthesis of the phosphine oxides

The phosphinobenzylamine (5 mmol) was dissolved in 50 mL of CH_2Cl_2 and H_2O_2 (2 mL, 35% solution in water) was added at 0°C . After 1 h 40 mL of water was added and the phases were separated. The organic layer was washed with saturated sodium bicarbonate solution, dried over MgSO_4 and concentrated to dryness.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.32-7.27 (m, 14H), 3.84 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 144.0, 137.0, 135.0, 134.0, 133.5, 128.6, 128.4, 127.2, 46.0.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 27.40 (s).

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.27 (dd, $^3J = 5.6$ Hz, $^3J = 2.6$ Hz, 2H), 7.00 (t, $^3J = 8.6$ Hz), 3.84 (s, 2H), 1.90-1.56 (m, 11H), 1.38-1.06 (m, 11H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 144.7, 133.1, 132.0, 112.0, 46.8, 32.8, 30.3, 29.1, 27.5, 26.7.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 44.9 (s).

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.55-7.60 (m, 1H), 7.49-7.46 (m, 1H), 7.39-7.30 (m, 2H), 7.25-7.16 (m, 4H), 3.96 (s, 2H), 1.85-1.55 (m, 12H), 1.20-0.85 (m, 10H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 150.51, 150.23, 141.47, 134.03, 133.83, 132.87, 132.84, 130.78, 130.74, 130.30, 130.24, 128.16, 126.39, 126.00, 46.31, 34.74, 34.6, 30.47, 30.3, 29.5, 29.16, 27.28, 27.22, 27.17, 27.14, 26.39.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 51.1 (s).

Synthesis of triflic azide

NaN₃ (1.09 g, 16.76 mmol) was dissolved in 2.75 mL of water, 2.75 mL of toluene were added and the mixture was cooled to 0°C. Triflic anhydride (1.79 mL, 8.38 mmol) was added dropwise at this temperature. The mixture was stirred for 30 min at 0°C and then for 2 h at 10°C. The reaction was quenched by addition of saturated NaHCO₃ solution. The phases were separated and the aqueous phase was washed with toluene. The combined toluene layers are the stock solution for the diazotransfer reaction.

General procedure for the diazotransfer reaction

The appropriate benzyl amine (3.6 mmol), NaHCO₃ (1.79 g, 21.4 mmol) and CuSO₄·5H₂O were suspended in 7 mL of water. The triflic azide stock solution was added under vigorous stirring, followed by the addition of 25 mL of MeOH. The mixture was stirred for 6 h at r.t., upon which the color turned from blue to green. The organic solvents were removed in vacuo and the product was extracted from the aqueous phase with CH₂Cl₂. The product was purified by column chromatography eluting with CH₂Cl₂.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.32-7.27 (m, 14H), 4.42 (s, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 144.0, 137.0, 135.0, 134.0, 133.5, 128.6, 128.4, 127.2, 47.0.

³¹P NMR (162 MHz, CDCl₃) δ (ppm): 27.1 (s).

IR ν (cm⁻¹): 2099 (N₃).

¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.27 (dd, ³J = 5.6 Hz, ³J = 2.6 Hz, 2H), 7.00 (t, ³J = 8.6 Hz), 4.44 (s, 2H), 1.90-1.56 (m, 11H), 1.38-1.06 (m, 11H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 144.7, 133.1, 132.0, 112.0, 48.8, 32.8, 30.3, 29.1, 27.5, 26.7.

³¹P NMR (162 MHz, CDCl₃) δ (ppm): 43.2 (s).

IR ν (cm⁻¹): 2102 (N₃).

¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.55-7.60 (m, 1H), 7.49-7.46 (m, 1H), 7.39-7.30 (m, 2H), 7.25-7.16 (m, 4H), 4.42 (s, 2H), 1.85-1.55 (m, 12H), 1.20-0.85 (m, 10H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 150.51, 150.23, 141.47, 134.03, 133.83, 132.87, 132.84, 130.78, 130.74, 130.30, 130.24, 128.16, 126.39, 126.00, 48.31, 34.74, 34.6, 30.47, 30.3, 29.5, 29.16, 27.28, 27.22, 27.17, 27.14, 26.39.

³¹P NMR (162 MHz, CDCl₃) δ (ppm): 49.3 (s).

IR ν (cm⁻¹): 2101 (N₃).

General procedure for the 'click' reaction

Tetra(4-ethynyl-phenyl)methane (0.85 g, 2.04 mmol) and the appropriate azide functionalized phosphine oxide (8.14 mmol) were dissolved in 60 mL of THF. Sodium ascorbate (600 mg, 3.05 mmol) in 10 mL of water and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (200 mg, 0.75 mmol) in 15 mL of water were added to the THF solution. The mixture was stirred at r.t. for 4h. THF was evaporated in vacuo and the product was extracted from the aqueous phase with CH_2Cl_2 . The organic layer was washed with diluted ammonia solution until to water phase stayed colorless. The organic phase was dried over MgSO_4 and concentrated to dryness.

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.71 (s, 4H), 7.66 (s, 8H), 7.39-7.14 (m, 72H), 5.56 (s, 8H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 54.74 (s), 119.93 (s), 124.98 (m), 127.93 (d, $J = 6.0$ Hz), 128.56 (d, $J = 6.9$ Hz), 128.91 (s), 131.35 (m), 133.62 (s), 133.78 (s), 134.27 (s), 134.12 (s), 135.57 (s), 136.90 (d, $J = 11.4$ Hz), 138.30 (s), 148.86 (s).

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 29.21.

MALDI-TOF: 1750.17 (M + 1).

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.72 (s, 4H), 7.68 (s, 8H), 7.49-7.39 (m), 7.29-7.15 (m), 5.57 (s, 8H), 1.88-1.56 (m, 48H), 1.40-1.01 (m, 40H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 26.72 (d, $J = 7.7$ Hz), 27.27 (d, $J = 7.5$ Hz), 27.50 (d, $J = 12.2$ Hz), 29.13 (d, $J = 6.9$ Hz), 30.29 (d, $J = 16.1$ Hz), 32.79 (d, $J = 10.7$ Hz), 54.28 (s), 120.03 (s), 125.47 (d, $J = 8.3$ Hz), 127.49 (d, $J = 7.7$ Hz), 128.56 (s), 129.37 (s), 131.17 (s), 131.75 (s), 135.60 (d, $J = 27.4$ Hz), 135.71

(d, $J = 19.1$ Hz), 148.18 (s).

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 44.9 (s).

MALDI-TOF: 1798.66 (M + 1).

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.77-7.64 (m), 7.60-7.45 (m), 7.38-7.20 (m), 5.60 (s), 1.85-1.55 (m), 1.39-0.94 (m).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 26.73 (s), 27.56 (m), 29.69 (s), 30.81 (d, $J = 17.6$ Hz), 35.12 (d, $J = 13.7$ Hz), 54.44 (s), 120.07 (s), 125.26 (s), 125.44 (m), 126.26 (s), 126.77 (s), 127.12 (m), 127.30 (s), 128.09 (m), 128.51 (m), 128.65

(s), 130.46 (d, $J = 5.3$ Hz), 131.14 (m), 131.72 (m), 133.19 (m), 134.40 (m), 143.86 (m), 148.08 (s), 150.01 (m).

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 51.16 (s).

MALDI-TOF: 2104.99 ($M + 1$).

General procedure for the phosphine deprotection

The appropriate click dendrimer was dissolved in toluene and NEt_3 and HSiCl_3 were added. The mixture was refluxed for 3h. Then, 100 mL of 20% sodium hydroxide solution was added, the phases were separated and the organic phase was washed twice with water. The organic phase was dried over MgSO_4 and concentrated to dryness.

L1

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.71 (s, 4H), 7.66 (s, 8H), 7.39-7.14 (m, 72H), 5.56 (s, 8H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 54.74 (s), 119.93 (s), 124.98 (m), 127.93 (d, $J = 6.0$ Hz), 128.56 (d, $J = 6.9$ Hz), 128.91 (s), 131.35 (m), 133.62 (s), 133.78 (s), 134.27 (s), 134.12 (s), 135.57 (s), 136.90 (d, $J = 11.4$ Hz), 138.30 (s), 148.86 (s).

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -6.0.

MALDI-TOF: 1750.17 ($M + 40$).

Elemental analysis: Calculated for $\text{C}_{109}\text{H}_{84}\text{N}_{12}\text{P}_4$: %C 77.66, %H 5.02, %N 9.97. Found: %C 77.7, %H 4.9, %N 9.4.

L2

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.72 (s, 4H), 7.68 (s, 8H), 7.49-7.39 (m), 7.29-7.15 (m), 5.57 (s, 8H), 1.88-1.56 (m, 48H), 1.40-1.01 (m, 40H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 26.72 (d, $J = 7.7$ Hz), 27.27 (d, $J = 7.5$ Hz), 27.50 (d, $J = 12.2$ Hz), 29.13 (d, $J = 6.9$ Hz), 30.29 (d, $J = 16.1$ Hz), 32.79 (d, $J = 10.7$ Hz), 54.28 (s), 120.03 (s), 125.47 (d, $J = 8.3$ Hz), 127.49 (d, $J = 7.7$ Hz), 128.56 (s), 129.37 (s), 131.17 (s), 131.75 (s), 135.60 (d, $J = 27.4$ Hz), 135.71 (d, $J = 19.1$ Hz), 148.18 (s).

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 1.18.

MALDI-TOF: 1798.66 ($M + 40$).

Elemental analysis: Calculated for $\text{C}_{109}\text{H}_{132}\text{N}_{12}\text{P}_4$: %C 75.5, %H 7.7, %N 9.7. Found: %C 75.7, %H 7.8, %N 9.4.

L3

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.77-7.64 (m), 7.60-7.45 (m), 7.38-7.20 (m), 5.60 (s), 1.85-1.55 (m), 1.39-0.94 (m).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 26.73 (s), 27.56 (m), 29.69 (s), 30.81 (d, $J = 17.6$ Hz), 35.12 (d, $J = 13.7$ Hz), 54.44 (s), 120.07 (s), 125.26 (s), 125.44 (m), 126.26 (s), 126.77 (s), 127.12 (m), 127.30 (s), 128.09 (m), 128.51 (m), 128.65 (s), 130.46 (d, $J = 5.3$ Hz), 131.14 (m), 131.72 (m), 133.19 (m), 134.40 (m), 143.86 (m), 148.08 (s), 150.01 (m).

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -13.43.

MALDI-TOF: 2104.99 ($M + 40$).

Elemental analysis: Calculated for $\text{C}_{133}\text{H}_{148}\text{N}_{12}\text{P}_4$ (found): %C 78.4, %H 7.3, %N 8.3. Found: %C 78.3, %H 7.3, %N 8.7.

General procedure for the recycling runs

The ceramic membrane was oven-dried and evacuated for 16 h in the antechamber of a nitrogen filled glovebox in order to remove air. Then, the ceramic membrane was placed in a stainless steel holder. The membrane tube was soaked in THF/water and then filled with catalyst solution: $\text{Pd}(\text{OAc})_2$ (2.2 mg, 0.01 mmol) and ligand (0.01 mmol) in 1 mL of THF. The membrane tube was closed and the holder was placed in a 50 mL Schlenk tube and a solution of 10 mmol aryl bromide and 15 mmol phenyl boronic acid in 30 mL of THF and 30 mmol Na_2CO_3 in 20 mL of water was added. This Schlenk tube was placed in a thermostatic shake bath at 60°C. The reaction was allowed to proceed for 16 h.

General procedure for the determination of tTON

The ceramic membrane was oven-dried and evacuated for 16 h in the antechamber of a nitrogen filled glovebox in order to remove air. Then, the ceramic membrane was placed in a stainless steel holder. The membrane tube was soaked in THF/water and then filled with catalyst solution: $\text{Pd}(\text{OAc})_2$ (0.22 mg, 0.001 mmol) and ligand (0.001 mmol) in 1 mL of THF. The membrane tube was closed and the holder was placed in a 50 mL Schlenk tube and a solution of 10 mmol aryl bromide and 15 mmol phenyl boronic acid in 30 mL of THF and 30 mmol Na_2CO_3 in 20 mL of water was added. This Schlenk tube was placed in a thermostatic shake bath at 60°C. The reaction was followed in time by means of GC and tTON is the number of turnovers that is reached when the conversion does not increase any more.

L1	15500
L2	12000
L3	16000

2.7 | References

- [1] B. Cornils, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, Wiley-VCH **2002**.
- [2] J.A.Gladysz (Guest Editor) Recoverable Catalysts and Reagents. In *Chemical Reviews* **2002**, *102*, 3215-3892.
- [3] B. Hamers, P. S. Buerlein, C. Mller, D. Vogt, *Adv. Synth. Cat.* **2008**, *350*, 332-342.
- [4] K. Kunna, C. Mller, J. Loos, D. Vogt, *Angew. Chem. Int. Ed.* **2006**, *45*, 7289-7292.
- [5] B. Cornils, W. A. Herrmann, I. T. Horvath, W. Leitner, S. Mecking, H. Olivier-Bourbigou, D. Vogt, *Multiphase Homogeneous Catalysis, Volume 1-2*, Wiley-VCH **2005**.
- [6] D. J. Cole-Hamilton, *Science* **2003**, *299*, 1702-1706.
- [7] C. Mller, M. G. Nijkamp, D. Vogt, *Eur. J. Inorg. Chem.* **2005**, 4011-4021.
- [8] D. Cole-Hamilton, R. Tooze, *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design*, Springer **2006**.
- [9] D. Astruc, F. Chardac, *Chem. Rev.* **2001**, *101*, 2991-3023.
- [10] D. de Groot, B. F. M. de Waal, J. N. H. Reek, A. P. H. J. Schenning, P. C. J. Kamer, E. W. Meijer, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2001**, *123*, 8453-8458.
- [11] R. J. M. Klein Gebbink, C. A. Kruithof, G. P. M. van Klink, G. van Koten, *Rev. Mol. Biotechnol.* **2002**, *90*, 183-193.
- [12] C. Mller, L. J. Ackerman, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2004**, *126*, 14960-14963.
- [13] G. E. Oosterom, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Angew. Chem. Int. Ed.* **2001**, *40*, 1828-1849.
- [14] J. N. H. Reek, D. de Groot, G. E. Oosterom, P. C. J. Kamer, P. W. N. M. van Leeuwen, *C. R. Chimie* **2003**, *6*, 1061-1077.
- [15] G. P. M. van Klink, H. P. Dijkstra, G. van Koten, *C. R. Chimie* **2003**, *6*, 1079-1085.
- [16] R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Rev.* **2002**, *102*, 3717-3756.
- [17] H. P. Dijkstra, N. Ronde, G. P. M. van Klink, D. Vogt, G. van Koten, *Adv. Synth. Cat.* **2003**, *345*, 364-369.
- [18] E. B. Eggeling, N. J. Hovestad, J. T. B. H. Jastrzebski, D. Vogt, G. van Koten, *J. Org. Chem.* **2000**, *65*, 8857-8865.
- [19] N. J. Hovestad, E. B. Eggeling, H. J. Heidbuchel, J. T. B. H. Jastrzebski, U. Kragl, W. Keim, D. Vogt, G. van Koten, *Angew. Chem. Int. Ed.* **1999**, *38*, 1655-1658.
- [20] R. Sablong, U. Schlotterbeck, D. Vogt, S. Mecking, *Adv. Synth. Cat.* **2003**, *345*, 333-336.
- [21] A. V. Gaikwad, V. Boffa, J. E. ten Elshof, G. Rothenberg, *Angew. Chem. Int. Ed.* **2008**, *47*, 5407-5410.
- [22] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.
- [23] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.
- [24] W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, *28*, 15-54.
- [25] M. Malkoch, R. J. Thibault, E. Drockenmller, M. Messerschmidt, B. Voit, T. P. Russell, C. J. Hawker, *J. Am. Chem. Soc.* **2005**, *127*, 14942-14949.
- [26] R. J. Detz, S. Arvalo Heras, R. de Gelder, P. W. N. M. van Leeuwen, H. Hiemstra, J. N. H. Reek, J. H. van Maarseveen, *Org. Lett.* **2008**, *10*, 1323.

- [27] D. Liu, W. Gao, Q. Dai, X. Zhang, *Org. Lett.* **2005**, *7*, 4907-4910.
- [28] E. M. Schuster, M. Botoshansky, M. Gandelman, *Angew. Chem. Int. Ed.* **2008**, *47*, 4555-4558
- [29] M. Meise, R. Haag, *ChemSusChem* **2008**, *1*, 637-642.
- [30] H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635-646.
- [31] R. W. Baker, *Membrane Technology and Applications*, Wiley **2000**.
- [32] U. Christmann, R. Vilar, *Angew. Chem. Int. Ed.* **2005**, *44*, 366-374.
- [33] J. P. Wolfe, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1999**, *38*, 2413-2416.
- [34] J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561.
- [35] E. Galoppini, R. Gilardi, *Chem. Commun.* **1999**, 173-174.
- [36] L. M. Wilson, A. C. Griffin, *J. Mater. Chem.* **1993**, *3*, 991-994.
- [37] M. Hingst, M. Tepper, O. Stelzer, *Eur. J. Inorg. Chem.* **1998**, 73-82.
- [38] A. Titz, Z. Radic, O. Schwardt, B. Ernst, *Tetrahedron Lett.* **2006**, *47*, 2383-2385.
- [39] K. Glegola, E. Framery, K. M. Pietrusiewicz, D. Sinou, *Adv. Synth. Cat.* **2006**, *348*, 1728-1733.
- [40] M. Nishimura, M. Ueda, N. Miyaara, *Tetrahedron* **2002**, *58*, 5779-5787.
- [41] H. Fritzsche, U. Hasserodt, F. Korte, G. Friesse, K. Adrian, *Chem. Ber.* **1965**, *98*, 171-174.
- [42] J. Lemo, K. Heuzé, D. Astruc, *Chem. Commun.* **2007**, 4351-4353.
- [43] <http://www.inopor.com>

3

Continuous homogeneous catalysis: POSS-enlargement of a hydroformylation catalyst

A simple and efficient approach for the molecular weight enlargement of a hydroformylation catalyst has been developed. This system has been applied for the production of aldehydes in a continuous flow nanofiltration reactor operating for an unprecedented period of up to two weeks, without showing typical deactivation or leaching phenomena. Based on a bulky, rigid, and robust POSS-modified PPh_3 ligand we found that the molecular weight enlarged catalyst combines for the first time efficient recovery with the advantages that homogeneous catalysts exhibit over heterogeneous systems, such as high activity and selectivity.

