CHIRAL PHANEPHOS DERIVED CATALYSTS AND THEIR APPLICATION IN ASYMMETRIC CATALYSIS

Tina Maria Konrad

A Thesis Submitted for the Degree of PhD
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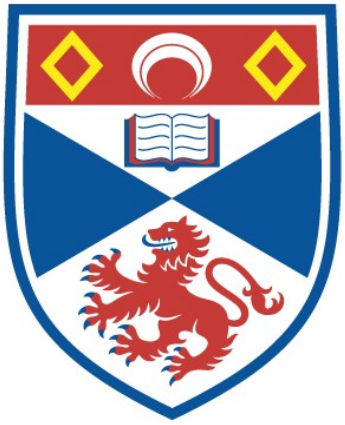

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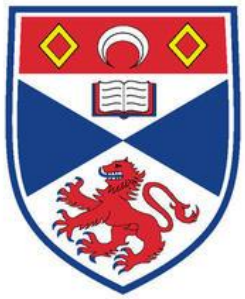

Chiral phanephos derived catalysts and their application in asymmetric catalysis

Tina Maria Konrad

In application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

September 2012

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I, Tina Maria Konrad hereby certify that this thesis, which is approximately 59.500 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in September 2008 and as a candidate for the degree of PhD in September 2008; the higher study for which this is a record was carried out in the University of St Andrews between 2008 and 2012.

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Auch aus Steinen

die einem in den Weg

gelegt werden,

kann man Schönes bauen.

(Johann Wolfgang von Goethe)

CONTENTS

CHAPTER I

Homogeneous and Heterogeneous Catalysis

Abstract *Chapter I* is divided into 2 main parts, beginning with a brief overview of carbonylation reactions and the importance of this type of reactions in industrial processes. A summary is given about the best Pd monophosphine and diphosphine systems for asymmetric hydroxy- and alkoxy-carbonylation reactions for aryl alkenes. Furthermore, studies evaluating the effect of various promoters on the styrene hydroxycarbonylations with Pd phosphine systems are reviewed.

The second part of this *chapter* shortly outlines different methodologies of immobilisation of homogeneous catalysts onto solid supports. Immobilisation by ionic interactions is a simple and facile method for heterogenising homogeneous catalysts and will be reviewed in more detail with the emphasis on ion-exchange resins.

1.1 Introduction

Catalysis is a key technology, enabling difficult reactions with high activation energy to be carried out under milder conditions, allowing energy savings or new transformations to be carried out. Enzymes were the first catalysts developed by nature over thousands of years. Generally catalysts can be divided into 3 main categories: enzymes, heterogeneous catalysts and homogeneous catalysts.

For around a century the chemical industry started using heterogeneous catalysts for producing compounds that nature did not provide. Heterogeneous catalysts are thermally stable, easy to separate and prepare, and can have long life times, but selective tuning of the catalyst species faces major drawbacks.[1] Homogeneous catalysts on the other hand can prepare individual well defined molecules, with a variety of ligands surrounding a metal center, therefore allowing each catalyst to be tailored for each reaction.[2] These molecularly designed homogeneous catalysts show astonishing synthetic possibilities combined with impressive selectivity. Its potential is reflected by 3 Nobel prices during the last decade (2001: W. Knowles, R. Noyori, B. Sharpless; 2005: Y. Chauvin, R. Grubbs, R. Schrock; 2010: R. Heck, E. Negishi, A. Suzuki). Homogeneous organometallic catalysis is applied in a few large scale bulk/commodity chemicals but is particularly suited for high value commodity, agrochemical and pharmaceutical products.

Homogeneous catalysis plays a more vital role in fine and speciality chemical production for the pharmaceutical and agrochemical market and is one of the most efficient and important methods in chemical synthesis. Due to high activity and selectivity asymmetric synthesis is largely dominated by homogeneous catalysis using organometallic catalysts.[3]

To be useful, a catalyst must be highly active, productive and chemo-, regio- and stereo-selective. A particularly appealing feature of homogeneous catalysts lies in their ease of tuning the coordination sphere of the metal, by simply changing the ligand properties. Modifications can have a major influence on the activity and selectivity towards certain products. Fine-tuning of the ligand is carried out by systematically changing the structure through their electronic and steric properties, as well as in changing their coordination mode. These changes affect the bond between the transition metal and substrate and therefore can alter activity, productivity and selectivity. In addition characterisation of the molecular catalysts is a convenient task by NMR spectroscopy (^{1}H, ^{13}C, ^{31}P and high pressure NMR for detecting active species during

catalysis),[4] IR spectroscopy (high pressure experiments), mass spectroscopy, X-ray single crystal determination, elemental analysis, EXAFS (extended X-ray absorption fine structure spectroscopy) and cyclic voltammetry.

Homogeneous catalysis is unfortunately also combined with costs associated with not only the loss of precious catalyst and the purification of the products but also the management of waste. All these factors can have a significant impact on the environment, as well as overall process costs; therefore organometallic catalysis can sometimes be too expensive to operate for certain low value products.

Heterogeneous catalysts have been preferred for bulk chemical industry due to practical benefits, such as separation and whereas qualities of homogeneous catalysts lie in their activity and tune-ability, merging these two worlds together would certainly be of great significance for catalytic processes in industry. By doing so, one could achieve higher process efficiency and selectivity with economically viable applications, creating an "ideal" catalyst system. As amazing as all this sounds, achievements of such economically and environmentally valuable catalysts are yet to be made. Over decades, a wide range of different immobilisation methods have been proposed, developed and tested with the aim of making easily separable molecular catalysts.[5] However, only a handful of examples of immobilized catalysts were found good enough for industrial applications.

The research presented in this thesis is a project funded by the EU-network of the Marie Curie project NANO-HOST in collaboration with partner institutes. The aims of this network are to develop innovative methods for the preparation, recovery and reuse of single-site, nanostructured catalytic materials, and further on apply them in combination with specifically engineered reactors for a sustainable production process for making high value fine chemicals.

One part of this project was to prepare chiral diphosphine ligands and their complexes for currently challenging reactions, such as asymmetric carbonylations (homogeneous catalysis). Catalytic studies of these chiral diphosphine ligands were carried out in asymmetric hydroxy-and alkoxy-carbonylations and hydrogenation reactions. The second part of this project was the heterogenisation of these chiral homogeneous complexes through collaborations with the network partners and furthermore their catalytic behavior was studied.

Chapter I mainly focuses on the recent developments in homogeneous palladium catalysed carbonylation reaction of styrene derivatives, with the main emphasis on asymmetric hydroxy- and methoxy-carbonylations, summarising the mechanistic details

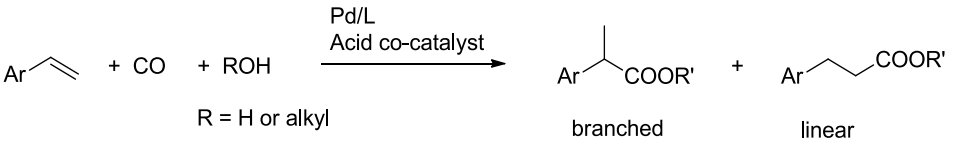
and important facts about the impact of acid/counter anion. This provides an introduction to the research on new chiral catalysts for asymmetric carbonylation reactions in *chapter II*.

At the end of this *chapter* a short overview of heterogeneous catalysis will point out the advantages of the chosen support methods used throughout *chapter III*.

1.2 Carbonylation reactions

Transition metal catalysed carbonylation reactions are important C-C bond formations that originate from the 1940's with the discoveries of Walter Reppe, who used a $[Ni(CO)_4]$ catalyst to react acetylene, carbon monoxide and water to form acrylic acid. [6] Ever since, carbonylation reactions, such as alkene hydroformylation ("oxo" synthesis)[7], methanol carbonylation, copolymerization, alkene hydroxy- and alkoxy-carbonylations[8] have received considerable attention and are nowadays among the largest scale chemical processes, making them a valuable tool for functionalising olefins in order to obtain valuable compounds.

Hydroxy- and alkoxy-carbonylations of alkenes and alkynes are useful ways to form carboxylic acids and their esters by combining alkenes or alkynes with CO and water or an alcohol (Scheme 1). Selective formation of either the branched or linear products can be conducted, depending on the olefin and catalytic system (metal + phosphine ligand). Among different catalytically active metals, mainly palladium catalysts have been found to allow hydroxy- or alkoxy-carbonylation reactions to proceed under mild conditions with satisfactory activity. Today's most active and selective catalyst systems used for alkene hydroxy- and alkoxy-carbonylation are based on palladium combined with phosphine ligands and an acidic co-catalyst.



Scheme 1 Hydroxycarbonylation (R' = H) or alkoxycarbonylation (R' = alkyl, aryl) of olefins.