3.1 | Introduction

The hydroformylation of alkenes is among the largest scale industrial applications of homogeneous catalysis today.^[1] However, efficient recovery and recycling of homogeneous catalysts remains one of the major drawbacks of this technology, certainly in view of the high costs of precious metals.^[2] In all larger scale applications seen today, more or less individual solutions have been developed. For future process intensification and development of sustainable and 'greener' processes, new generic methods are highly desired, preferably with a low energy profile. The various approaches that have been studied so far, each having its own advantages and disadvantages, can be divided into two main categories: biphasic catalysis,^[3-5] and immobilization on either soluble (molecular weight enlargement, MWE) or insoluble supports (heterogenization).^[6-8]

An elegant example of biphasic catalysis is the Ruhrchemie-Rhône Poulenc (RCH/RP) process for the hydroformylation of propene. The water-soluble catalyst (TPPTS/Rh) is immobilized in the aqueous phase and the product, *n*-butanal, forms the organic phase, which can easily be removed by phase separation. It is important to note, however, that this approach is limited to lower alkenes with sufficient solubility in the aqueous phase (commercially up to butenes). For the hydroformylation of higher alkenes, a range of methods have been investigated, addressing this point. Table 1 gives a concise overview of results obtained so far in the Rh-catalyzed hydroformylation of alkenes followed by catalyst recycling, either by means of biphasic catalysis (entries 1-5) or MWE (entry 6). In all cases a modified version of triphenylphosphine was applied as ligand (TPPTS, entries 1-3; TPPMS, entry 4; P(4-C₆H₄C₆F₁₃)₃, entry 5;).

Table 1 | Literature overview of Rh-catalyzed alkene hydroformylation in combination with catalyst recycling.

Entry	Method	Substrate	TOF (h ⁻¹)	TON	Ref.
1	Water/organic + latex ^a	1-octene	150	n.d.	[5]
2	Water/organic + CD ^b	1-decene	n.d.	2 x 770	[9]
3	Ionic Liquid	1-hexene	2000	10 x 1600	[10]
4	scCO ₂	1-octene	180	n.d.	[11]
5	Fluorous phase	1-octene	4400	n.d.	[12]

^a PS-latex used as a phase transfer agent; ^b CD = cyclodextrine.

Nanofiltration is still a rather unexploited field for the recovery of MWE-catalysts. Recently, we and others showed the application of nanofiltration to recycle and reuse homogeneous catalysts in a diffusion driven process.^[13,14] However, traditional systems for MWE have proven to be rather inefficient in continuous processes, as either low conversions were reached due to rapid catalyst deactivation, significant metal leaching, or poor retention. Consequently, new concepts have to be developed in order to circumvent these severe drawbacks. Here, we report on the synthesis of MWE triphenylphosphine, its application as a ligand in the Rh-catalyzed hydroformylation of 1-octene and its long term behavior in a continuous flow nanofiltration reactor setup.

Polyhedral Oligomeric Silsesquioxanes (POSS) have received relatively little attention as a means for MWE.^[15-19] The trisilanol POSS T7(OH)₃ moiety is easy to synthesize in a LiOH-catalyzed condensation reaction of the appropriate trimethoxysilane in the presence of an exact amount of water (Scheme 1). Moreover, they are commercially available at low cost, have a highly defined structure, and are kinetically and thermally stable, which makes them ideal candidates for this purpose. The rigid, cubical shape of the POSS cages (1.4 nm in size) is beneficial in nanofiltration, since rigid 3-dimensional structures are known to display better retention and less membrane fouling than more flexible macromolecules.^[20]

Scheme 1 | Synthesis of ^tBu-trisilanol POSS.

Based on the fact that triphenylphosphine (PPh₃) has been the ligand of choice in industrial Rh-catalyzed hydroformylation of alkenes we chose to immobilize this ligand at first. A facile synthetic procedure for the preparation of POSS-enlarged PPh₃ was developed and the MWE ligand was applied in the hydroformylation of 1-octene, both in batch and in continuous flow membrane reactor.

3.2 | Synthesis and characterization of POSS-enlarged PPh₃

The synthesis of POSS-enlarged PPh₃ turned out to be straightforward. First, 4-bromostyrene (**1**) is hydrosilylated with HSiCl₃ in the presence of a Pt catalyst. The

product (**2**) is subsequently used in a corner-capping reaction with trisilanol ⁱBu POSS (**3**) in the presence of Et₃N yielding (**4**). After lithiation of 4-bromophenylethylPOSS (**4**) with *n*-BuLi and reaction with PCl₃, POSS-enlarged PPh₃ (**5**) is obtained in 80% yield (Figure 1). The ligand was fully characterized by NMR spectroscopy, elemental analysis, and MALDI-TOF, and has a molecular mass of 2791 g/mol. The molecular weight of the ligand is about 4 times larger than the molecular weight cut-off of the ceramic membranes used (450 g/mol), and it should therefore be retained very well by the membrane.

Figure 1 | **a**) Synthesis of POSS-enlarged PPh₃. **b**) 3D model (MM+) of POSS-enlarged PPh₃ showing the additional steric bulk induced by the POSS moieties.

3.3 | Rh-catalyzed hydroformylation of 1-octene

In order to justify MWE of homogeneous catalysts, several requirements have to be fulfilled: straightforward synthesis, high activity, high total turnover number (TTN), and high retention. Therefore, the activity of POSS-enlarged PPh₃ in the hydroformylation of 1-octene was compared with PPh₃ in an autoclave (batch) experiment. The conversion vs. time plots, based on the gas uptake of CO/H₂, are depicted in Figure 2. The turnover frequencies (TOF) are determined at 20% conversion, and are high with 1350 h⁻¹ and 3150 h⁻¹ for POSS-enlarged PPh₃ and unsupported PPh₃, respectively. No degradation of the POSS moieties was observed after the reaction was finished.

Figure 2 | Comparison of catalytic activity between PPh₃/Rh and POSS-enlarged PPh₃/Rh.

Since our catalytic system based on POSS-enlarged PPh₃/Rh fulfilled all the requirements discussed above, it was applied in an in-house designed and developed continuous flow nanofiltration reactor. This reactor (Figure 3a) can be filled with substrate solution by an HPLC pump, while a capacitive level sensor (**L**) controls the liquid level in the reaction vessel by operating the HPLC pump. The reactor consists of 2 loops: a gas-saturation/reaction loop, and a membrane filtration loop. The gas-saturation loop contains the reaction vessel with gas phase, in which the reaction mixture is injected into the gas phase for gas-saturation. In the cross-flow chamber both loops meet. The reaction mixture then flows along the ceramic nanofiltration membrane in which the product containing phase is separated from the MWE-catalyst. The product phase is collected and weighted continuously, enabling constant monitoring of the flux through the membrane.

The flow in the membrane loop is higher than in the reaction loop to guarantee turbulent flow along the membrane ($Re = 4400$), which prevents formation of a polarization layer. The reaction pressure forms the driving force for the nanofiltration in this setup. The flux through the membrane is controlled with a Rheodyne 2 position 6 port fluid processor (PR700-100-01) equipped with a 500 μ L sample loop controlled by a flip flop relay, and is kept constant during the course of the reaction. The whole reactor, including the membrane unit, is kept at the operation temperature of 80°C. The molecular weight cut-off (MWCO) of this membrane is 450 Da.^[21] Further reactor and reaction specifications are given in Figure 3b.

Figure 3 | Continuous flow nanofiltration reactor. a) Schematic representation of the in-house developed continuous flow nanofiltration reactor.

Reaction volume	220 mL
Temperature of reaction	80°C
Rh concentration	0.065 mM
1-octene concentration	1.92 M
Flow, reaction loop	0.45 L/min
Flow, membrane loop	2.27 L/min
Pressure reactor	20 bar CO/H ₂ (1/1)
Backpressure	16.5 bar
Flux through membrane	10 g/h
Supplier membrane	Inopor ^[21]
Support layer membrane	AlO ₃
Active layer membrane	TiO ₂
MWCO membrane	450 Da
Pore size	0.9 nm

Figure 3 | Continuous flow nanofiltration reactor. **b)** Reactor and reaction specifications.

From our batch experiments (Figure 2) we can conclude that under the reaction conditions applied (T , p , [1-octene], [Rh], see Figure 3b), the reaction proceeds pseudo 0th order in 1-octene up to about 90% conversion. For a 0th order reaction we can derive an equation for the conversion X in a CSTR (equation 1).

$$X = \frac{[oct]_{in} - [oct]_{out}}{[oct]_{in}} = \frac{\tau \cdot k}{[oct]_{in}} \quad (1)$$

Where $[oct]_{in}$ and $[oct]_{out}$ are the concentration of 1-octene flowing into and out of the reactor, respectively, τ is the space time and k is the rate constant.

In Figure 4 the results of a variable flux experiment are depicted and compared with the expected values according to equation (1). In this experiment the conversion was determined at a certain space time τ , after the system had reached steady-state conditions. Figure 4 shows that the conversion that is reached in the CSTR is systematically lower than the expected conversion based on equation (1). This behavior can be rationalized by *e.g.* non-ideal mixing, premature catalyst decomposition, slight differences in temperature between the batch and continuous setup causing a different value for k , *etc.*

Figure 4 | Comparison between experimentally obtained conversion and conversion predicted by the kinetic model.

Prior to use, the reactor was purged 5 times with 20 bar of syngas. Then, the reactor was filled with substrate solution by HPLC pump, and again purged 5 times with 20 bar of syngas. The reactor was heated to the reaction temperature of 80°C and pressurized to the reaction pressure of 20 bar syngas. At time $t = 0$, the catalyst was added to the reaction mixture by means of a dropping funnel connected to the reactor, which allows to add the catalyst solution to the reactor under reaction conditions. Samples were taken at regular intervals, and analyzed by GC to monitor the development of conversion and regioselectivity (l/b ratio) in time (Figure 5).

Figure 5 | Conversion and regioselectivity *versus* time for the continuous hydroformylation of 1-octene in the continuous flow membrane reactor.

After a gradual increase, the highest conversion of 99% was obtained after 17 h. The conversion remained > 90% for almost 2 weeks, which is absolutely unprecedented in literature. In this period, about 7 L of product solution (1.92 M in toluene) was obtained and the regioselectivity in terms of l/b ratio remained constant at 2.5, which is identical to the regioselectivity of its unsupported analogue.

The accumulated turnover number (ATN) versus time is depicted in Figure 6. It shows that the ATN steadily increases to a value of about 120,000 Rh⁻¹ after 13 days. This demonstrates the stability and robustness of our POSS-enlarged PPh₃/Rh catalyst.

The significant drop in activity after 13 days needs further investigations, but it is clear that it is not caused by a substantial loss of Rh, since ICP-OES analysis of the total product solution revealed a total Rh leaching of only 0.045% and a total P leaching of 0.74% of the total amount of Rh and P added, respectively. This means that 99.96% of the Rh is effectively retained by the nanofiltration membrane, which tremendously simplifies the workup as the Rh-concentration in the product is extremely low.

Typical causes of catalyst/ligand degradation and/or ageing are: i) the cleavage of the P-C bond in the ligand causing substituent scrambling at the phosphorus, as well as other degrading processes and ii) the formation of inactive Rh clusters.^[22, 23] In practice, fresh catalyst solution could be added continuously together with the substrate solution.

Figure 6 | Accumulated turnover number obtained in the continuous flow membrane reactor.

3.4 | Concluding remarks

In summary, we have developed a molecular weight enlarged Rh-catalyst based on a bulky, rigid, and robust POSS-modified PPh_3 ligand, which is suitable for the hydroformylation of alkenes in an in-house engineered continuous flow nanofiltration reactor.

Unprecedented results in terms of activity, stability, and retention of the POSS-enlarged catalyst system were achieved as the hydroformylation setup was continuously operated for several days without any significant deactivation or leaching of the catalyst.

These results highlight a major breakthrough in the sustainable conversion of alkenes under homogeneous catalytic conditions without the usual drawback of tedious and often expensive catalyst recovery and recycling.

3.5 | Experimental part

General considerations

Chemicals were purchased from Aldrich, Acros or Merck and used as received. All manipulations and reactions were performed under argon atmosphere using standard Schlenk techniques. Solvents were taken HPLC-grade from an alumina filled argon flushed column. NMR spectra were recorded on a Varian Mercury 200, Mercury 400 or Inova 500 spectrometer. Elemental analyses were measured on a Perkin-Elmer 2400 apparatus. IR spectra were recorded on an Avatar 360 FT-IR instrument in ATR mode. Ceramic nanofiltration membranes were purchased from Inopor GmbH Germany and have a pore size of 0.9 nm and a molecular weight cut-off of 450 Da (www.inopor.com). Catalytic conversions were determined by GC on a PONA column (50 m x 0.20 mm) using pentadecane as an internal standard. Retention times were compared with authentic samples.

Synthesis of POSS-enlarged PPh₃

4-BromophenylethylPOSS (11 g, 10.92 mmol) was dissolved in 100 mL of THF and the mixture was cooled to -78°C. *n*-BuLi (2.5 M in hexanes, 4.8 mL, 12 mmol) was added dropwise, and the mixture was stirred at this temperature for 1h. PCl₃ (0.5 g, 3.64 mmol) was added dropwise. The reaction mixture was allowed to warm to r.t. and stirred overnight. The solvent was removed *in vacuo*. 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 MgSO₄. The solvents were removed *in vacuo*, leaving the product as a white solid in 78% yield (8 g, 2.84 mmol).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.24 (dd, *J* = 12.4 Hz, *J* = 14.4 Hz, 12H), 2.69 (m, 6H), 1.87 (sept, *J* = 6.7 Hz, 7H), 0.97 (d, *J* = 6.6 Hz, 42H), 0.62 (d, *J* = 7 Hz, 14H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 145.15, 133.83, 127.94, 125.61, 28.97, 25.70, 23.88, 22.53, 14.07.

³¹P NMR (162 MHz, CDCl₃) δ (ppm): - 7.76 (s).

Maldi-Tof: *m/z* = 2809.07 (M+Na).

Elemental Analysis: calculated (found): C 46.45 (46.54), H 7.69 (7.77).

Hydroformylation of 1-octene in a batch reactor

Hydroformylation experiments were performed in a stainless steel autoclave equipped with temperature sensor, dropping funnel, and mechanical gas-inlet stirrer. Before use, the autoclave was evacuated and filled back with argon three times. The catalyst solution (3 mg (11.6 μmol) $\text{Rh}(\text{acac})\text{CO}_2$, and 163 mg (58 μmol) POSS-enlarged PPh_3 in 17 mL of toluene) was injected into the autoclave and 1-octene (5 g, 45 mmol) was inserted into the dropping funnel. After 2h of catalyst preformation at 80°C and 20 bar of CO/H_2 (1:1), the substrate was added to the reactor ($t = 0$). The reaction was performed for 16h at 80°C and 20 bar of CO/H_2 (1:1). Then, the pressure was released and the conversion of 1-octene and the regioselectivity (l/b ratio) were determined by means of GC analysis.

Hydroformylation of 1-octene in a continuous flow membrane reactor

Before use, the reactor was purged five times with 20 bar of CO/H_2 (1:1). Under a gentle stream of argon, the substrate solution (1.92 M 1-octene in toluene) was pumped into the reactor by HPLC pump. The reactor was heated to 80°C and pressurized to 20 bar of CO/H_2 (1:1). The system was allowed to equilibrate for 1h before the catalyst solution, consisting of 15 mg (58 μmol) of $\text{Rh}(\text{acac})(\text{CO})_2$ and 815 mg (290 μmol) of POSS-enlarged PPh_3 in 14 mL of toluene, was added via dropping funnel ($t = 0$). The reaction was allowed to proceed for 14 days, during which samples were taken at regular intervals. The conversion of 1-octene and the regioselectivity (l/b ratio) were determined by means of GC analysis.

3.6 | References

- [1] P.W.N.M. Van Leeuwen, *Homogeneous Catalysis: Understanding the Art*, Kluwer Academic Publishers, **2004**.
- [2] J.A. Gladysz (Guest Editor), Recoverable Catalysts and Reagents in *Chem. Rev.* **2002**, 3215-3892.
- [3] B. Cornils, W. A. Herrmann, I. T. Horvath, W. Leitner, S. Mecking, H. Olivier-Bourbigou, D. Vogt, *Multiphase Homogeneous Catalysis, Volume 1* (2005).
- [4] B. Hamers, P. S. Bäuerlein, C. Müller, D. Vogt, *Adv. Synth. Cat.* **2008**, 350, 332-342.
- [5] K. Kunna, C. Müller, J. Loos, D. Vogt, *Angew. Chem. Int. Ed.* **2006**, 45, 7289-7292.
- [6] D. Cole-Hamilton, R. Tooze, *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design. [In: Catal. Met. Complexes., 2006; 30]* Springer, **2006**.
- [7] D. J. Cole-Hamilton, *Science* **2003**, 299, 1702-1706.
- [8] C. Müller, M. G. Nijkamp, D. Vogt, *Eur. J. Inorg. Chem.* **2005**, 4011-4021.
- [9] N. Badi, P. Guégan, F.-X. Legrand, S. Tilloy, E. Monflier, *J. Mol. Catal. A: Chem.* **2010**, 318, 8-14.
- [10] Q. Lin, W. Jiang, H. Fu, H. Chen, X. Li, *Appl. Catal. , A* **2007**, 328, 83-87.

- [11] A.C. Frisch, P.B. Webb, G. Zhao, M.J. Muldoon, P.J. Pogorzelec, D.J. Cole-Hamilton, *Dalton Trans.* **2007**, 5531-5538.
- [12] D.F. Foster, D. Gudmunsen, D.J. Adams, A.M. Stuart, E.G. Hope, D.J. Cole-Hamilton, *Tetrahedron* **2002**, 58, 3901-3910.
- [13] A.V. Gaikwad, V. Boffa, J. E. ten Elshof, G. Rothenberg, *Angew. Chem. Int. Ed.* **2008**, 47, 5407-5410.
- [14] M. Janssen, C. Müller, D. Vogt, *Adv. Synth. Catal.* **2009**, 351, 313-318.
- [15] L. Ropartz, R.E. Morris, D.J. Cole-Hamilton, D.F. Foster, *Chem. Commun.* **2001**, 361-362.
- [16] L. Ropartz, K. J. Haxton, D.F. Foster, R.E. Morris, A.M.Z. Slawin, D.J. Cole-Hamilton, *J. Chem. Soc., Dalton Trans.* **2002**, 4323-4334.
- [17] L. Ropartz, R.E. Morris, D.F. Foster, D.J. Cole-Hamilton, *J. Mol. Catal. A: Chem.* **2002**, 182-183, 99-105.
- [18] L. Ropartz, D.F. Foster, R. E. Morris, A.M.Z. Slawin, D.J. Cole-Hamilton, *J. Chem. Soc., Dalton Trans.* **2002**, 1997-2008.
- [19] N.R. Vautravers, D.J. Cole-Hamilton, *Chem. Commun.* **2009**, 92-94.
- [20] R.W. Baker, *Membrane Technology and Applications*, Wiley **2000**.
- [21] www.inopor.com
- [22] D. R. Bryant. *Catal. Met. Complexes* **2006**, 30, 9-37.
- [23] P. W. N. M. van Leeuwen. *Appl. Catal. A* **2001**, 212, 61-81.