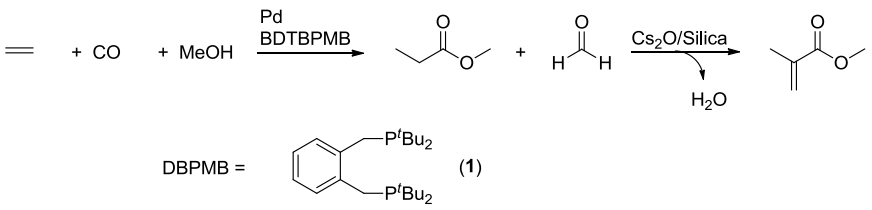
Many papers and patents were published over the years about hydroxy- and alkoxy-carbonylations, showing the latter to have more widespread use as they can be

conducted under milder reaction conditions, but also spurred by an industrial demand for synthesising methyl propionate from ethylene and methanol.

Early catalysts for olefin alkoxycarbonylation contained monophosphine ligands, such as classic palladium systems e.g. $[PdCl_2(PPh_3)_2]$. These complexes gave high yields of 2-arylpropionic acids derivatives combined with good selectivities towards the branched acid.[9]

Soon the potential of bidentate ligands was discovered resulting in higher acitivity and selectivity. In particular, 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DBPMB, (**1**)) was found to be quite outstanding for alkoxycarbonylation reactions of ethylene and higher olefins, providing higher activity and selectivity than any monophosphine ligand.

One of the most important processes (in 2005 estimated production of 2.1 million metric tonnes), involving ligand DBPMB (**1**) in the methoxycarbonylation of ethylene, is Lucite's "Alpha" process.[10] Methyl methacrylate (MMA) is a bulk chemical, used as the monomer for the production of polymethyl methacrylate (pMMA) an acrylic plastic (brand name Perspex or Lucite). The alpha process involves 2 steps: 1) Methoxycarbonylation of ethylene to methyl propanoate (MeP) using a Pd diphosphine catalyst (DBPMB, 1,2-bis(di-*tert*-butylphosphinomethyl)benzene); 2) additional aldol condensation of MeP with formaldehyde followed by elimination of water over a heterogeneous catalyst (Cs_2O on silica), with water as by-product making this process outstanding (Scheme 2).



Scheme 2 Alpha Process for MMA production.

Hydroxy- and alkoxy-carbonylations of vinylarenes are of great importance and were extensively studied over the last 30 years, due to their attractive synthetic approach to α-aryl-carboxylic acids that are pharmaceutically active compounds, such as common non-steroidal anti-inflammatory agents, but are also useful chiral building blocks (Figure 1).[9b, 11] In only one step they can deliver carboxylic acid derivatives with almost no waste products. Regioselectivity towards the branched isomer when vinyl-arenes were used as substrates differ from alkyl olefins that tend to favour the production of linear acids.

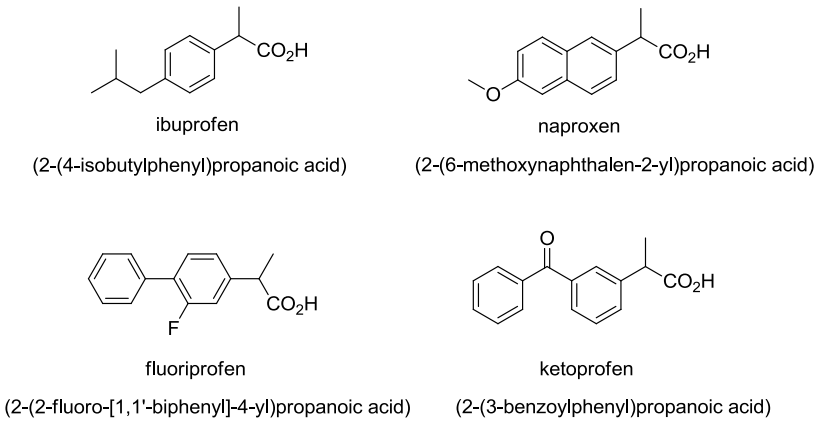
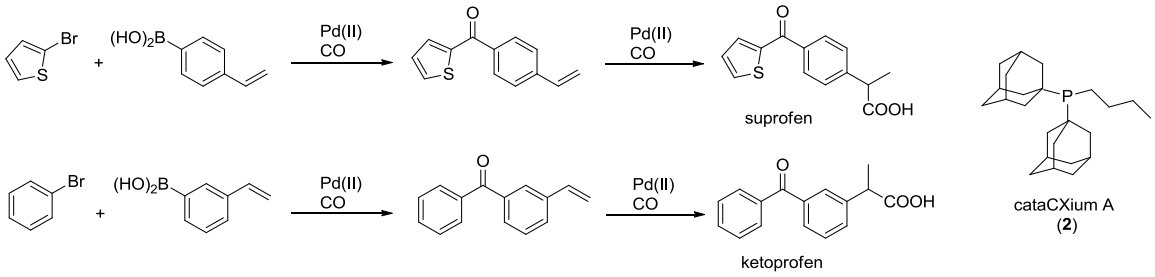