4

POSS-enlarged ligands in the continuous hydroformylation: broadening the scope

The simple and efficient approach of molecular weight enlargement (MWE) by POSS-units of a hydroformylation catalyst (chapter 3) has been extended to ligands that are expected to show a better performance than PPh_3 . Besides the bidentate ligands DPEphos and Xantphos that are known for their higher regioselectivity in the Rh-catalyzed hydroformylation of 1-octene, a bulky monophosphite has been modified with POSS. In this way a very active and recyclable ligand was obtained. These ligands were applied in the continuous hydroformylation of 1-octene in the continuous flow membrane reactor. XantPOSS showed long-term stability under the conditions applied, but showed a rather peculiar regioselectivity pattern, whereas monoPOSSphite showed rapid loss in catalytic activity. In both cases, however, both Rh and P losses were extremely low.

4.1 | Introduction

The hydroformylation of alkenes is among the largest scale industrial applications of homogeneous catalysis today.^[1] Apart from the clear advantages of homogeneous catalysts, such as high selectivity and high activity, they suffer from a major disadvantage: it is very difficult to recover and recycle them in their active form. Since often precious metals are applied, in combination with valuable ligands, solutions to this major drawback are most wanted.^[2,3]

In recent years, numerous possibilities to recycle homogeneous catalysts have been studied, both in academia as in industrial laboratories. The solutions found can roughly be divided into biphasic catalysis and immobilization on insoluble (heterogenization) or soluble supports (molecular weight enlargement, MWE).^[4,5]

MWE catalysts, in principle, can be recycled by means of ultracentrifugation, precipitation or nanofiltration. Especially, nanofiltration has received substantial attention as basis for process intensification.^[6,7]

Recently, we have shown that MWE of triphenyl phosphine with polyhedral oligomeric silsesquioxanes (POSS) enables efficient catalyst recycling by means of nanofiltration in the hydroformylation of 1-octene. We demonstrated the use of POSS-enlarged PPh_3 , because PPh_3 is one of the most frequently used ligands in homogeneous catalysis in general, and in the hydroformylation in particular (Chapter 3 of this thesis).

Besides triphenyl phosphine (PPh_3), several other ligands show improved catalytic performance in terms of activity and regioselectivity. In this study, molecular weight enlargement has been applied to a monodentate bulky phosphite, which is expected to show high activity due to its increased π -acceptor character^[8] and to the bidentate phosphine ligands DPEphos and Xantphos. The latter one is known for its excellent regioselectivity induced by the rigid backbone and wide bite angle.^[9,10]

4.2 | Synthesis of the POSS-enlarged ligands

The synthesis of the POSS-enlarged ligands was relatively straightforward (Scheme 1). The bis(dichlorophosphines) **2** and **4** that form the basis for the bidentate ligands DPEPOSS and XantPOSS were synthesized according to literature procedures.^[11,12] Subsequently, 4-bromophenylethylPOSS **5** was reacted with *n*-BuLi and added to the bis(dichlorophosphines) **2** and **4** to obtain the desired POSS-enlarged bidentate phosphine ligands DPEPOSS and XantPOSS in 62% and 48% yield, respectively. These ligands were fully characterized by means of NMR spectroscopy (¹H, ¹³C, and ³¹P), and Maldi-ToF mass spectrometry. XantPOSS has a mass of 3946 g/mol and shows a singlet in the ³¹P NMR spectrum at $\delta_P = -20.5$ ppm, which is slightly upfield from its unsupported analogue Xantphos ($\delta_P = -17.5$ ppm). This also counts for DPEPOSS, which shows a singlet at $\delta_P = -18.7$ ppm (DPEphos $\delta_P = -14.5$ ppm), and has a molecular mass of 3934 g/mol.

Scheme 1 | Synthesis of the bidentate phosphines DPEPOSS and XantPOSS.

The synthesis of the POSS-enlarged monodentate bulky phosphite is depicted in Scheme 2. The POSS-enlarged phenol **6** was obtained after neat reaction of 3-aminopropylPOSS with methyl 3-(3-*tert*-butyl-4-hydroxyphenyl)propanoate in the presence of a catalytic amount of *p*-toluenesulfonic acid under a gentle stream of argon to remove MeOH at 150°C in the melt. The monoPOSSphite ligand was obtained after reaction of POSS-enlarged phenol **6** with PCl_3 in the presence of Et_3N in toluene at -10°C.^[13] This ligand was fully characterized by means of NMR spectroscopy and Maldi-ToF mass spectrometry and showed a singlet in ^{31}P NMR at $\delta_{\text{P}} = 130$ ppm, which is in line with its non-enlarged counterpart tris(2,4-di-*tert*-butylphenyl)phosphite ($\delta_{\text{P}} = 130$ ppm). MonoPOSSphite has a molecular mass of 3258 g/mol.

Scheme 2 | Synthesis of POSS-enlarged monodentate bulky phosphite monoPOSSphite.

4.3 | Hydroformylation of 1-octene in a batch reactor

The POSS-enlarged ligands were first applied in the Rh-catalyzed hydroformylation of 1-octene in a batch reactor at 80°C and 20 bar of syngas (CO/H_2 , 1:1) pressure. The activity of the MWE ligands was compared with their unsupported analogues. The syngas pressure was kept constant during the course of the reaction by means of a mass flow controller. The conversion vs. time plots, based on the gas uptake of CO/H_2 , are depicted in Figure 1. The turnover frequencies (TOF) are determined at 20% conversion. In all cases the POSS-enlarged catalysts show lower activities in this reaction (Figure 1 and Table 1). However, the regioselectivities expressed in terms of *l/b* ratio, show no significant differences between the MWE ligands and their unsupported counterparts.

Figure 1 | Comparison of activities of conventional ligands with their POSS-enlarged counterparts in the hydroformylation of 1-octene. **a**, PPh_3POSS , **b**, XantPOSS, **c**, monoPOSSphite.

Conditions: $V_{\text{Tot}} = 22 \text{ mL}$, $T = 80^\circ\text{C}$, $P = 20 \text{ bar}$, solvent = toluene, preformation = 2 h, reaction time = 16 h, Rh precursor = $\text{Rh}(\text{acac})(\text{CO})_2$, Rh:Oct = 1:4000, $[\text{Rh}] = 0.48 \text{ mM}$, $\text{CO}:\text{H}_2 = 1:1$.

Figure 1 | Comparison of activities of conventional ligands with their POSS-enlarged counterparts in the hydroformylation of 1-octene. **d**, DPEPOSS.

Conditions: $V_{\text{Tot}} = 22$ mL, $T = 80^\circ\text{C}$, $P = 20$ bar, solvent = toluene, preformation = 2 h, reaction time = 16 h, Rh precursor = $\text{Rh}(\text{acac})(\text{CO})_2$, Rh:Oct = 1:4000, $[\text{Rh}] = 0.48$ mM, $\text{CO}:\text{H}_2 = 1:1$.

Table 1 | Comparison of POSS-enlarged ligands with unsupported analogues in the hydroformylation of 1-octene.

Entry	Ligand	L:Rh ratio	Conversion (%)	TOF ^a	l/b ^b
1	PPh_3	5:1	100	3150	2.53
2	PPh_3POSS	5:1	100	1350	2.51
3	Xantphos	2:1	79	800	28
4	XantPOSS	2:1	74	500	25
5	DPEphos	2:1	86	1400	2.45
6	DPEPOSS	2:1	76	800	2.25
7	Tris(2,4-di-tert-butylphenyl)phosphite	5:1	100	18300	0.81
8	MonoPOSSphite	5:1	100	6400	0.79

Conditions: $V_{\text{Tot}} = 22$ mL, $T = 80^\circ\text{C}$, $P = 20$ bar, solvent = toluene, preformation = 2 h, reaction time = 16 h, Rh precursor = $\text{Rh}(\text{acac})(\text{CO})_2$, Rh:Oct = 1:4000, $[\text{Rh}] = 0.48$ mM, $\text{CO}:\text{H}_2 = 1:1$ a) Turnover frequency determined at 20% conversion b) l/b ratio is (amount of linear aldehyde)/(sum of all branched aldehydes) determined after 16 h.

Since the POSS-enlarged ligands show lower activities in all cases, we wondered if this phenomenon is caused by the increased steric bulk due to the POSS cages, or that there is a different reason for the decrease in activity, like diminished solubility of either syngas (CO/H_2) or 1-octene. In order to investigate this, T8 POSS (Figure 2) was added to the reaction mixture of the non-enlarged ligand. The results are depicted in Figure 1, and show no significant influence on the activity nor on the selectivity in the hydroformylation of 1-octene, compared to the non-enlarged

ligands. We argue, therefore, that the lower activity of the MWE ligands is purely caused by the increased steric bulk of the POSS cages.

Figure 2 | T8 isobutyl POSS.

4.4 | Kinetic considerations

Based on the reaction kinetics obtained in the batch experiments the expected conversion in the continuous nanofiltration setup can be calculated, assuming that this setup behaves ideally.^[14-16] The Rh-catalyzed hydroformylation of *n*-alkenes is generally regarded to be pseudo first order in alkene.^[1] However, both DPEPOSS and monoPOSSphite did not exhibit strict first-order kinetics in substrate under the conditions applied (see Figure 1). This makes the translation from a batch reactor to a continuously stirred tank reactor (CSTR) rather difficult, and therefore only the kinetic deviation for XantPOSS is given.

The rate law for a first order reaction, combined with the mole balance is:

$$-\frac{d[\text{alkene}]}{dt} = k[\text{alkene}] \quad (1)$$

where *k* is the rate constant that also includes all dependences on CO, H₂, ligand and rhodium concentration. This assumption is valid as long as these variables stay constant. The syngas pressure was kept constant during the batch experiments by means of a mass flow controller. Furthermore, rhodium and the ligand are part of the catalyst. Consequently, by definition, they are not consumed and hence their concentrations are constant.

Since the reactor is operated isothermally the differential equation (1) can be solved to obtain:

$$\ln \frac{[\text{alkene}]}{[\text{alkene}]_0} = -kt \quad (2)$$

A plot of $\ln([alkene]/[alkene]_0)$ as a function of t should give a straight line with slope $-k$ (Figure 3). However, close inspection of the gas-uptake plots (Figure 1) reveals that only XantPOSS shows well-behaved pseudo first order kinetics in 1-octene.^[17] From Figure 3 it can be concluded that $k = 0.129 \text{ h}^{-1}$.

Figure 3 | $\ln(\text{conversion})$ vs. time plot that demonstrates first order kinetics in 1-octene for XantPOSS/Rh.

Using the design equation for a CSTR in combination with a first order rate law equation (3) is obtained:^[18]

$$V = \frac{v_0[alkene]_0 X}{k[alkene]} \quad (3)$$

in which V is the volume of the CSTR, v_0 is the flow of substrate into the reactor and X is the conversion.

After dividing by v_0 , the space time τ is obtained:

$$\tau = \frac{V}{v_0} = \frac{[alkene]_0 X}{k[alkene]} = \frac{[alkene]_0 X}{[alkene]_0 k(1 - X)} \quad (4)$$

Dividing by $[alkene]_0$ yields an expression for τ in terms of the rate constant k and the conversion X :

$$\tau = \frac{1}{k} \left(\frac{X}{1 - X} \right) \quad (5)$$

Equation (5) can be written as:

$$X = \frac{\tau k}{1 + \tau k} \quad (6)$$

This implies that when a flow rate of 12.5 mL h⁻¹ is applied, τ is 17.6 h and the expected conversion will be 70%.^[18]

4.5 | Continuous hydroformylation of 1-octene

The MWE ligands that perform best with respect to activity (monoPOSSphite) and regioselectivity (XantPOSS) in the hydroformylation of 1-octene were chosen for application in the continuous flow membrane reactor. A schematic representation of the continuous flow membrane reactor is given in Figure 4. The continuous hydroformylation of 1-octene was initially performed with 5 equivalents of monoPOSSphite in toluene. Because of the high activity of the monoPOSSphite/Rh catalyst in the batch reactions, the concentration of Rh in this experiment was relatively low (0.088 mM). The reaction starts ($t = 0$) when the catalyst is added to the substrate containing reactor via dropping funnel. The reaction was carried out without catalyst preformation. Samples of the product flow are taken at regular intervals. A relatively fast decrease in conversion was observed (Figure 5a). The experiment was repeated with 10 equivalents of monoPOSSphite, in order to determine the nature of the relatively fast decomposition of the catalyst. The conversion curve is depicted in Figure 5b.

Figure 4 | Schematic representation of the continuous flow membrane reactor.

Figure 5 | Continuous hydroformylation of 1-octene with monoPOSSphite, **a)** 5 eq. of ligand, **b)** 10 eq. of ligand, **c)** lower catalyst concentration. *Conditions:* $V_{\text{Tot}} = 220$ mL, $T = 80^\circ\text{C}$, $P = 20$ bar, solvent = toluene, no preformation, Rh precursor = $\text{Rh}(\text{acac})(\text{CO})_2$, $[\text{Oct}] = 1.92$ M, $[\text{Rh}] = 0.088$ mM (**a**, **b**), 0.035 mM (**c**), $\text{CO}:\text{H}_2 = 1:1$.

Again a relatively fast decrease in conversion was observed. The decomposition rate is even higher than with only 5 equivalents on monoPOSSphite ligand (conversion of 70% after 45 h vs. 24 h). Poor stability of phosphite ligands under hydroformylation conditions has been observed and described before by van Leeuwen and Bryant.^[19,20] Another possibility is that the observed catalyst decomposition is caused by high conversion of 1-octene, although at all times there was about 10% of internal octenes present. To exclude this reason, the reaction was performed with 2.5 times less catalyst (but still with 10 eq. of monoPOSSphite). The conversion curve is depicted in Figure 5c. From this reaction profile we can conclude that the catalyst is not deactivated by low octene concentration.

ICP-OES analysis was performed on the permeate of the reaction performed with 5 equivalents of monoPOSSphite ligand, in order to determine Rh and P loss during the reaction. Both Rh and P losses were low (0.07% and 0.97%, respectively). Clearly, the drop in conversion is not caused by catalyst leaching.

The ligand XantPOSS was investigated under continuous flow conditions as well, as it showed the highest regioselectivity in the batch experiments. Because XantPOSS/Rh shows lower activity than the monoPOSSphite system mentioned above, a higher Rh concentration of 0.53 mM was used. This concentration was also used in the batch experiments discussed before (Figure 1). From the conversion curve in Figure 5a we can conclude that the XantPOSS/Rh catalyst shows higher stability under the applied catalytic reaction conditions compared to monoPOSSphite, but similar to PPh₃POSS (see chapter 3 of this thesis). Remarkably, the conversion in this continuous process is around 20% higher than expected, based on the kinetics (equation (6)). It has to be noted, that this kinetic model applies only for ideal systems.

Whereas the regioselectivity in the batch experiments was high ($l/b = 25$), the regioselectivity in the continuous experiment proceeds through an optimum of $l/b = 7$ and then decreases rapidly (Figure 5). In the batch processes a preformation of 2h was performed, whereas in the continuous experiment no catalyst preformation was applied. Batch experiments without catalyst preformation were performed, both with non-supported Xantphos and with XantPOSS. In both cases the regioselectivity was poor (2.5 for both cases), and comparable with monodentate phosphine ligands. Obviously, catalyst preformation is essential for high regioselectivities. Apparently, without preformation, the chelating coordination mode of the ligand is not achieved, leading to poor selectivities.

Figure 5 | Continuous hydroformylation of 1-octene. **a)** without catalyst preformation **b)** with catalyst preformation (3h). Conditions: $V_{\text{Tot}} = 220$ mL, $T = 80^{\circ}\text{C}$, $P = 20$ bar, solvent = toluene, Rh:L = 1:2, Rh precursor = $\text{Rh}(\text{acac})(\text{CO})_2$, $[\text{Oct}] = 1.92$ M, $[\text{Rh}] = 0.53$ mM, $\text{CO}:\text{H}_2 = 1:1$.

In order to perform a continuous hydroformylation experiment, with preformation at 20 bar of syngas and at 80°C for 3h, the experimental protocol was adjusted. In earlier studies the reactor was first filled with substrate solution and then heated to 80°C and pressurized to 20 bar. Subsequently, the catalyst solution was added via the dropping funnel. In the modified protocol, the reactor was filled first with catalyst solution, then heated to 80°C and pressurized to 20 bar. In this way catalyst preformation was performed for 3h, after which the substrate solution was added. The outcome of the experiment was surprising as only a small improvement of the regioselectivity was observed ($I/b = 4$ vs. 2.5). It has to be noted

that there are no precedents in literature for continuous hydroformylation in a continuous flow membrane reactor. Therefore, it is difficult to say how long it takes for the rhodium hydrido rhodium carbonyl species to be formed in this setup. Possibly, the regioselectivity could increase when a longer preformation time is applied.

4.6 | Concluding remarks

In conclusion, three new POSS-enlarged phosphorus ligands were successfully synthesized, characterized and applied in the continuous hydroformylation of 1-octene. The increased sterics, caused by the molecular weight enlarging POSS moieties is likely to influence the activity. Yet, reaction rates of up to 6400 h^{-1} were observed for the POSS-enlarged ligands. The most active (monoPOSSphite) and the most regioselective (XantPOSS) ligands were applied in the continuous hydroformylation of 1-octene in an in-house developed continuous flow membrane reactor. Catalyst retentions were high and Rh and P leaching were extremely low for both examples.

The translation from a conventional batch reactor to a continuous flow reactor has been made, which enables detailed investigation of long-term behavior of a Rh-based hydroformylation catalyst. This is typically something that remains unnoticed when a catalyst is studied only in batch reactions, but on the other hand of is fundamental importance for research in continuous homogeneous catalysis. Long-term behavior of a catalyst also includes deactivation or “catalyst aging” during the reaction. Both phenomena have been observed: the relatively rapid decrease in activity of the Rh/monoPOSSphite catalyst and the peculiar behavior in the regioselectivity of the XantPOSS based catalyst.