Figure 1 Important profen 2-aryl propionic acids.

Beller and co-workers were able to achieve excellent selectivity for the anti-inflammatory drugs ketoprofen and suprofen using a sequential double carbonylation reaction.[12] By a one-pot carbonylative Suzuki coupling reaction and hydroxycarbonylation the branched product was obtained in 94% yield, using the catalyst $Pd(OAc)_2$ with di-1-adamantyl-*n*-butylphosphane (cataCXium®A, (**2**)) (Scheme 3). [12]



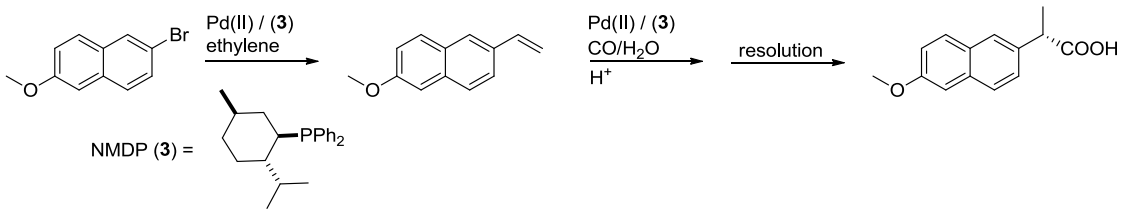
Scheme 3 One-pot synthesis of suprofen and ketoprofen by sequential Suzuki carbonylation and hydroxycarbonylation.

Palladium catalysed hydroxy- and methoxy-carbonylations of styrene have for years left the notion that bidentate diphosphine ligands yield preferably the linear regioisomer, whereas monophosphine ligands have been found to favour the branched isomer.[13]

Tanaka and coworkers recently reported that, in contrast to most diphosphines, a bulky diphosphine-palladium catalyst system, derived from (**1**), gave excellent selectivity in methoxycarbonylation favoring the branched products, obtaining a B/L ratio of 8.1 (B:L = 8.1:1) and 99% yield (Scheme 2).[14] Attempts to enhance the catalytic performance via minor changes of the phosphine ligand resulted in a drastic loss of regio- and chemo-selectivity.

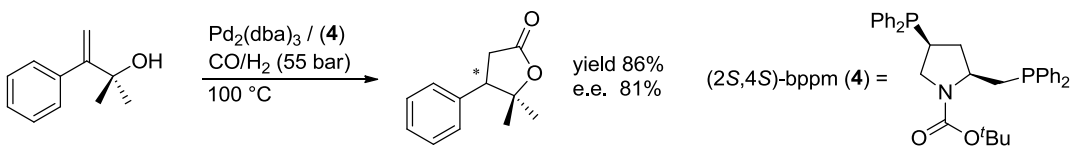
Despite the activity and selectivity for the formation of the branched isomer, enantioselective hydroxy- and alkoxy-carbonylations have been less successful. An optimised process that produces enantioenriched aryl carboxylic acids would certainly be valuable and could be of commercial significance.

There are different synthetic pathways to chiral propanoic acids, although none of them allows a straight forward and an atom-efficient system as an enantioselective hydroxycarbonylation could provide. The clinically used drug (*S*)-Naproxen, for example is prepared by the Abermarle Company starting from 2-bromo-6-methoxynaphtalene by a Heck reaction to form the vinylnapthalene, followed by a palladium catalysed hydroxycarbonylation, with additional resolution of the enantiomers.[11a] The branched acid is generated as the only product by using $PdCl_2$ with the monophosphine ligand neomenthyldiphenylphosphine NMDP (**3**) and acidic co-catalyst (Scheme 4).[15]



Scheme 4 Abermarle process: (*S*)-Naproxen synthesised from 2-bromo-6-methylnaphtalene by a Heck reaction followed by palladium catalysed hydroxycarbonylation.