Here, a successful proof of principle for continuous hydroformylation in combination with catalyst recycling by means of nanofiltration is demonstrated. However, the scope of both ligands and substrates can be enlarged to e.g. prochiral substrates and chiral ligands. This technology has great potential for application in all kinds of homogeneously catalyzed reactions, such as (asymmetric) hydrogenation or hydroaminomethylation (HAM).

4.7 | Experimental part

General considerations

Chemicals were purchased from Aldrich, Acros or Merck and used as received. POSS starting compounds were obtained from Hybrid Catalysis B.V.. All reactions were performed under argon atmosphere using standard Schlenk techniques. Solvents were taken HPLC-grade from an alumina filled argon flushed column.

NMR spectra were recorded on a Varian Mercury 200, Mercury 400 or Inova 500 spectrometer. Elemental analyses were measured on a Perkin-Elmer 2400 apparatus. Ceramic nanofiltration membranes were purchased from Inopor GmbH Germany with a pore size of 0.9 nm and a molecular weight cut-off of 450 Da (www.inopor.com). Catalytic conversions were determined by GC on a PONA column (50 m x 0.20 mm) or on a DB1 (30 m x 0.32 mm) using decane as an internal standard. Retention times were compared with authentic samples.

Synthesis of 4,5-dichlorophosphino-9,9-dimethylxanthene (**2**)^[12]

9,9-Dimethylxanthene (2.5 g, 11.89 mmol) was dissolved in 50 mL of Et₂O. TMEDA (3.83 mL, 25 mmol) was added dropwise and the mixture was cooled to 0°C. n-BuLi (2.5 M in hexanes, 10 mL, 25 mmol) was added dropwise at this temperature. The reaction mixture was slowly warmed to r.t. and stirred overnight. At 0°C a solution of ZnCl₂ (3.41 g, 25 mmol) in 20 mL of Et₂O was added slowly to the reaction mixture. A precipitate was formed. The mixture was stirred for 2h at r.t., then cooled with liquid nitrogen to -196°C. PCl₃ (3.43 g, 25 mmol) was added dropwise at this temperature. The temperature was slowly raised by addition of EtOH to the nitrogen and accordingly slowly to r.t. The product was filtered to remove salts and concentrated *in vacuo*. Yield: 1.5 g, 3.64 mmol, 31%.

¹H NMR (200 MHz, CDCl₃) δ (ppm): 7.94 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 7 Hz, 2H), 7.28 (m, 2H), 1.68 (s, 6H).

³¹P NMR (81 MHz, CDCl₃) δ (ppm): 157.62 (s).

Synthesis of XantPOSS

4-BromophenylethylPOSS (14.55 g, 14.56 mmol) was dissolved in 60 mL of THF. The mixture was cooled to -78°C and *t*-BuLi (1.5 M in pentane, 11 mL, 16 mmol) was added dropwise. The mixture was stirred at -78°C for 2h. To a solution of 4,5-Dichlorophosphino-9,9-dimethylxanthene (1.5 g, 3.64 mmol) in 20 mL of THF was added dropwise the aforementioned reaction mixture at -78°C.

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.36 (d, *J* = 8.2 Hz), 7.29-7.10 (m), 6.94 (t, *J* = 7.4 Hz), 6.59 (d, *J* = 6 Hz), 2.73 (m, 16H), 1.89 (sept, *J* = 6.6 Hz, 28H), 0.98 (d, *J* = 6.8 Hz, 168H), 0.63 (d, *J* = 7 Hz, 56H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 144.69, 134.32, 132.10, 128.28, 127.62, 126.4, 122.9, 32.32, 28.94, 28.69, 26.57, 25.72, 25.68, 23.88, 22.48, 14.03.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -20.54 (s).

Maldi-ToF m/z : 3985.26 (M+K).

Synthesis of dichlorophosphino-diphenylether (4)^[11]

Di-*p*-tolylether (2.5 g, 12.63 mmol) was dissolved in 50 mL of Et_2O . TMEDA (4 mL, 27.5 mmol) was added dropwise and the mixture was cooled to -78°C . *n*-BuLi (2.5 M in hexanes, 11 mL, 27.5 mmol) was added dropwise at this temperature. The reaction mixture was slowly warmed to

r.t. and stirred overnight. The mixture was cooled again to -78°C and $\text{ClP}(\text{NEt}_2)_2$ (3.43 g, 25 mmol) in 10 mL of Et_2O was added dropwise at this temperature. The temperature was slowly raised to 0°C and HCl (2M in Et_2O , 105 mmol, 52.5 mL). The salts were filtered off and all volatiles were evaporated *in vacuo*. Yield: 2.93 g, 7.32 mmol, 58%.

^1H NMR (200 MHz, CDCl_3) δ (ppm): 7.8 (s, 2H), 7.28 (dd, $J = 1.6, 8.4$ Hz, 2H), 6.78 (dd, $J = 2.8, 8.4$ Hz, 2H), 2.4 (s, 6H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 155.8, 134.8, 131.3, 131.0, 130.3, 117.9, 20.8.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 158.0 (s).

Synthesis of DPEOSS

4-BromophenylethylPOSS (3.5 g, 3.5 mmol) was dissolved in 15 mL of THF. The mixture was cooled to -78°C and *t*-BuLi (1.5 M in pentane, 2.4 mL, 3.6 mmol) was added dropwise. The mixture was stirred at -78°C for 2h. To a solution of dichlorophosphino-4,4-dimethylphenylether (350 mg, 0.875 mmol) in 5 mL of THF was added dropwise the aforementioned reaction mixture at -78°C .

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.29-7.10 (m), 2.69 (m, 16H), 1.86 (sept, $J = 6.6$ Hz, 28H), 0.95 (d, $J = 6.6$ Hz, 168H), 0.60 (d, $J = 7$ Hz, 56H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 144.71, 133.81, 127.57, 28.69, 26.68, 25.62, 23.82, 22.43, 14.13.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): -18.72 (s).

Maldi-ToF m/z : 3973.26 (M+K).

Synthesis of monoPOSSphite

POSSphenol (20 g, 18.55 mmol) was dissolved in 300 mL of toluene, Et_3N was added and the mixture was cooled to -10°C . PCl_3 (0.83 g, 6.16 mmol) was added dropwise and the mixture was allowed to warm to r.t. The mixture was filtered over neutral alumina and concentrated to dryness. Yield: 16.1 g, 14.8 mmol, 79.9%.

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.25 (d, $J = 2.8$ Hz, 3H), 7.16 (s, 3H), 6.91 (d, $J = 2.8$ Hz, 3H), 5.41 (br s, 3H), 3.25 (q, $J = 6.4$ Hz, 6H), 2.89 (t, $J = 8.8$ Hz, 6H), 2.42 (t, $J = 8$ Hz, 6H), 1.86

(m, 24H), 1.59 (quint, $J = 8$ Hz, 6H), 1.35 (s, H), 0.96 (d, $H = 6.8$ Hz, 126 H), 0.61 (d, $J = 7.2$ Hz, 42H).

^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 171.81, 149.78, 139.84, 135.64, 127.48, 126.38, 119.34, 41.78, 38.78, 34.74, 31.36, 30.04, 25.67, 23.87, 23.83, 23.05, 22.47, 22.44, 9.44.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 131 (s).

Maldi-ToF m/z : 3281.15 (M+Na).

Hydroformylation of 1-octene in a batch reactor

Hydroformylation experiments were performed in a stainless steel autoclave equipped with temperature sensor, dropping funnel and mechanical gas-inlet stirrer. Before use, the autoclave was evacuated and refilled with argon three times. The catalyst solution (3 mg (11.6 μmol) $\text{Rh}(\text{acac})(\text{CO})_2$, and 163 mg (58 μmol) POSS-enlarged PPh_3 in 17 mL of toluene was injected into the autoclave and 1-octene (5 g, 45 mmol) was inserted into the dropping funnel. After 2h of catalyst preformation at 80°C and 20 bar of CO/H_2 (1:1), the substrate was added to the reactor ($t = 0$). The reaction was performed for 16h at 80°C and 20 bar of CO/H_2 (1:1). Then, the pressure was released and the conversion of 1-octene and the regioselectivity (l/b ratio) were determined by means of GC analysis.

Typical hydroformylation of 1-octene in a continuous flow membrane reactor

Before use, the reactor was purged five times with 20 bar of CO/H_2 (1:1). Under a gentle stream of argon, the substrate solution (1.92 M 1-octene in toluene) was pumped into the reactor by HPLC pump. The reactor was heated to 80°C and pressurized to 20 bar of CO/H_2 (1:1). The system was allowed to equilibrate for 1h before the catalyst solution, consisting of 30 mg (116 μmol) of $\text{Rh}(\text{acac})(\text{CO})_2$ and 2 equivalents (232 μmol) of POSS-enlarged ligand in 14 mL of toluene, was added via dropping funnel ($t = 0$). The reaction was allowed to proceed for 14 days, during which samples were taken at regular intervals. The conversion of 1-octene and the regioselectivity (l/b ratio) were determined by means of GC analysis.

Determination of Rh and P leaching by ICP-OES

The complete permeate was combined and all volatiles were removed by distillation at reduced pressure. The heavy fraction was collected and calcined for 48 h in air. The remains were dissolved in 2 mL of concentrated sulphuric acid to which was added concentrated nitric acid in 4 portions of 0.5 mL. The mixture was heated until nitrous vapors appeared. The mixture was allowed to cool down to r.t. and transferred to a 25 mL volumetric flask.

4.8 | References

- [1] P. W. N. M. van Leeuwen. *Homogeneous Catalysis: Understanding the Art*, **2004**.
- [2] B. Cornils, W. A. Herrmann. *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, Wiley-VCH, **2002**.
- [3] B. Cornils, W. A. Herrmann, I. T. Horvath, W. Leitner, S. Mecking, H. Olivier-Bourbigou, D. Vogt. *Multiphase Homogeneous Catalysis*, Wiley-VCH, **2005**.
- [4] C. Müller, M. G. Nijkamp, D. Vogt. *Eur. J. Inorg. Chem.* **2005**, 4011-4021.
- [5] C. Müller, D. Vogt. Immobilization and compartmentalization of homogeneous catalysts, In: *Handbook of Green Chemistry: Green Catalysis*, **2009**, pp. 127-152.
- [6] H. P. Dijkstra, G. P. M. van Klink, G. van Koten. *Acc. Chem. Res.* **2002**, 35, 798-810.
- [7] G. P. M. van Klink, H. P. Dijkstra, G. van Koten. *C. R. Chim.* **2003**, 6, 1079-1085.
- [8] A. Van Rooy, E. N. Orij, P. C. J. Kamer, F. Van den Aardweg, P. W. N. M. van Leeuwen. *J. Chem. Soc., Chem. Commun.* **1991**, 1096-1097.
- [9] P. W. N. M. van Leeuwen, C. Claver, Editors. *Rhodium Catalyzed Hydroformylation. [In: Catal. Met. Complexes, 2000; 22]*, **2000**.
- [10] L. A. Van der Veen, P. H. Keeven, G. C. Schoemaker, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, M. Lutz, A. L. Spek. *Organometallics* **2000**, 19, 872-883.
- [11] M. Caporali, C. Müller, B. B. P. Staal, D. M. Tooke, A. L. Spek, P. W. N. M. van Leeuwen. *Chem. Commun.* **2005**, 3478-3480.
- [12] L. A. Van der Veen, M. D. K. Boele, F. R. Bregman, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, H. Schenk, C. Bo. *J. Am. Chem. Soc.* **1998**, 120, 11616-11626.
- [13] J. Wilting, M. Janssen, C. Müller, M. Lutz, A. L. Spek, D. Vogt. *Adv. Synth. Catal.* **2007**, 349, 350-356.
- [14] B. M. Bhanage, S. S. Divekar, R. M. Deshpande, R. V. Chaudhari. *J. Mol. Catal. A: Chem.* **1997**, 115, 247-257.
- [15] R. M. Deshpande, R. V. Chaudhari. *Ind. Eng. Chem. Res.* **1988**, 27, 1996-2002.
- [16] R. Paciello, L. Siggel, H. J. Kneuper, N. Walker, M. Roper. *J. Mol. Catal. A: Chem.* **1999**, 143, 85-97.
- [17] R. P. J. Bronger, J. P. Bermon, J. Herwig, P. C. J. Kamer, P. W. N. M. van Leeuwen. *Adv. Synth. Catal.* **2004**, 346, 789-799.
- [18] H. Scott Fogler. *Elements of Chemical Reaction Engineering*, Prentice Hall, **2006**.
- [19] D. R. Bryant. *Catal. Met. Complexes* **2006**, 30, 9-37.
- [20] P. W. N. M. van Leeuwen. *Appl. Catal., A* **2001**, 212, 61-81.

5

Hydroformylation of styrene: in search for selectivity

Rh-catalyzed hydroformylation of styrene usually yields predominantly the chiral, branched aldehyde. An inversion of regioselectivity can be achieved by using strong π -acceptor ligands, such as diphosphites or bis(phosphordiamidite) ligands. Binaphthol-based diphosphite and bis(pyrrolyl-phosphoramidite) ligands have been prepared and fully characterized. Their coordination chemistry towards Rh(I) and Ni(0) was investigated spectroscopically and structurally. The ligands that performed best in the Rh-catalyzed hydroformylation of styrene were molecular weight enlarged with a Polyhedral Oligomeric Silsesquioxane (POSS) moiety, which potentially enables their recovery by nanofiltration in a continuous flow membrane reactor.

5.1 | Introduction

The hydroformylation reaction is an atom efficient route for the functionalization of alkenes towards aldehydes.^[1] Aldehydes are versatile intermediates for the synthesis of various fine chemicals.^[2] Styrene is an often applied model substrate in the hydroformylation reaction of vinylarenes and usually the branched product that contains a stereogenic center is formed predominantly (Scheme 1).

Scheme 1 | Hydroformylation of styrene.

However, especially in pharmaceutical chemistry, catalysts that selectively produce the linear aldehyde gain more and more interest, also because their synthesis *via* other routes is often cumbersome. The linear 3-phenylpropanal is also accessible *via* selective hydrogenation of the C-C double bond in cinnamaldehyde or *via* selective oxidation of the hydroxyl moiety in 3-phenylpropanol with e.g. CrO₃.

Few examples concerning hydroformylation of styrene towards the linear product exist in literature. Sémeril *et al.* reported l/b ratios of about 3 in the Rh-catalyzed hydroformylation of styrene with calixarene-based diphosphites.^[3] Reek and co-workers used a small SUPRAphos phosphine-phosphoramidite ligand library and obtained 72% of the linear aldehyde (l/b = 2.6).^[4] The catalyst that shows the highest selectivity towards 3-phenylpropanal was recently described by Zhang *et al.* Their tetraphosphorus/Rh catalyst shows l/b ratios of up to 22 in this reaction (see Figure 1, **L5**).^[5]

Binaphthol-based ligands have been applied in various homogeneously catalyzed reactions.^[6] Diphosphite ligands based on binaphthol, for example, have been applied in the hydrocyanation of styrene and 1,3-cyclohexadiene.^[7, 8] Bini *et al.* used binaphthol-based diphosphites in the hydrocyanation of styrene towards the linear product.^[9] Here we describe our investigations on the application of those ligands and of related pyrrole-substituted ligands in the hydroformylation of styrene.

5.2 | Synthesis of binaphthol-based ligands

Binaphthol is a common building block for the modular synthesis of ligands for homogeneous catalysis. Modularity allows tailor-made modifications of the ligand in order to fine-tune the catalytic performance of the corresponding metal complexes. [1,1']-Binaphthyl-2,2'-bis-(diarylphosphite) is such a ligand, and it has been applied in the asymmetric hydroformylation of vinyl acetate and aryl vinyl ethers.^[10, 11] The binaphthol-based ligands were synthesized according to literature procedures (Scheme 2).^[7] Typically, to a solution of PCl_3 and the substituted phenol of choice, Et_3N is added dropwise at -10°C . The formation of the phosphochloridite is verified by ^{31}P NMR spectroscopy of the crude mixture (ca. 30 min.). Subsequently, a concentrated solution of racemic binaphthol in THF is added to the reaction mixture yielding the desired ligands in good to excellent yields (Scheme 2).

Scheme 2 | Synthesis of binaphthol-based phosphites.

It is important to note that, especially in the case of ligand **L2** (Figure 1), the yield is dramatically increased when the base Et_3N is added dropwise to a solution of the phenol and PCl_3 . Apart from the order of addition of reactants, it was found that the use of toluene as a solvent for this reaction leads to higher yields and less impurities compared to THF. Also, lowering the temperature from r.t. to -10°C leads to better results.

In contrast to the phosphochloridites in the phosphite synthesis, 1,1'-(chlorophosphinodiyl)bispyrrole was isolated and purified by means of distillation. Subsequently, it was reacted with the appropriate diol in the presence of Et_3N as base (Scheme 3).^[12]

Scheme 3 | Synthesis of the bidentate pyrrole-substituted ligands.

The binaphthol-based diphosphite ligands **L1-L3** carry different moieties in the *ortho* position of the phenoxy group of the ligand, leading to small differences in their steric properties (Figure 1). The phosphorodiamidite ligands **L4-L6** differ in their backbone from binaphthyl, *via* biphenyl to xanthenes. Ligands **L7-L9** are literature examples and are used for comparison. [13, 14]

Figure 1 | Ligands used in the coordination chemistry studies and the Rh-catalyzed hydroformylation of styrene.

5.3 | Coordination chemistry towards Rh(I) and Ni(0)

5.3.1 | Synthesis and characterization of the Rh(I) complexes

The pre-catalyst complexes $[\text{Rh}(\text{acac})\text{L}]$ were investigated spectroscopically and structurally. Reaction of $[\text{Rh}(\text{acac})(\text{CO})_2]$ with one equivalent of bidentate ligand in toluene yields the corresponding $[\text{Rh}(\text{acac})\text{L}]$ complexes. Table 1 gives an overview of the ^{31}P NMR chemical shifts of selected complexes along with their corresponding Rh-P coupling constants. The diphosphite ligands show a Rh-P coupling of approximately 310 Hz in accordance with literature values.^[15] The bis(phosphordiamidite) ligands typically show somewhat smaller Rh-P coupling constants (~270 Hz, Table 1).

Table 1 | Spectroscopic data of $\text{Rh}(\text{acac})(\text{L})$ complexes in toluene.

Ligand	δ_{P} (ppm)	$J_{\text{Rh-P}}$ (Hz)
L1	127.4	300
L8	140.5	313.5
L4	129.36	265.7
L5	127.0	270.5
L6	124.35	276.5

Figure 2 | ^{31}P NMR spectrum of $[\text{Rh}(\text{acac})\text{L4}]$.

In order to obtain structural information for the precatalysts, attempts to crystallize the selected complexes were made. Crystals of $[\text{Rh}(\text{acac})\text{L4}]$ were obtained from a mixture of toluene and methanol at room temperature. Figure 3 shows the molecular structure of $[\text{Rh}(\text{acac})\text{L4}]$ in the crystal as well as selected bond lengths and angles. The solvent molecules present in the crystal (MeOH and toluene), have been removed for clarity. The coordination geometry around the Rh center is square planar. As expected, both enantiomers of the ligand are present in the crystal.

Figure 3 | The molecular structure of $[\text{Rh}(\text{acac})\text{L4}]$ in the crystal. Displacement ellipsoids are drawn at 50% probability level. Selected bond lengths ($\text{\AA}$): Rh-P1 = 2.17, Rh-P2 = 2.15, Rh-O3 = 2.05, Rh-O4 = 2.06. Bite angle ($^\circ$): P1-Rh-P2 = 99.

Crystals of $[\text{Rh}(\text{acac})\text{L6}]$ were obtained from acetonitrile. The molecular structure $[\text{Rh}(\text{acac})\text{L6}]$ in the crystal is depicted in Figure 4, along with selected bond lengths. The coordination geometry around the central Rh atom is square planar and the bite angle P1-Rh-P2 is with 93° relatively small.

Figure 4 | The molecular structure of $[\text{Rh}(\text{acac})\text{L6}]$ in the crystal. Displacement ellipsoids are drawn at 50% probability level. Selected bond lengths ($\text{\AA}$): Rh-P1 = 2.16, Rh-P2 = 2.15, Rh-O4 = 2.04, Rh-O5 = 2.05. Bite angle ($^\circ$): P1-Rh-P2 = 93.

5.3.2 | Electronic properties

Reaction of 1 equivalent of the bidentate ligands depicted in Figure 1 with $\text{Ni}(\text{cod})_2$ in toluene led to the corresponding $[\text{Ni}(\text{cod})\text{L}]$ complexes. Purging the toluene solutions with carbon monoxide for 30 s, during which the color of the solution turned from yellow to colorless, afforded the corresponding $[\text{Ni}(\text{CO})_2\text{L}]$ complexes (Figure 5).^[16]

Figure 5 | Synthesis of $[\text{Ni}(\text{CO})_2\text{L}]$.

The $\text{Ni}(0)$ complexes were investigated by means of IR spectroscopy in the ATR mode. By evaluating the A_1 and B_1 frequencies of the CO ligands, the electronic properties of the phosphorus ligands can be compared.^[16] An overview of these frequencies is given in Table 2.

Table 2 | ATR IR frequencies of the A_1 and B_1 vibrations of CO in $[(\text{L})\text{Ni}(\text{CO})_2]$.

Entry	Ligand	A_1 (cm^{-1})	B_1 (cm^{-1})
1	L1	2041	1987
2	L2	2044	1990
3	L3	2049	2001
4	L4	2048	1993
5	L5	2050	1998
6	L6	2041	1989
7	L7	2014	1954
8	L9	1985	1919

10 mg (0.036 mmol) $\text{Ni}(\text{cod})_2$ and 1 equiv. (0.036 mmol) ligand were dissolved in 3 mL toluene. The slightly yellow solution was purged with CO for 30 s, during which the solution turned colorless. All volatiles were removed in vacuo and the remaining solid was used in the IR measurement in ATR mode.

Ligands **L1-L6** show relatively high values for the A_1 and B_1 frequencies as compared with the diphosphinite and diphosphine ligands in entries 7 and 8. This means that ligands **L1-L6** have pronounced π -acceptor character.

5.4 | Mechanistic considerations

Relatively few studies on the mechanism of the hydroformylation of styrene to the linear product have appeared in literature. The proposed catalytic cycle is depicted in Figure 6. Lazzaroni and co-workers have shown that at lower temperature (room temperature) the kinetic, branched product is predominantly formed and deuterium labeling studies prove that the formation of both the linear and the branched alkyl species **3** is not reversible at low temperature. At higher temperature, the insertion into the Rh-H bond becomes reversible. The branched alkyl species **3b** can convert back to complex **2** under β -hydrogen elimination, whereas this happens to a far lesser extent for the linear alkyl species **3a**.^[17] Complexes **3a** and **3b** are coordinatively and electronically (16 VE) unsaturated. Complex **3b** is stabilized by forming the 18 VE η^3 -benzyl complex **3c**. This equilibrium slows down the formation of complex **4b**.

On the other hand, complex **3a** can only form an 18 electron complex via coordination of CO. Therefore, the coordination of CO (**3a**→**4a**) is very fast.^[18]

When applying strong π -acceptor ligands, such as phosphites or bis(phosphorodiamidites), the 16 VE σ -alkyl complexes **3a** and **3b** are destabilized. This in combination with high temperature causes fast equilibrium between **2**↔**3b** and **2**↔**3c**. The regioselectivity is now determined by the rate of CO coordination. This causes the exceptionally high l/b ratios for this kind of ligands, and explains why the l/b ratio increases when ligands with more π -acceptor character are applied.

Figure 6 | Proposed catalytic cycle for the hydroformylation of styrene.

5.5 | Rh-catalyzed hydroformylation of styrene

The ligands depicted in Figure 1 were tested in the Rh-catalyzed hydroformylation of styrene, and their performance in terms of activity and regioselectivity towards the linear product was compared.

After initial screening of the diphosphite ligands **L1-L3** at 80°C and 10 bar of syngas pressure, the difference in performance was rather pronounced. Whereas catalysts based on ligands **L1** and **L2** showed good activity in the reaction (Table 3, entry 1 and 2), the catalyst based on ligand **L3** did not show any conversion (entry 3). The poor activity of the latter one might be caused by the sterically demanding tert-butyl groups in the ortho position of the phenoxy moiety of the ligand. In terms of selectivity, the diphosphites **L1** and **L2** were compared with a well-known diphosphite from literature **L8** (entry 5), and a higher l/b ratio was observed for the catalysts based on **L1** and **L2**. Ligand **L3** was tested again, but this

time at a substantially higher reaction temperature of 140°C. In this case, a conversion of 58% was obtained as well as an excellent regioselectivity to the linear aldehyde (*l/b* = 5.9, 85.5%, entry 4).

Table 3 | Hydroformylation of styrene with binaphthol-based diphosphite ligands.

Entry	Ligand	P (CO/H ₂)	T _{reaction}	Conv. (%)	TOF (h ⁻¹)	Hydrogenation (%)	<i>l/b</i>
1	L1	10	80	99	325	<1	0.37
2	L2	10	80	99.9	1010	<1	0.97
3	L3	10	80	0	-	-	-
4	L3	10	140	58	25	8	5.9
5	L8	10	80	99	440	1.8	0.12

*Rh:L:S = 1:2:2000, [Rh] = 0.9 mM, solvent = toluene, *l/b* ratio is determined when no more gas was absorbed, turnover frequencies (TOF) were determined at 20% conversion and are given in (mol aldehyde)(mol Rh)⁻¹h⁻¹.*

Under our initial testing conditions at 80°C and 10 bar of syn gas pressure, the catalyst based on diphosphite **L2** showed the most promising results both with respect to activity and selectivity. Based on the mechanistic considerations in the previous section we can conclude that a higher linearity in the product aldehyde is expected when the temperature is increased and the syngas pressure is lowered (both leading to faster β-hydrogen elimination). Therefore, the reaction conditions were screened applying ligand **L2**. The results are summarized in Table 4.

Indeed, when the temperature was increased from 80°C, *via* 100°C, to 120°C, the regioselectivity in terms of *l/b* ratio increased from 0.97 at 80°C to 4.81 at 120°C (entries 6 to 8). However, when the reaction was performed at 140°C, 93% of the styrene was converted, but no product aldehyde was observed by means of GC analysis. This is probably caused by polymerization of styrene at elevated temperature. Also, a side reaction, namely the hydrogenation of styrene to ethylbenzene, increases with temperature.

Encouraged by the improved regioselectivity at higher temperatures, an experiment was performed in which the catalyst preformation and the reaction temperature were decoupled. After catalyst preformation at 80°C the substrate was added and the temperature was increased to 140°C, leading to a very high turnover frequency of 13874 h⁻¹ and an excellent *l/b* ratio of 7.1 (Figure 7).

Figure 7 | Conversion plot, based on the gas-uptake, for the Rh-catalyzed hydroformylation of styrene with binaphthol-based diphosphite **L2**.

When screening different syngas pressures, an optimum pressure of 10 bar was found (entries 9 to 11), in contrast to what can be expected based on the mechanistic considerations in the last paragraph. At lower pressure, the equilibrium between complexes **3a** and **4a**, and **3b** and **4b**, respectively, would be more on the side of **3a** and **3b**. Apparently, the effect on the regioselectivity is marginal at the pressures applied here.

Table 4 | Hydroformylation of styrene with diphosphite ligand **L2**.

Entry	Ligand	P (CO/H ₂)	T _{pref}	T _{reaction}	Conv. (%)	TOF (h ⁻¹)	Hydrogenation (%)	I/b
6	L2	10	100	100	99.9	3619	2.8	2.74
7	L2	10	120	120	99.9	7126	8	4.81
8	L2	10	140	140	93	-	12	-
9	L2	10	80	140	99.9	13874	14	7.1
10	L2	5	80	140	95	5895	30	6.7
11	L2	20	80	140	99.9	16933	8.6	5.3

Rh:L:S = 1:2:2000, [Rh] = 0.9 mM, solvent = toluene, I/b ratio is determined when no more gas was absorbed, turnover frequencies (TOF) were determined at 20% conversion and are given in (mol aldehyde)(mol Rh)⁻¹h⁻¹.

Accordingly, the bis(phosphordiamidite) ligands **L4-L6** were applied in the Rh-catalyzed hydroformylation of styrene under our initial testing conditions of 10 bar of syngas and 80°C (Table 4, entries 12, 14 and 15). For all the catalysts based on these three ligands high activities as well as high regioselectivities were obtained (l/b varying from 2.5 for **L6** to 5.8 for **L5**). Ligand **L4** was also applied in the hydroformylation of styrene at 140°C (Figure 8), but this did not lead to improved regioselectivity, as has been observed for ligand **L5** before by Zhang and co-workers.^[5]

Table 5 | Hydroformylation of styrene with binaphthol-based bis(phosphordiamidite) ligands.

Entry	Ligand	P (CO/H ₂)	T _{pref}	T _{reaction}	Conv. (%)	TOF (h ⁻¹)	Hydrogenation (%)	l/b
12	L4	10	80	80	99	3901	1	4.9
13	L4	10	80	140	99	11657	15	4.5
14	L5	10	80	80	99	2293	<1	5.8
15	L6	10	80	80	99	7726	<1	2.5

Rh:L:S = 1:2:2000, [Rh] = 0.9 mM, solvent = toluene, l/b ratio is determined when no more gas was absorbed, turnover frequencies (TOF) were determined at 20% conversion and are given in (mol aldehyde)/(mol Rh)⁻¹h⁻¹.

Figure 8 | Conversion plot, based on the gas-uptake, for the Rh-catalyzed hydroformylation of styrene with binaphthol-based bis(phosphordiamidite) **L4**.

Based on our observations in the Rh-catalyzed hydroformylation of styrene in combination with the electronic properties as determined in section 6.3.2 we can conclude that the catalysts based on ligands with more π -acceptor character show higher activity as well as higher selectivity towards the linear product. The linearity also increases with higher temperature (140°C vs. 80°C), which can be rationalized by the fact that at higher temperature the reversibility of the insertion into the Rh-H bond ($2 \rightleftharpoons 3b$) increases.

5.6 | Molecular weight enlargement with POSS

Based on the performance in the hydroformylation of styrene, the ligands **L1** and **L2** were selected for molecular weight enlargement (MWE), which can make them suitable for continuous hydroformylation in combination with catalyst recycling by means of nanofiltration (see chapter 3 and 4). Again, Polyhedral Oligomeric Silsesquioxanes (POSS) were chosen as MWE units, because of their proven stability and commercial availability.

The copper-catalyzed 1,3-dipolar cycloaddition reaction between an organo-azide and an alkyne (often referred to as ‘click’ reaction) is an interesting reaction that exhibits several attractive features, such as high and often quantitative yields as well as a high functional group tolerance. These interesting characteristics have already been widely exploited in polymer and materials science,^[19,20] while examples in the field of catalysis are yet in its infancy.^[21–24]

For reasons of synthetic convenience, we chose to decorate the POSS moiety with an azide functionality, and the binaphthol backbone with an alkyne group.

3-ChloropropylPOSS was treated with sodium azide in a mixture of THF and DMF at 70°C to obtain 3-azidopropylPOSS in high yield according to a literature procedure (Scheme 4).^[25]

Scheme 4 | Synthesis of (3-azidopropyl)hepta(*t*Bu)POSS.

The binaphthol backbone was brominated in the 6- and 6'-positions, and subsequently protected with acetic anhydride in the presence of pyridine, and used in a Sonogashira coupling with TMS-protected acetylene. Afterwards, both the trimethylsilyl and the acetyl protecting groups were removed with NaOH to obtain 6,6'-diethynylbinaphthol in moderate yield (Scheme 5).^[26, 27]

Scheme 5 | Synthesis of 6,6'-diethynyl-binaphthol.

The 3-azidopropylPOSS and diethynylbinaphthol were subsequently connected in the triazole-forming Cu-catalyzed 1,3-dipolar cycloaddition reaction.^[28] In the last step, the MWE binaphthol moiety is reacted with the phosphochloridite to obtain the POSS-enlarged diphosphite ligands **L1'** and **L2'** (Scheme 6). The molecular weight of these ligands was determined by means of Maldi-TOF MS (2316 g/mol for **L1'** and 2364 g/mol for **L2'**). The chemical shifts in the ³¹P NMR spectra are similar to their non-enlarged analogues ($\delta_P = 130$ ppm).

Scheme 6 | Synthesis of POSS-enlarged binaphthol and corresponding ligands.

5.7 | POSS-enlarged ligands in the hydroformylation of styrene

The two POSS-enlarged diphosphite ligands **L1'** and **L2'** were applied in the Rh-catalyzed hydroformylation of styrene. Their performance with respect to activity and regioselectivity in this reaction was compared to their non-enlarged counterparts **L1** and **L2**. The conversion plots, based on the gas-uptake monitored by a mass flow controller, are depicted in Figure 9. In terms of selectivity, the differences are small. For the catalyst based on ligand **L2'** the l/b ratio is 5, whereas the ratio is 7 for the non-supported analogue **L2**. This difference seems pronounced, but is relatively small: 83.3 vs. 87.5% selectivity towards the linear product. Also for the catalysts based on ligands **L1** and **L1'** the differences are small. **L1** shows a l/b ratio of 4.78 vs. 5.35 for the POSS-enlarged ligand **L1'**.

Figure 9 | Comparison of the performance of catalysts based on POSS-enlarged ligands **L1'** and **L2'** with their non-enlarged counterparts **L1** and **L2**.

Table 6 | Rh-catalyzed hydroformylation of styrene with POSS-enlarged binaphthol-based diphosphite ligands.

Entry	Ligand	P (CO/H ₂)	T _{pref}	T _{reaction}	Conv. (%)	TOF (h ⁻¹)	Hydrogenation (%)	l/b
16	L1	10	80	140	99	5880	19.5	4.78
17	L1'	10	80	140	99	2000	17	5.35
18	L2	10	80	140	99	13874	14	7.1
19	L2'	10	80	140	99	7200	11.6	5

Rh:L:S = 1:2:2000, [Rh] = 0.9 mM, solvent = toluene, l/b ratio is determined when no more gas was absorbed, turnover frequencies (TOF) were determined at 20% conversion and are given in (mol aldehyde)(mol Rh)⁻¹h⁻¹.

These POSS-enlarged systems were applied in the continuous flow membrane reactor that was described in chapter 3. However, after 5 h of reaction in the continuous flow membrane setup, the flow sensors in both loops of the reactor did not measure any flow anymore. A possible explanation for this behavior is the formation of foam inside the reactor and the fact that the centrifugal pumps are not able to set this in motion. Still, the conversion showed the gradual increase as expected and the regioselectivity was the same as observed in the batch reactions ($l/b = 5$).

5.8 | Concluding remarks

The Rh-catalyzed hydroformylation of styrene usually yields predominantly the branched product. By careful choice of the ligand, this regioselectivity can be inverted. It was demonstrated that ligands with pronounced π -acceptor properties show both enhanced activity and linearity in this reaction.

The diphosphite ligands that showed good performance in catalysis, **L1** and especially **L2**, were decorated with POSS moieties to make application in a continuous flow membrane reactor feasible. The activity in the hydroformylation reaction remained high (TOF = 7100), but was lower than for the non-enlarged counterparts, probably due to the increased bulk caused by the POSS units, and the regioselectivity ($l/b = 5$) towards the desired linear product was similar as compared with their unsupported analogues.

5.9 | Experimental part

General considerations

Chemicals were purchased from Aldrich, Acros or Merck and used as received. All manipulations and reactions were performed under argon atmosphere using standard Schlenk techniques. Solvents were taken HPLC-grade from an alumina-filled argon-flushed column.

NMR spectra were recorded on a Varian Mercury 200 or Mercury 400 spectrometer. Elemental analyses were measured on a Perkin-Elmer 2400 apparatus. IR spectra were recorded on an Avatar 360 FT-IR instrument in ATR mode.

Catalytic conversions were determined by GC on an ULTRA 2 column (25 m x 0.20 mm) using *n*-decane as an internal standard. Retention times were compared with authentic samples.

Ligands **L5**, **L6**, **L7**, **L8** and **L9** were synthesized according to literature procedures. 3-Chloropropyl-hepta-*iso*-butyl POSS was generously provided by Hybrid Catalysis B.V.

General procedure for the Rh-catalyzed hydroformylation of styrene

Hydroformylation experiments were performed in a stainless steel autoclave equipped with temperature sensor, dropping funnel, and mechanical gas-inlet stirrer. Before use, the autoclave was evacuated and refilled with argon three times. The catalyst solution Rh(acac)(CO)₂ (3.7 mg (14.4 μmol)), and 29 μmol (2 equiv.) of the appropriate ligand in 15 mL of toluene was injected into the autoclave and styrene containing 10% of *n*-decane as an internal standard (3.6 mL, 28.8 mmol, 2000 eq.) in 5 mL of toluene were inserted into the dropping funnel. After 2h of catalyst preformation at the appropriate temperature and 10 bar of CO/H₂ (1:1), the substrate was added to the reactor (*t* = 0). When no more gas was absorbed, the pressure was released and the conversion of styrene and the regioselectivity (*l/b* ratio) were determined by means of GC analysis.