It is worth noting that another approach towards enantio-enriched aromatic carboxylic acids could be through enantioselective hydroformylation of styrene.[7, 16] Styrene hydroformylation has been found to give great stereoselectivity in terms of high branched ratios and enantiomeric excess, but a drawback is the requirement for further oxidation of the chiral aldehydes to the desired carboxylic acids, generating more waste. Among the variety of methods developed to synthesise chiral aryl propionic acids, an enantioselective version of hydroxy-and alkoxy-carbonylations would certainly offer a simple and atom efficient route towards enantioenriched carboxylic acids and esters in one step.



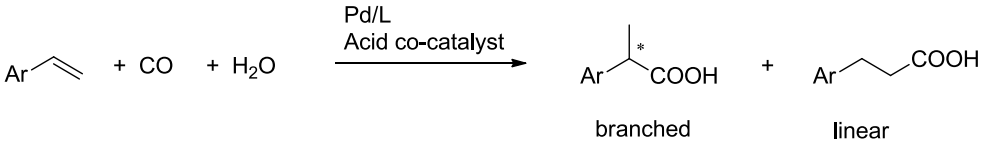
Scheme 5 Intramolecular asymmetric carbonylation reaction.

Interestingly, intramolecular carbonylation reactions have been found to be very selective, giving optically active lactones. Enantiomeric induction by the chiral diphosphine ligand butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine ((-)-(2*S*,4*S*)-bppm) (**4**) was observed to be very active and selective towards chiral lactones (Scheme 5). Further Pd/phosphine systems have been reported to be useful for the selective preparations of different ring sized lactams.[17]

1.2.1 Asymmetric hydroxycarbonylation of vinylarenes

Hydroxycarbonylation of alkenes is a useful way for obtaining a mixture of linear and branched carboxylic acids by combining alkenes with CO and water in the presence of a palladium system (using mono- or bi-dentate phosphine ligands) and an acidic co-catalyst.

As mentioned earlier, styrene derivatives are among the most studied substrates in hydroxycarbonylation, due to their potential for the simple and atom efficient preparation of enantioenriched 2-aryl propionic acids (Scheme 6).



Scheme 6 Palladium catalysed hydroxycarbonylation of prochiral aryl alkenes.

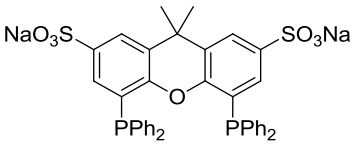
It is common knowledge that the catalytic efficiency of a palladium/phosphine system is dependent on several factors such as, pressure, temperature, reaction medium, the electronic and steric properties of the phosphine ligand, bite angle of diphosphine ligand and the acid co-catalyst. Over the last 30 years different palladium phosphine systems with variations in their electronic and steric properties have been tested but there are still many limitations.[13] Many reports with different catalytic systems have been investigated in order to understand the mechanism and design better catalysts. Unfortunately differences in palladium precursors, acid co-catalysts and reaction conditions do not allow a methodical comparison of all these results. Only some of this data can be used to assemble generally useful information.

Most of the already existing methodologies need very high pressure of carbon monoxide, high temperatures and/or high concentrations of inorganic acids, salts and co-catalysts.[18] Additionally the control of regioselectivity can be problematic and

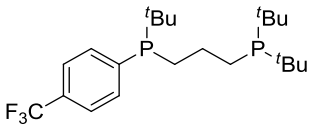
synthetically useful enantioselectivity was achieved for the first time in the studies reported in *chapter II*. The regioselectivity of styrene hydroxycarbonylation was found to be controlled well by modifying the auxiliary phosphorus ligand applying the general norm that monodentate ligands give branched carboxylic acids as the major product and bidentate ligands favor the linear isomer.

Although diphosphine ligands usually result in lower selectivity and activity in styrene hydroxycarbonylation, chiral diphosphines have a strong track record in asymmetric catalysis, and hence developments are eagerly anticipated. To obtain similar yields in alkene carbonylation, diphosphine ligands generally require more severe reaction conditions compared to monophosphine systems. Several diphosphine ligands were studied under different conditions and the most interesting results obtained are discussed and summarised below. The tuneability of P-ligands as well as their well known coordinating capacity towards late transition metals makes them valuable ligands in homogeneous catalysis. Ligand effects can have a great influence onto various reaction parameters, such as activity, chemo- and stereo-selectivity. The *cone*- and *bite-angle* properties of phosphines have been extensively studied.