General synthesis of binaphthol-based diphosphites L1-L3

To a solution of the appropriate phenol (14 mmol) in 200 mL of toluene was subsequently added at -10°C PCl₃ (0.95 g, 6.99 mmol) and Et₃N, (6 mL, 43 mmol). The mixture was stirred for 1h. (±)-Binaphthol (1.00 g, 3.5 mmol) dissolved in 10 mL of THF was added to the mixture at -10°C. The mixture was stirred for 1h at r.t. The salts were filtered off over a short pat of basic alumina (4 cm) and all volatiles were removed *in vacuo*. The ligands were purified by column chromatography over silica (heptane/EtOAc, 8:1).

(±)-[1,1']-Binaphthyl-2,2'-bis(di(*o*-isopropyl)phosphite) L1

¹H NMR: (400 MHz, CDCl₃) δ (ppm): 7.93 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 6.2 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.43 (t, *J* = 6.6 Hz, 2H), 7.32-7.26 (m, 4H), 7.19 (d, *J* = 7.7 Hz, 4H), 7.02 (t, *J* = 7.3 Hz, 4H), 6.84 (dt, *J* = 8.1 Hz, 4H), 6.70 (d, *J* = 8.1 Hz, 2H), 6.67 (d, *J* = 8.1 Hz, 2H), 3.30 (sept, *J* = 6.2 Hz, 4H), 0.97 (m, 24H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 148.9, 148.0, 139.41, 139.37, 134.0, 130.8, 129.7, 127.9, 126.6, 126.29, 126.25, 126.21, 126.16, 126.10, 124.9, 123.8, 121.24, 121.20, 121.15, 120.07, 120.01, 119.95, 119.91, 119.86, 26.64, 26.59, 22.82, 22.78, 22.69.

³¹P NMR (162 MHz, CDCl₃) δ (ppm): 131.4 (s).

Maldi-TOF: 885.57 (M⁺-1), 919.60 (M⁺⁺O₂).

Elemental analysis: calculated (found): %C 75.8 (75.0), %H 6.4 (6.5).

(±)-[1,1']-Binaphthyl-2,2'-bis(di(*o*-[1,3]-dioxan-2-ylphenyl)phosphite) L2

¹H NMR: (400 MHz, CDCl₃) δ (ppm): 7.89 (d, *J* = 8.79 Hz, 2H), 7.86 (d, *J* = 8.06 Hz, 2H), 7.65 (d, *J* = 9.15 Hz, 2H), 7.55 (dd, *J* = 7.69 Hz, *J* = 1.83 Hz, 2H), 7.52 (dd, *J* = 7.69 Hz, *J* = 1.83 Hz, 2H), 7.36 (dt, *J* = 7.51 Hz, *J* = 1.47 Hz, 2H), 7.29-7.16 (m, 4H), 7.05-6.94 (m, 6H), 6.89 (dt, *J* = 7.69 Hz, *J* = 1.83 Hz, 2H), 6.66 (d, *J* = 8.06 Hz, 2H), 6.52 (d, *J* = 8.05 Hz, 2H), 5.55 (s, 2H), 5.51 (s, 2H), 4.04-3.92 (m, 8H), 3.69-3.51 (m, 8H), 2.13-1.99 (m, 4H), 1.19 (d, *J* = 12.45 Hz, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 148.81, 147.96, 133.91, 130.82, 129.86, 129.81, 129.71, 127.88, 127.26, 127.19, 126.80, 126.13, 125.06, 123.88, 123.82, 121.20, 119.70, 96.7, 67.2, 26.9, 25.7.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 130.3 (s).

Maldi-TOF: 1061.71 (M^+-1), 1085.73 (M^++Na), 1101.73 (M^++K).

($\pm$)-[1,1']-Binaphthyl-2,2'-bis(di(*o*-tert-butylphenyl)phosphite) L3

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.82 (d, $J = 8.42$ Hz, 2H), 7.80 (d, $J = 8.79$ Hz, 2H), 7.45 (d, $J = 9.15$ Hz, 2H), 7.37-7.32 (m, 2H), 7.23-7.17 (m, 8H), 6.91-6.84 (m, 6H), 6.77-6.67 (m, 6H), 1.20 (s, 18H), 1.18 (s, 18H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 151.1, 139.6, 134.0, 130.8, 129.8, 127.9, 126.9, 126.7, 126.1, 124.9, 122.9, 120.8, 120.0, 119.8, 119.6, 34.5, 29.9.

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 129.4 (s).

Maldi-TOF: 941.37 (M^+-1), 965.40 (M^++Na), 981.39 (M^++K).

Elemental analysis: calculated (found): %C 76.4 (76.2), %H 6.8 (6.9).

Synthesis of bis(phosphorodiamidite) ligand L4

Et_3N (6.5 mL, 46.2 mmol) and 2,2'-binaphthol (3 g, 10.5 mmol) were dissolved in 30 mL THF and added dropwise to a solution of chlorodipyrrolylphosphine (5.6 g, 30 mmol) at 0 °C. A purple suspension has formed. The reaction mixture was stirred overnight after which a white suspension has formed. Salts were filtered off twice over a short path of basic alumina (4 cm) and all volatiles were evaporated. A white solid was obtained after recrystallization from EtOAc/hexane. Yield: 3 g (4.9 mmol, 47%).

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.91 (d, $^3J = 8$ Hz, 4H), 7.45 (t, $^3J = 8$ Hz, 2H), 7.33 (t, $^3J = 8$ Hz, 2H), 7.24 (d, $^3J = 8.8$ Hz, 2H), 7.17 (d, $^3J = 8.8$ Hz, 2H), 6.50 (dt, $^3J = 8.8$ Hz, $^4J = 2.0$ Hz, 8H), 6.17 (t, $^4J = 2.0$ Hz, 4H), 6.11 (t, $^4J = 2.4$ Hz, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 149.2, 133.7, 130.9, 130.5, 128.2, 127.2, 125.9, 125.3, 122.5, 121.2 (pyrrole), 119.2, 112.1 (pyrrole).

^{31}P NMR (162 MHz, CDCl_3) δ (ppm): 104.98.

Maldi-TOF: 609.09 (M^+-1 , 100%), 633.12 (M^++Na , 40%).

Synthesis of 6,6'-dibromo-1,1'-binaphthol

In 40 mL of CH_2Cl_2 2.5 gram of 1,1'-binaphthol were dissolved and the solution was cooled to -75 °C. 1.1 mL of bromine was added in approximately 30 minutes. After stirring an additional 2.5 h, while warming to room temperature, the reaction mixture was stirred further for 0.5 h followed by the addition of sodium thiosulfate (10% in water) until the bromine disappears. After addition of another 40 mL of CH_2Cl_2 , the reaction mixture is washed with a saturated NaCl solution. Thereafter the organic phase is dried over magnesium sulfate and the solvent is removed under reduced pressure. The yellow solid was recrystallized from ethyl acetate/heptane to give a white solid (2.6 g, 70%).

m.p. 200-202 °C; (lit. 12 m.p. 197-198 °C);

^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.05 (s, 2H), 7.90 (d, 2H, $^3J = 8.8$ Hz), 7.38 (m, 4H), 6.97 (d, 2H, $^3J = 8.8$ Hz), 5.04 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 153.0, 131.9, 130.9, 130.7, 130.6, 130.4, 125.9, 119.0, 118.0, 110.6.

6,6'-dibromo-2,2'-diacetoxy-1,1'-binaphthyl

To a solution of 6,6'-dibromo-1,1'-binaphthol (3.1 g, 7.7 mmol) in CH₂Cl₂ (100 mL) were added acetic anhydride (3.8 mL, 40 mmol) and pyridine (3.2 mL, 40 mmol). The mixture was stirred at room temperature for 24 h. The mixture was diluted with CH₂Cl₂ (100 mL) and washed with water twice. The organic layer was dried over anhydrous Na₂SO₄. After the evaporation of organic volatiles a light yellow solid remained (1.9 g, 80% yield).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.10 (s, 2H), 7.90 (d, 2H), 7.42 (d, 2H), 7.38 (d, 2H), 7.00 (d, 2H), 1.88 (s, 6H).

6,6'-Diethynyl-2,2'-dihydroxy-1,1'-binaphthalene

To a degassed solution of 6,6'-dibromo-2,2'-diacetoxy-1,1'-binaphthalene (2 g, 3.8 mmol) and Pd(PPh₃)₂Cl₂ (355 mg, 0.5 mmol) in toluene (25 mL) and triethyl amine (30 mL) was added trimethylsilylacetylene (9 mL, 64 mmol) and CuI (190 mg, 1 mmol). After heated to 50 °C for 2 days, the reaction mixture was cooled to room temperature. The solid was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in tetrahydrofuran (40 mL) and methanol (40 mL), followed by the addition of 2M of aqueous sodium hydroxide solution (10 mL). After being stirred for ~2h, the product was extracted with dichloromethane and washed with water. The organic layer was dried over anhydrous MgSO₄, and the organic volatiles were evaporated *in vacuo*. The crude product was purified by flash chromatography with ethyl acetate/heptane (1:2 v/v) to afford light yellow solid (0.73 g, 60 %).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.05 (d, ⁴J = 1.5 Hz, 2 H), 7.92 (d, ³J = 9.1 Hz, 2 H), 7.38 (d, ³J = 9.1 Hz, 2 H), 7.34 (dd, ³J = 8.7 Hz, ⁴J = 1.5 Hz, 2 H), 7.04 (d, ³J = 8.7 Hz, 2 H), 3.11 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 153.6, 133.1, 132.7, 131.5, 130.3, 129.0, 124.2, 118.6, 117.8, 110.6, 83.7, 77.4.

IR: ν(-C≡C-H) 3279 cm⁻¹ (s); ν(-C≡C-) 2101 cm⁻¹ (w).

Synthesis of (3-azidopropyl)hepta(i-Bu)POSS

To a solution of (3-chloropropyl)hepta(i-Bu)POSS (10 g, 11.2 mmol) in a mixture of DMF (350 mL) and THF (100 mL) 3 equivalents of sodium azide were added (2.18 g, 33.55 mmol). The mixture was stirred at 70 °C for 24h. The reaction mixture was allowed to cool to r.t. and the reaction was quenched by pouring the mixture in 400 g ice to precipitate the product. The product was filtered off and recrystallized from THF/MeOH to obtain the desired product as a white solid in 90% yield (9.1 g, 10.08 mmol).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 3.27 (t, 2H), 1.89 (m, 7H), 1.74 (quin, 2H), 0.97 (d, 42H), 0.69 (2H), 0.62 (m, 14H).

¹³C NMR (100MHz, CDCl₃) δ (ppm): 53.62, 25.68, 25.65, 23.89, 23.84, 22.46, 22.41, 9.29.

Maldi-TOF: 922.96 (M⁺+Na).

Elemental analysis: calculated (found): %C 41.34 (41.23), %H 7.72 (7.83), %N 4.67 (4.47).

Synthesis of POSS-enlarged binaphthol

6,6'-Diethynyl-2,2'-dihydroxy-1,1'-binaphthalene (730 mg, 2.2 mmol) and (3-azidopropyl)hepta(i-butyl)octasilsesquioxane (586 mg, 4.4 mmol) were dissolved in 60 mL of THF. Sodium ascorbate (600 mg, 3.05 mmol) and CuSO₄·5H₂O (200 mg, 0.75 mmol) were dissolved in 15 mL water and added to the THF solution. The mixture was stirred at

room temperature for 48h. THF was evaporated in vacuo and the product was extracted from the aqueous phase with CH₂Cl₂. The organic layer was washed with diluted ammonia solution until the water phase stayed colorless. The organic phase was dried over MgSO₄ and concentrated to dryness. A white solid remained after precipitation from chloroform (0.6 g, 45%).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.43 (s, 2H), 7.75 (s, 2H), 8.03 (d, ³J = 8.8 Hz, 2H), 7.75 (s, 2H), 7.70 (d, ³J = 8.8 Hz, 2H), 7.41 (d, ³J = 8.8 Hz, 2H), 7.25 (s, 2H), 7.23 (d, ³J = 8.8 Hz, 2H), 5.19 (s, 2H), 4.39 (t, ³J = 6.8 Hz, 4H), 2.03 (q, ³J = 7.6 Hz, 4H), 1.83 (m, 14H), 0.96 (m, 84H), 0.65 (t, ³J = 6.8 Hz, 4H), 0.59 (m, 28H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm): 153.1, 147.5, 137.0, 133.1, 131.6, 125.3, 124.9, 124.8, 124.8, 119.3, 118.5, 111.1, 52.6, 31.8, 25.7, 25.6, 23.9, 23.8, 22.4, 22.4, 9.8.

MALDI-TOF: 2135.6 (M⁺, 100%).

5.10 | References

- [1] P. W. N. M. van Leeuwen. *Homogeneous Catalysis: Understanding the Art*, **2004**.
- [2] P. W. N. M. van Leeuwen, C. Claver, Editors. *Rhodium Catalyzed Hydroformylation. [In: Catal. Met. Complexes, 2000; 22]*, **2000**.
- [3] D. Semeril, D. Matt, L. Toupet. *Chem.Eur. J.* **2008**, *14*, 7144-7155.
- [4] P. E. Goudriaan, M. Kuil, X. B. Jiang, P. W. N. M. van Leeuwen, J. N. H. Reek. *Dalton Trans.* **2009**, 1801-1805.
- [5] S. Yu, Y. m. Chie, Z. h. Guan, Y. Zou, W. Li, X. Zhang. *Org. Lett.* **2009**, *11*, 241-244.
- [6] Y. Chen, S. Yekta, A. K. Yudin. *Chem Rev* **2003**, *103*.
- [7] J. Wilting, M. Janssen, C. Müller, M. Lutz, A. L. Spek, D. Vogt. *Adv. Synth. Catal.* **2007**, *349*, 350-356.
- [8] J. Wilting, M. Janssen, C. Müller, D. Vogt. *J. Am. Chem. Soc.* **2006**, *128*, 11374-11375.
- [9] L. Bini, E. A. Pidko, C. Müller, R. A. van Santen, D. Vogt. *Chem.Eur. J.* **2009**, *15*, 8768-8778.
- [10] C. Botteghi, G. Delogu, M. Marchetti, S. Paganelli, B. Sechi. *J. Mol. Catal. A: Chem.* **1999**, *143*, 311-323.
- [11] N. Sakai, K. Nozaki, K. Mashima, H. Takaya. *Tetrahedron: Asymmetry* **1992**, *3*, 583-586.
- [12] B. Hamers, E. Kosciusko-Morizet, C. Müller, D. Vogt. *ChemCatChem* **2009**, *1*, 103-106.
- [13] C. J. Copley, R. D. J. Froese, J. Klosin, C. Qin, G. T. Whiteker, K. A. Abboud. *Organometallics* **2007**, *26*, 2986-2999.
- [14] M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje. *Organometallics* **1995**, *14*, 3081-3089.
- [15] A. M. Trzeciak, J. J. Ziolkowski. *Inorg. Chim. Acta* **1985**, *96*, 15-20.
- [16] C. A. Tolman. *Chem. Rev.* **1977**, *77*, 313-348.
- [17] R. Lazzaroni, A. Raffaelli, R. Settambolo, S. Bertozzi, G. Vitulli. *J. Mol. Catal.* **1989**, *50*, 1-9.
- [18] A. van Rooy, E. N. Orij, P. C. J. Kamer, P. W. N. M. van Leeuwen. *Organometallics* **1995**, *14*, 34-43.
- [19] W. H. Binder, R. Sachsenhofer. *Macromol. Rapid Commun.* **2007**, *28*, 15-54.
- [20] M. Malkoch, R. J. Thibault, E. Drockenmuller, M. Messerschmidt, B. Voit, T. P. Russell, C. J. Hawker. *J. Am. Chem. Soc.* **2005**, *127*, 14942-14949.
- [21] R. J. Detz, S. A. Heras, R. de Gelder, P. W. N. M. van Leeuwen, H. Hiemstra, J. N. H. Reek, J. H. van Maarseveen. *Org. Lett.* **2008**, *10*, 1323.
- [22] D. Liu, W. Gao, Q. Dai, X. Zhang. *Org. Lett.* **2005**, *7*, 4907-4910.

- [23] M. Meise, R. Haag. *ChemSusChem* **2008**, *1*, 637-642.
- [24] E. M. Schuster, M. Botoshansky, M. Gandelman. *Angew. Chem. , Int. Ed.* **2008**, *47*, 4555-4558.
- [25] V. Ervithayasuporn, X. Wang, Y. Kawakami. *Chem. Commun.* **2009**, 5130-5132.
- [26] H. Jiang, A. Hu, W. Lin. *Chem. Commun.* **2003**, 96-97.
- [27] G. D. Y. Sogah, D. J. Cram. *J. Am. Chem. Soc.* **1979**, *101*, 3035-3042.
- [28] M. Janssen, C. Müller, D. Vogt. *Adv. Synth. Catal.* **2009**, *351*, 313-318.

Compartmentalized bidentate ligands in the Ni-catalyzed isomerization of 2M3BN:

An initial study

The DuPont adiponitrile process is a large scale industrial process that consists of three reaction steps that are all nickel catalyzed. The isomerization of 2M3BN to 3PN is the second step in this process. The bidentate ligands sixantphos, DPEphos, Triptycene-PPh₂, and BIPPP were studied in the nickel catalyzed isomerization of 2M3BN to 3PN. Triptycene-PPh₂ showed the highest activity in this reaction and was compartmentalized inside a ceramic nanofiltration membrane. For the first time, the catalyst could be efficiently recycled and reused for 7 consecutive runs in this reaction. In order to maximize the catalyst retention, POSS-enlarged ligands were applied, but the catalytic activity decreased dramatically. The 'click' dendritic monodentate ligands described in chapter 2 showed similar catalytic activities as their unmodified analogues in the Pd-catalyzed Suzuki coupling reaction. Therefore attempts were undertaken to extend this synthetic strategy to bidentate ligands.

6.1 | Introduction

The DuPont adiponitrile process is so far the only industrial example of a Ni-catalyzed hydrocyanation reaction. 1,3-Butadiene is hydrocyanated twice to form adiponitrile, which is the precursor of 1,6-diaminohexane, one of the building blocks for nylon(6,6).^[1, 2]

The adiponitrile process consists of three consecutive steps that are all nickel catalyzed (Figure 1). First, 1,3-butadiene is hydrocyanated in presence of a Ni/phosphite catalyst, to obtain a mixture of the linear product (3-pentenitrile, 3PN) and the branched product (2-methyl-3-butenitrile, 2M3BN), typically in a ratio up to 70:30, depending on the ligand applied. In the second reaction step, the branched 2M3BN is isomerized to the linear 3PN. The third step is a second hydrocyanation reaction, in which the linear 3PN is converted into adiponitrile (AdN) in presence of a Lewis acid co-catalyst.^[1, 3]

Figure 1 | The DuPont adiponitrile process.

Despite the fact that the DuPont process is a relatively large scale homogeneously catalyzed industrial process, only one attempt for catalyst recycling has appeared in literature so far. Santini and co-workers described the nickel catalyzed isomerization of 2M3BN in an ionic liquid-organic biphasic system applying TPPTS as the ligand. A total turnover number of 450 was obtained after 7 recycle runs.^[4]

Homogeneous catalysis in combination with nanofiltration has proven to be versatile technology for homogeneous catalysts recovery and recycling. ^[5, 6] The possibility to extend the scope of reactions to the Ni-catalyzed isomerization of 2M3BN, in which nanofiltration is used for catalyst compartmentalization is investigated in this chapter.

6.2 | The Ni-catalyzed isomerization of 2M3BN

Typically, almost all bidentate phosphorus containing ligands show activity in the Ni-catalyzed isomerization of 2M3BN to 3PN. Wilting *et al.* investigated a catalyst based on Ni(cod)₂ in combination with DPEphos in this reaction, whereas Bini *et al.* reported on the high activity of a Ni-catalyst based on triptycene-PPh₂ as compared with Ni-catalysts based on Sixantphos and BIPPP (Figure 2).^[7-9]

Figure 2 | Phosphorus ligands applied in the Ni-catalyzed isomerization reaction.

Diphosphine ligands (DPEphos, Sixantphos and Triptycene-PPh₂) show higher reaction rates in this reaction than diphosphite BIPPP. The conversion vs. time plot is depicted in Figure 3 and an overview of the turnover frequencies is given in Table 1. Triptycene-PPh₂ shows a very high initial rate of 880 h⁻¹. All four ligands show good selectivities towards 3PN.

Table 1 | Turnover frequencies for the selected ligands.

Entry	Ligand	TOF (h ⁻¹)
1	DPEphos	160
2	Sixantphos	385
3	Triptycene-PPh ₂	880
4	BIPPP	130

Conditions: Ni:L:Substrate = 1:1.1:2050, [Ni] = 0.9 mM, T = 110°C, solvent = toluene, V_{Tot} = 8 mL.

Figure 3 | Conversion of 2M3BN versus time.

Conditions: Ni:L:Substrate = 1:1.1:2050, [Ni] = 0.9 mM, $T = 110^{\circ}\text{C}$, solvent = toluene, $V_{\text{Tot}} = 8 \text{ mL}$.

6.3 | Catalyst recycling studies

In the ideal case, the homogeneous ligand is not altered in order to make it recyclable. Often the activity and/or the selectivity of the catalyst changes when the ligand is modified with molecular weight enlargement units or tags that make them soluble in e.g. ionic liquids or the fluorous phase. Still, they need to show high retention, high activity and high selectivity. All four ligands that were tested in this reaction, have a molecular weight that is higher (Figure 2) than the molecular weight cut-off (MWCO) of the ceramic nanofiltration membrane that is used (450 g/mol, 0.9 nm).^[10]

Until now, there is only few literature precedents for catalyst recycling by means of nanofiltration in which unmodified catalysts are used. Vankelecom and co-workers demonstrated this for rhodium and ruthenium based catalysts (Figure 4) in the hydrogenation of dimethyl itaconate and methyl-2-acetamidoacrylate in a continuous flow membrane reactor. High conversion of 90% and high enantiomeric excess of 93% for Ru/BINAP and 80% for Rh-EtDUPHOS, respectively, were obtained and remained constant for 23 h. The catalyst retention was 97%.^[11,12]

Figure 4 | Ru-BINAP and Rh-EtDUPHOS used by Vankelecom *et al.*

Before use, the nanofiltration membrane tubes were carefully dried at 80°C *in vacuo* for 2 days in order to remove traces of water and air, and then fitted into the stainless steel holder (Figure 5). The Ni(0) pre-catalyst [LNi(cod)] is sensitive towards air and moisture, but showed good compatibility with the membrane.

Figure 5 | Ceramic nanofiltration membrane setup.

Initial retention measurements with the four ligands depicted in Figure 2 show a good retention of the catalyst of 98%, as determined by means of ICP-OES analysis.

Triptycene-PPh₂ was chosen for the repetitive batch experiments, because it showed the highest activity and good stability during the normal batch experiments. The ligand has a molecular weight of 623 g/mol, which is substantially larger than the MWCO of the membrane (450 g/mol).

The membrane tube was soaked in toluene, filled with catalyst solution, and placed in a Schlenk tube containing a 2M3BN solution in toluene. Then, the Schlenk tube was placed in a thermostatic shaking bath at 100°C, and the reaction was allowed to proceed for 5 h or 12 h. At the end of the reaction, the complete reaction mixture was collected by syringe and replaced by a fresh substrate solution. Between these recycling runs no catalyst was added. The results obtained in the repetitive batch experiment are shown in Figure 6.

Figure 6 | Triptycene-PPh₂/Ni catalyst recycling runs.

Conditions: Ni:L:Substrate = 1:1.1:250, 10 mg Ni(cod)₂, T = 100°C, solvent = toluene, V_{Tot} = 30 mL. Reaction time runs 1, 2, 4, 6: 5 h; runs 3, 5, 7: 12 h.

The Ni/triptycene-PPh₂ catalyst could be efficiently recycled for seven consecutive runs. The total turnover number that was achieved in this recycling experiment was 1014, which is more than twice as high as the best literature example of 450.^[4] These initial results demonstrate the proof of principle that nanofiltration can be used in the Ni-catalyzed isomerization with unmodified ligands in a diffusion driven process.

6.4 | Molecular weight enlarged ligands in the isomerization reaction

The retention of 98% as obtained with the unmodified ligands seems to be high at first glance. However, after seven consecutive runs only 86.8% of the catalyst remains. In order to maximize catalyst retention, MWE analogues of the ligands depicted in Figure 2 were applied in the Ni-catalyzed isomerization of 2M3BN. POSS-enlarged BIPPP (chapter 5) showed relative good activity in this reaction, whereas the POSS-enlarged analogues of DPEphos and Xantphos hardly showed any activity (Figure 7 and 8).

Figure 7 | MWE ligands applied in the isomerization of 2M3BN.

The major difference between BIPPP_POSS on one hand and XantPOSS and DPEPOSS on the other hand, is the location of the molecular weight enlarging POSS units. In case of the diphosphite ligand the steric bulk is positioned at the rear end of the binaphthol backbone, whereas in case of the diphosphine ligands the metal center might be shielded by the sterically demanding POSS cages.

Figure 8 | Conversion of 2M3BN versus time with POSS-enlarged catalysts.

Conditions: $Ni:L:Substrate = 1:1.1:2050$, $[Ni] = 0.9 \text{ mM}$, $T = 110^\circ\text{C}$, solvent = toluene, $V_{Tot} = 8 \text{ mL}$.

6.5 | Outlook: towards the synthesis of bidentate ‘click’ dendrimers

Taking the results of the catalytic reactions into consideration (*vide supra*), future studies will consequently focus on a MWE strategy that does not lead to a tremendous increase in steric bulk around the metal center. In case of the POSS-enlarged ligands, the actual ligand and the nickel atom are positioned in the core of MWE ligand, and the sterically demanding POSS cages are located at the periphery of the system. A system in which the actual ligand is placed at the periphery and the MWE unit is in the center of the system could lead to a catalytic system that shows both high activity in the Ni-catalyzed isomerization reaction, and high catalyst retention.

The MWE strategy described in chapter 2 of this thesis is an example in which the ligands are situated at the periphery of the system, and showed approximately the same activities for the MWE systems as for their non-enlarged analogues in the Pd-catalyzed Suzuki-Miyaura cross coupling reaction. In principle, the same synthetic strategy can be applied for bidentate ligands. Figure 9 shows the retrosynthetic analysis for this approach. The soluble support that is decorated with an alkyne moiety and the bidentate phosphine that is functionalized with an azide group are connected *via* the copper catalyzed 1,3-dipolar cycloaddition (‘click’ reaction) in which the triazole ring is formed (see chapter 2). The ligands are functionalized with the azide group in order to prevent a larger number of azide

moieties on the soluble support, since this might lead to explosive elimination of N_2 from the azides.

Figure 9 | Retrosynthetic analysis.

The ligands of choice have to be functionalized with one azide moiety in order to be able to attach them to the alkyne substituted support. In practice this means that an unsymmetrically substituted analogue of the ligand has to be synthesized. Both for xantphos and for DPEphos such examples are described in literature.^[13, 14]

In the following section, potential synthetic strategies for the preparation of such ligands are described. After mono lithiation and subsequent reaction with $ClPPh_2$ the mono-substituted analogue of either xantphos or DPEphos is obtained in moderate yield. This lithiation procedure can be repeated giving compound **3** after reaction with 4-(chloro(phenyl)phosphino)benzonitrile (Scheme 1).

Scheme 1 | Potential synthetic route to unsymmetrically substituted diphosphines **3**.

The benzonitrile group can be reduced to the corresponding benzyl amine with LiAlH_4 . Subsequently, the phosphine moieties have to be protected, for example as the corresponding phosphine oxides or borane adducts, in order to circumvent the Staudinger reaction (reaction between phosphine and azide in which iminophosphorane and N_2 are formed). After a copper-mediated diazotransfer reaction with triflic azide, the corresponding benzyl azide can be prepared (Scheme 2).^[15]

Scheme 2 | Potential synthetic approach of protected azides **4**.

The starting compound for the xantphos analogue, di-bromo-9,9-dimethyl-di-tert-butyl xanthene, is commercially available. 2-Bromo-2'-iodobiphenyl ether can be synthesized according to a literature procedure in high yield (Scheme 3).^[16-18]

Scheme 3 | Synthesis of 2-bromo-2'-iodobiphenyl ether **8**.

After attaching compound **4** to the soluble, alkyne functionalized support, the protecting groups can be removed from the phosphine moieties.^[15]

A possible synthetic route to a 'click' BIPPP ligand is shown in Scheme 4. After protection of only one of the hydroxyl moieties of binaphthol **9** with pivaloyl chloride, and subsequent bromination, compound **10** can be prepared. Removal of the pivaloyl group and protection of both hydroxyl groups with methyl iodide could result in compound **11**, which in turn can be converted into the corresponding nitrile, after reaction with cuprous cyanide.^[19, 20] Reduction of the nitrile to obtain the corresponding benzyl amine, deprotection of the methoxy group with BBr₃ and a copper-mediated diazotransfer reaction can result in benzyl azide **12**.^[15]

Scheme 4 | Potential synthetic strategy for azido-binaphthol **12**.

After the Cu-catalyzed 1,3-dipolar cycloaddition reaction ('click' reaction) in which azide **12** is connected to the soluble support, the binaphthol analogue is converted into its corresponding diphosphite BIPPP.

6.6 | Concluding remarks

The Ni-catalyzed isomerization reaction of 2M3BN to 3PN was performed with three bidentate phosphine ligands and one bidentate phosphite. Triptycene-PPh₂ performed best with respect to activity and was therefore chosen for the compartmentalization study.

The triptycene-PPh₂/Ni catalyst could be efficiently recycled for seven consecutive runs, achieving a total turnover number of 1014, which is substantially higher than the best literature example by Santini and co-workers (450 turnovers).

In order to maximize catalyst retention, POSS-enlarged analogues of the aforementioned ligands were applied in combination with Ni(cod)₂. The catalytic activity in the isomerization reaction dropped dramatically, probably due to the steric bulk induced by the large POSS moieties.

Therefore, we started to focus on MWE systems that do not increase the steric bulk around the metal center. The monodentate 'click' ligands that were applied in the Suzuki-Miyaura coupling showed comparable catalytic activities as their unmodified analogues (chapter 2). A potential synthetic strategy to 'click' Xantphos, DPEphos and BIPPP is described.

6.7 | Experimental part

General considerations

Chemicals were purchased from Aldrich, Acros or Merck and used as received. All reactions were performed under argon atmosphere using standard Schlenk techniques. Solvents were taken HPLC-grade from an alumina filled argon flushed column. NMR spectra were recorded on a Varian Mercury 200 or Mercury 400 spectrometer. Elemental analyses were measured on a Perkin-Elmer 2400 apparatus. Ceramic nanofiltration membranes were purchased from Inopor GmbH Germany and have a pore size of 0.9 nm and a molecular weight cut-off of 450 Da (www.inopor.com). Catalytic conversions were determined by GC on a ULTRA (25 m x 0.20 mm) or DB1 column (30 m x 0.32 mm) using decane as an internal standard. Retention times were compared with authentic samples.

General procedure for the isomerization experiments

A solution of ligand (0.010 mmol) in 1 mL of toluene was added to Ni(cod)₂ (2 mg, 0.007 mmol) in a Schlenk tube and stirred for 5 minutes. A stock solution of 2M3BN (3.5M in toluene) was added to the catalyst solution. The Schlenk tube was placed in a pre-heated oil bath at 110°C and samples for GC analysis were taken over time. The selectivity is defined as 3PN/(Σ nitriles).

General procedure for the repetitive batch isomerization experiments

A solution of ligand (0.020 mmol) dissolved in 3 mL of toluene was added to Ni(cod)₂ (5 mg, 0.018 mmol). This catalyst solution was injected into a ceramic membrane tube that is fitted in a stainless steel holder and capped with Teflon discs. The stainless steel holder is then placed in a Schlenk tube containing 30 mL of 1.24 M 2M3BN (37.1 mmol) solution in toluene. The Schlenk tube was placed in a thermostatic shaking bath at 110°C. After 12h the Schlenk tube was cooled down to r.t. and the substrate solution was replaced by fresh solution. Conversion was determined by GC analysis. The selectivity is defined as 3PN/(Σ nitriles).

6.8 | References

- [1] C. A. Tolman. *J. Chem. Educ.* **1986**, 63, 199-201.
- [2] P. W. N. M. van Leeuwen. *Homogeneous Catalysis: Understanding the Art*, **2004**.
- [3] G. W. Parshall, S. D. Ittel. *Homogeneous Catalysis, 2nd Edition. The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes*, **1992**.
- [4] C. Vallee, C. Valerio, Y. Chauvin, G. P. Niccolai, J. M. Basset, C. C. Santini, J. C. Galland, B. Didillon. *J. Mol. Catal. A: Chem.* **2004**, 214, 71-81.
- [5] A. V. Gaikwad, V. Boffa, J. E. ten Elshof, G. Rothenberg. *Angew. Chem., Int. Ed.* **2008**, 47, 5407-5410.
- [6] M. Janssen, C. Müller, D. Vogt. *Adv. Synth. Catal.* **2009**, 351, 313-318.
- [7] L. Bini, C. Müller, J. Wilting, L. Von Chrzanowski, A. L. Spek, D. Vogt. *J. Am. Chem. Soc.* **2007**, 129, 12622-12623.
- [8] L. Bini, E. Houben, E. A. Pidko, C. Müller, D. Vogt. *Catalysis Today* **2009**.
- [9] J. Wilting, C. Müller, A. C. Hewat, D. D. Ellis, D. M. Tooke, A. L. Spek, D. Vogt. *Organometallics* **2005**, 24, 13-15.
- [10] www.inopor.com
- [11] K. De Smet, S. Aerts, E. Ceulemans, I. F. J. Vankelecom, P. A. Jacobs. *Chem. Commun.* **2001**, 597-598.
- [12] D. Nair, H.-T. Wong, S. Han, I. F. J. Vankelecom, L. S. White, A. G. Livingston, A. T. Boam, *Org. Process Res. Dev.* **2009**, 13, 863-869.
- [13] M. W. P. Bebbington, G. Bouhadir, D. Bourissou. *Eur. J. Org. Chem.* **2007**, 4483-4486.
- [14] L. A. van der Veen, P. K. Keeven, P. C. J. Kamer, P. W. N. M. van Leeuwen. *Chem. Commun.* **2000**, 333-334.
- [15] M. Janssen, C. Müller, D. Vogt. *Adv. Synth. Catal.* **2009**, 351, 313-318.
- [16] D. Clive, A. G. Angoh, S. M. Bennett. *J. Org. Chem.* **1987**, 52, 1339-1342.
- [17] C. J. Dinsmore, C. B. Zartman. *Tetrahedron Lett.* **1999**, 40, 3989-3990.
- [18] M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, C. L. Zirkle. *J. Org. Chem.* **1961**, 26, 1901-1907.
- [19] H. Hocke, Y. Uozumi. *Tetrahedron* **2003**, 59, 619-630.
- [20] Y. Otomaru, T. Senda, T. Hayashi. *Org. Lett.* **2004**, 6, 3357-3359.

Summary

Molecular weight enlargement – a molecular approach to continuous homogeneous catalysis

Homogeneous catalysts play an increasingly important role in organic synthesis today, because of their high activity and selectivity. Usually, precious metals are used in combination with valuable ligands and since metal prices are expected to increase further in the future, methods for their efficient recycling and reuse are of utmost importance.

A range of approaches have been studied over the years, all with their own strengths and weaknesses, leading to the conclusion that one ultimate solution does not exist. This is inherently due to the vast variety of applications, each with its own specific requirements and conditions. Hence, there is a great need for the development of complementary generic methods - a toolbox for practical application. These methods can roughly be divided in biphasic catalysis and immobilization on insoluble (heterogenization) and soluble supports (molecular weight enlargement, MWE).

Molecular weight enlargement (MWE) is an attractive method for homogeneous catalyst recycling. Applications of MWE in combination with either catalyst precipitation or nanofiltration that have demonstrated their great potential as a method for process intensification in homogeneous catalysis are discussed in **chapter 1**. Selected, recent advances in MWE in combination with catalyst recovery are discussed, together with their implication for future developments. These examples demonstrate that this strategy is applicable in many different homogeneously catalyzed transformations.

In **chapter 2** a new synthetic route towards stable molecular-weight enlarged monodentate phosphine ligands *via* 'click' chemistry is described. These ligands were applied in the Pd-catalyzed Suzuki-Miyaura coupling of aryl halides and phenyl boronic acid. The supported systems show very similar activities compared to the unsupported analogues. Moreover, recycling experiments by means

of nanofiltration using ceramic nanofiltration membranes demonstrate that these systems can be recovered and reused efficiently.

Chapter 3 describes a simple and efficient approach for the molecular weight enlargement of a hydroformylation catalyst. This system has been applied for the production of aldehydes in a continuous flow nanofiltration reactor operating for an unprecedented period of up to two weeks, without showing typical deactivation or leaching phenomena. Based on a bulky, rigid and robust POSS-modified PPh_3 ligand we found that the molecular weight enlarged catalyst combines for the first time efficiently recovery with the advantages that homogeneous catalysts exhibit over heterogeneous systems, such as high activity and selectivity.

In **chapter 4**, the simple and efficient approach for the molecular weight enlargement of a hydroformylation catalyst (chapter 3) has been extended to ligands that are expected to show a better performance than PPh_3 . Besides the bidentate ligands DPEphos and Xantphos that are known for their higher regioselectivity in the Rh-catalyzed hydroformylation of 1-octene, a bulky monophosphite has been modified with POSS. In this way a very active and recyclable ligand was obtained. These ligands were applied in the continuous hydroformylation of 1-octene in the continuous flow membrane reactor. XantPOSS showed long-term stability under the conditions applied, but showed a rather peculiar regioselectivity pattern, whereas monoPOSSphite showed rapid loss in catalytic activity. In both cases, however, both Rh and P losses were extremely low.

Chapter 5 reports on the Rh-catalyzed hydroformylation of styrene. Usually, this reaction yields predominantly the chiral, branched aldehyde. An inversion of regioselectivity can be achieved by using strong π -acceptor ligands, such as diphosphites or diphosphorodiamidite ligands. Binaphthol-based ligands have been investigated spectroscopically and structurally to obtain valuable information on the coordination geometry and the electronic properties of the ligands. The ligands that perform best in the Rh-catalyzed hydroformylation of styrene were enlarged with a POSS moiety, which enables their potential application in a continuous flow membrane reactor.

The Dupont adiponitrile process is a large scale industrial process that consists of three reaction steps that are all nickel catalyzed. The isomerization of 2M3BN to 3PN is the second step in this process. In **chapter 6**, the bidentate ligands sixantphos, DPEphos, Triptycene- PPh_2 , and BIPPP were studied in the nickel catalyzed isomerization of 2M3BN to 3PN. Triptycene- PPh_2 showed the highest activity in this reaction and was compartmentalized inside a ceramic nanofiltration membrane. For the first time, the catalyst could be efficiently recycled and reused for 7 consecutive runs in this reaction. In order to maximize the catalyst retention,

POSS-enlarged ligands were applied, but the catalytic activity decreased dramatically. The 'click' dendritic monodentate ligands described in chapter 2 showed approximately the same catalytic activities as their unmodified analogues in the Pd-catalyzed Suzuki coupling reaction. Therefore attempts were undertaken to extend this synthetic strategy to bidentate ligands.

Samenvatting

Molecular weight enlargement – a molecular approach to continuous homogeneous catalysis

Homogene katalysatoren spelen tegenwoordig een steeds belangrijkere rol in de organische synthese, vanwege hun hoge activiteit en selectiviteit. Meestal worden edelmetalen gebruikt in combinatie met kostbare liganden. Naar verwachting zullen de prijzen van deze metalen verder stijgen in de toekomst, wat het belang van hun efficiënt hergebruik onderstreept.

De laatste jaren zijn er velerlei oplossingen voor het hergebruik van homogene katalysatoren onderzocht. Elke benadering heeft zijn sterke en zwakke punten, waardoor dé oplossing niet bestaat. Dit is inherent aan het enorme aantal verschillende toepassingen, elk met zijn specifieke eisen en voorwaarden. Daarom bestaat er grote behoefte aan een gereedschapskist voor praktisch gebruik - aan het ontwikkelen van complementaire, generieke methoden voor hergebruik. Deze zijn ruwweg te verdelen in tweefase katalyse en immobilisatie op onoplosbare dragers (heterogenisatie) of oplosbare dragers (moleculgewicht vergroting).

Moleculgewicht vergroting (MGV) is een aantrekkelijke methode voor het hergebruik van homogene katalysatoren. Toepassingen van MGV in combinatie met precipitatie of nanofiltratie die hun enorme potentieel tot procesintensificatie in homogeen gekatalyseerde processen hebben laten zien, worden besproken in **hoofdstuk 1**. Ook geselecteerde, recente ontwikkelingen in MGV in combinatie met het hergebruik van de katalysator worden, samen met hun implicatie voor de toekomst, hier besproken. Deze voorbeelden tonen de toepasbaarheid van deze strategie in verschillende homogeen gekatalyseerde transformaties.

In **hoofdstuk 2** wordt een nieuwe syntheseroute naar stabiele, moleculair verzwaarde, monodentaat fosfine liganden met behulp van 'click' chemie beschreven. Deze liganden zijn toegepast in de palladium gekatalyseerde Suzuki-Miyaura koppeling van arylhaliden en fenyloorzuur. De activiteit van de MGV systemen is zeer vergelijkbaar met hun ongemodificeerde tegenhangers. Bovendien laten recycling experimenten met behulp van keramische nanofiltratie membranen zien dat deze systemen efficiënt hergebruikt kunnen worden.

Hoofdstuk 3 beschrijft een eenvoudige, efficiënte methode voor MGv van een hydroformyleringskatalysator. Dit systeem is toegepast bij de productie van aldehydes in een doorstroom nanofiltratiereactor; voor het eerst was een dergelijke reactor twee weken onafgebroken in bedrijf zonder de typische deactiveringsverschijnselen van de katalysator of het weglekken van het metaal. Wij hebben voor het eerst laten zien dat een MGv katalysator, gebaseerd op een star en robuust POSS-gemodificeerd PPh_3 ligand, de voordelen van homogene systemen, zoals hoge activiteit en selectiviteit combineert met de goede recycling eigenschappen van heterogene systemen.

In **hoofdstuk 4** is de eenvoudige, efficiënte methode, beschreven in hoofdstuk 3, uitgebreid naar liganden waarvan verwacht kan worden dat ze beter presteren dan PPh_3 . Naast de bidentaat liganden DPEphos en Xantphos, die bekend staan om hun hogere regioselectiviteit in de rhodium gekatalyseerde hydroformylering van 1-octeen, is een bulky monodentaat fosfiet met POSS gemodificeerd. Op deze manier is een zeer actief en herbruikbaar ligand verkregen. Deze liganden zijn toegepast in de continue hydroformylering van 1-octeen in de doostroom membraanreactor. XantPOSS heeft een goede lange termijn stabiliteit onder de reactiecondities laten zien, maar ook een opmerkelijk regioselectiviteitspatroon. Daarentegen vertoonde MonoPOSSphite een snelle afname van de katalytische activiteit. In beide gevallen waren de Rh en P verliezen echter extreem laag.

Hoofdstuk 5 beschrijft de rhodium gekatalyseerde hydroformylering van styreen. Normaalgesproken levert deze reactie voornamelijk het chirale, vertakte aldehyde op. Inversie van de regioselectiviteit kan worden verkregen door het gebruik van sterke π -acceptor liganden, zoals difosfieten of difosfordiamidieten. Op binaftol gebaseerde liganden zijn structureel en spectroscopisch bestudeerd om waardevolle informatie over de coördinatie geometrie en de elektronische eigenschappen van de liganden te verkrijgen. De liganden die het beste presteren in de rhodium gekatalyseerde hydroformylering van styreen zijn met een POSS-eenheid vergroot, waardoor ze mogelijk kunnen worden toegepast in een doorstroom membraanreactor.

Het Dupont adiponitril proces is een grootschalig industrieel proces dat uit drie nikkel gekatalyseerd reactiestappen bestaat. De isomerisatie van 2-methyl-3-buteennitril (2M3BN) naar 3-penteennitril (3PN) is de tweede stap in dit proces. In **hoofdstuk 6** zijn de bidentaat liganden sixantphos, DPEphos, Triptyceen- PPh_2 en BIPPP in deze reactie bestudeerd, waarbij Triptyceen- PPh_2 de hoogste activiteit heeft laten zien en daarom gecompartmenteerd is in een keramisch nanofiltratie membraan. Voor het eerst is het in deze reactie mogelijk gebleken om de katalysator 7 keer achtereen efficiënt te hergebruiken. Om de retentie van de katalysator te maximaliseren zijn POSS-gemodificeerde liganden toegepast, waardoor de katalytische activiteit echter dramatisch afnam. De monodentaat 'click' liganden, beschreven in hoofdstuk 2, lieten vrijwel dezelfde katalytische activiteit in de

Pd-gekatalyseerde Suzuki koppeling zien als hun ongemodificeerde tegenhangers. Daarom zijn er pogingen ondernomen deze synthese strategie uit te breiden naar bidentaatsliganden.

Dankwoord

Het proefschrift is af, nu rest me alleen nog het meest gelezen deel. Het is duidelijk dat een promotie-onderzoek geen éénmans (éénvrouws?) onderneming is, daarom wil ik hier een aantal mensen in het bijzonder bedanken.

Allereerst mijn promotor. Dieter, bedankt dat je me als één van je aio's hebt aangenomen, voor je enorme enthousiasme voor technische chemie in het algemeen en voor continue homogene katalyse in het bijzonder, voor je geduldige uitleg als het om de vertaalslag van batch naar continue reactoren ging en voor alle discussies. In den beginne wist ik niets over rekenen aan reactoren, nu weet ik een beetje en daar heb jij een belangrijke rol in gespeeld. Dank hiervoor!

Dan Christian, mijn co-promoter. Bedankt voor je kritische blik op al mijn schrijfsels en voor het starten van het POSS project. Het heeft even geduurd, maar het is een gouden idee gebleken, dat tot mooie publicaties heeft geleid.

Dan de mannen van de Hybrid. Erik, ik heb met veel plezier het werkcollege Anorganische Chemie begeleid en op deze manier leuk met je samengewerkt. Verder dank voor je gezelligheid tijdens borrels en koffiepauzes (koffietje?). Gijsbert, heel erg bedankt voor de POSS-verbindingen die ik van je gekregen heb.

Wout, je hebt zonder twijfel meer dan gemiddeld aan mijn onderzoek bijgedragen. Zonder jouw inbreng in de vorm de membraanreactor, maar ook het stalen membraanhoudertje uit hoofdstuk 2 en 6 zou mijn proefschrift er heel anders hebben uitgezien. Bedankt hiervoor en geniet van je vrije tijd!

Laura, we hebben ongeveer anderhalf jaar samen aan het Tetraphenolproject gewerkt, en hoewel we daarvoor ook al 2 jaar in dezelfde groep werkten, heb ik je pas toen echt leren kennen en daar ben ik heel blij mee. Bedankt voor de lange, maar gezellige dagen (weken?) die we samen bij de 500 MHz NMR hebben doorgebracht. Vaak was je de enige die mijn frustraties begreep, misschien omdat jij ze net zo voelde. Ik heb veel met en van je geleerd en je hebt me met je lef, italiaans temperament en doorzettingsvermogen vaak geïnspireerd. Succes met je verdere loopbaan, je gaat het ver schoppen.

Evgeny, thanks for all the nice conversations and discussions we've had in the last five years. Your door was always open, thank you for the many tea-breaks. Apart from that, your sense of style and talent to work with complicated computer

programs (for me at least), like 3D Studio and Photoshop has led my TOC pictures, and, even more important, to the design of the cover of my thesis. All the best in the future, paranimf!

En toen was er Evert, mijn enige echte afstudeerder. Het moet echt niet altijd even makkelijk voor je geweest zijn, een begeleider in de allerlaatste fase van haar promotie-onderzoek, maar jij hebt het er met je motivatie en zelfstandigheid heel goed vanaf gebracht. Jouw werk is voor een groot deel terug te vinden in hoofdstuk 5, dank hiervoor en succes met je verdere carrière!

Dan natuurlijk met 2 roomies van de laatste bijna 2 jaar. Dennis en Jarno, bedankt voor de gezelligheid en dat ik met jullie alle opgelopen frustraties van werkcolleges, OGO's en practica kon delen. Heel veel succes met de tweede helft van jullie promotie-onderzoek! Dank ook aan Jarl Ivar, met wie ik daarvoor ongeveer een jaar het kantoor deelde. Bedankt voor je kritische blik (op alles) en voor het beantwoorden van alle "Wat is de impact-factor van....?"-vragen en voor de frisbee-avonturen. Veel succes verder in Amsterdam.

Dank ook aan mijn collega-aio's van de oude garde: Bart, Leandra, Patrick en Katharina. Bedankt voor alle gezellige conferentie-bezoeken en voor de leuke tijd in Eindhoven. Succes met jullie verdere loopbaan!

Arjan en Coen, partners in crime in Nijmegen, bedankt voor alles de afgelopen jaren, wat meestal resulteerde in, of samenging met het nuttigen van de nodige speciaal biertjes. Uiteindelijk heeft het lot ons weer samengebracht in Eindhoven. Arjan, veel succes met het afronden van je proefschrift en Coen, veel plezier met je postdoc.

Zeer veel dank gaat uit naar de (mede-)borrelcommissie uit heden en verleden. Gilbère, Jarno, Andreas, Thijs, Dilip, Arjan en Jos, dank voor jullie goede zorgen op de vrijdagmiddag en aan alle regelmatige deelnemers aan de borrel voor de gezelligheid en aan alle SKA-leden die moeite deden om de goede sfeer in de groep goed te houden, door middel van het jaarlijkse uitje en andere spontane activiteiten.

Ton, bedankt voor al je hulp bij de apparatuur op het lab, met name voor je goede zorgen voor de GC's. Adelheid, bedankt voor je hulp bij alle ICP-analyses.

Lots of luck to the new generation PhD students: Leen, Sabriye, Andreas, Alberto and Atila.

Graag wil ik ook mijn schoonouders Sjef en Rina en mijn schoonzusje Marleen bedanken voor hun interesse en de gezellige etentjes. Verder wil ik mijn oma en de rest van de Janssen-clan bedanken voor de leuke weekendjes in Mol.

Zonder de steun van mijn ouders was ik nooit zover gekomen. Pap en mam, bedankt hiervoor! Verder wil ik mijn vader bedanken voor zijn hulp bij de Nederlandse vertaling van de samenvatting van dit proefschrift. Mijn zusje Melanie wil ik graag

bedanken voor onze gezellige shop-avonturen en voor het feit dat je op de openbare verdediging van dit proefschrift naast me staat als paranimf.

Als allerlaatste wil ik Jos bedanken. Het lijkt nog zo kort geleden dat ik bij jou mijn bijvakstage kwam lopen. Van jou heb ik ècht Schlenk techniek geleerd en ook hoe je met ècht gevaarlijke substanties als HCN kunt werken. Bedankt voor al je hulp met de verbeteringen aan de membraanopstelling, mede door jou zitten we nu niet meer op versie 1.0. Bedankt voor je inzet en inzicht, voor alle manuscripten die je als eerste hebt gelezen en gecorrigeerd, voor je raad en advies (Focus!). Bedankt dat je al jaren mijn geliefde en mijn maatje bent, dat je zonder klagen mijn kook-experimenten ondergaat en opeet. Ik denk dat we zowel qua werk als privé een heel goed team zijn en ik kijk uit naar een mooie toekomst met jou.

Scientific publications

Publications of the work described in this thesis:

M. Janssen, J. Wilting, C. Müller, D. Vogt

POSS-enlarged PPh₃ in the continuous hydroformylation of 1-octene

Submitted for publication

M. Janssen, C. Müller, D. Vogt

Molecular weight enlargement – a molecular approach to continuous homogeneous catalysis

Dalton Transactions, 2010, accepted for publication

M. Janssen, C. Müller, D. Vogt

‘Click’ dendritic ligands: design, synthesis, application in Suzuki coupling and recycling by nanofiltration

Adv. Synth. Catal. **2009**, 351, 313

Other publications:

L. Bini, M. Janssen, B. Hamers, C. Müller, R. Franke, D. Vogt

Application of tetraphenol based diphosphites in the hydrocyanation of 3-pentenitril

Submitted for publication

M. Janssen, L. Bini, B. Hamers, A. Christiansen, D. Hess, R. Franke, C. Müller, D. Vogt

Synthesis of tetraphenol based diphosphites and their application in the hydroformylation of octenes

Tetrahedron Lett. **2010**, 51, 1971

J.I. van der Vlugt, M.A. Siegler, M. Janssen, D. Vogt, A.L. Spek

A Cationic Ag^I(PNP^{tBu}) Species Acting as PNP Transfer Agent: Facile Synthesis of Pd(PNP^{tBu})(alkyl) Complexes and Their Reactivity Compared to PCP^{tBu} Analogues

Organometallics **2009**, 28, 7025

J. Wilting, M. Janssen, C. Müller, M. Lutz, A. Spek, D. Vogt
Binaphthol based diphosphite ligands in asymmetric hydrocyanation of styrene and
1,3-cyclohexadiene: influence of steric properties
Adv. Synth. Catal. **2007**, 349, 350

Wilting, M. Janssen, C. Müller, D. Vogt
The enantioselective step in the nickel catalyzed hydrocyanation of 1,3-
cyclohexadiene
J. Am. Chem. Soc. **2006**, 128, 11374

Curriculum Vitae

Michèle Janssen was born on October 31st 1981 in Geleen, The Netherlands. In 2000 she graduated from S.G. Groenewald in Stein. In the same year, she started her Chemistry studies at the Radboud University Nijmegen, where she obtained her Master's degree in 2006. She did her major in synthetic organic chemistry, in part in the group of prof. Carmen Carreño at Universidad Autónoma de Madrid, Spain, and in part in the group of dr. Floris van Delft and prof. Floris Rutjes at the Radboud University Nijmegen. She did her minor in the group of prof. Dieter Vogt at Eindhoven University of Technology on the nickel-catalyzed asymmetric hydrocyanation of dienes and vinylarenes. In 2006 she started her PhD research on molecular weight enlargement of homogeneous catalysts and their application in continuous processes in the same group, which has resulted in this thesis.

Michèle Janssen werd geboren op 31 oktober 1981 in Geleen. In 2000 behaalde ze haar VWO diploma aan S.G. Groenewald in Stein en begon ze haar Scheikunde studie aan de Radboud Universiteit Nijmegen, waar ze in 2006 haar diploma behaalde. Ze deed haar hoofdvakstage in de synthetische organische chemie, voor een deel in de groep van prof. Carmen Carreño aan de Universidad Autónoma de Madrid, Spanje, en voor een deel in de groep van dr. Floris van Delft en prof. Floris Rutjes aan de Radboud Universiteit Nijmegen. Ze deed haar bijvakstage in de groep van prof. Dieter Vogt aan de Technische Universiteit Eindhoven aan de nikkel gekatalyseerde asymmetrische hydrocyanering van diënen en vinylarenen. In 2006 begon ze haar promotieonderzoek in dezelfde groep op het gebied van molecuulgewicht vergroting van homogene katalysatoren en hun toepassing in continue processen, wat geleid heeft tot dit proefschrift.