The importance of the influence of acidic co-catalysts will be discussed in more detail below, whereas the impact of changes to the phosphine properties will be explained in *chapter II*.



(**5**)



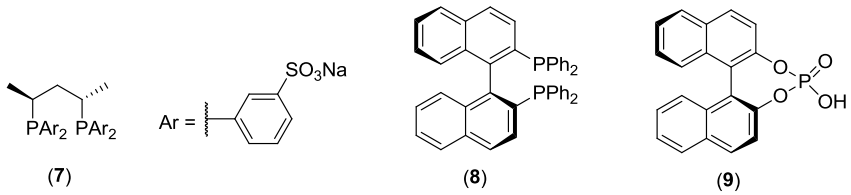
(**6**)

Figure 2 Diphosphine ligands examined in hydroxycarbonylation reactions.

First developments for regioselective hydroxycarbonylation with diphosphine ligands were approached by using dicationic water soluble palladium xanthenes type (**5**) in water without the addition of any organic solvents**,** resulting in a poor B/L ratio of 0.5 and moderate conversions (Figure 2).[19]

Clarke and coworkers achieved excellent regioselectivity with bidentate ligands by preparing a racemic bulky fluorinated diphosphine (**6**). These novel ligands did not only give high yields, but also the highest B/L ratio (76.0) reported so far for hydroxycarbonylation reactions with diphosphines under such mild reaction conditions.

Introducing very bulky, electron donating groups has a great influence on the catalytic activity and product selectivity.[20]



(**7**) (**8**) (**9**)

Figure 3 Chiral diphosphine ligands used in asymmetric hydroxycarbonylation of styrene and styrene derivatives.

The best diphosphine reported gave 43% e.e. and moderate selectivity of 0.8 towards the branched isomer applying a chiral sulfonated (2*S*,4*S*)-bis(diphenylphosphino)pentane ((*S*,*S*)-BDPPTS) (**7**).[21] The reaction was carried out in water with no addition of organic solvents. Furthermore this catalyst could be recycled twice with no loss of activity, regio-and enantio-selectivity in the second cycle.

Another Pd/phosphine system in asymmetric hydroxycarbonylation with palladium and (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl ((*S*)-BINAP) (**8**) could achieve 11% e.e. with poor B/L ratio (0.4) and moderate conversion (42%).[18a] (Figure 3)

Whilst development of catalytic regioselective hydroxycarbonylation has rendered a high selectivity towards the branched product, highly enantio- and regio-selective control of aryl olefins still remains a huge challenge. In Table 1 more experimental details are summarised about the catalysis conditions of ligand (**5**)-(**9**).

Table 1 Summary of catalytic condition of hydroxycarbonylation of styrene and derivatives.

Phosphine (P)	Pd (mol%)	P/Pd	Acid (mol%)	Promotor (mol%)	Time (h)	Temp (°C)	Conversion (%){acid}	B/L
(**5**)	15.8	1	17	-	3	70	81{81}	0.5
(**6**)	1	1	20	20 LiCl	16	120	84{84}	76
(**7**)	1.6	2	3.2	-	16	100	98{98}	0.8
(**8**)	1.6	10	100	-	24	150	42{42}	0.4
(**9**)	13	0.38	15	2 $CuCl_2$	18	r. t.	64{64}	b

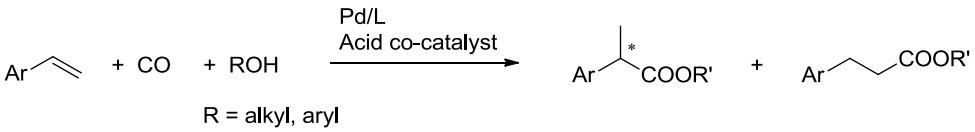
The reactions were carried out under 30 bar CO and *p*-TsOH was the acid, unless otherwise stated. (**7**) Acid used was HCl, 20 bar; (**8**) Oxalic acid, 20 bar CO pressure; (**9**) HCl as acid, 1 bar CO and O_2 bubbled through solution.

Only few examples of asymmetric hydroxycarbonylation have been reported. To date only one monophosphine ligand has been published about inducing stereoselectivity and only a handful of chiral diphosphine ligands have been reported to do so.

Excellent enantioselectivity has been reported by Alper and coworkers using (*S*)-(+)-1,1'-binapthyl-2-2'-diyl hydrogen phosphate ((*S*)-BNPPA) (**9**) as chiral ligand for hydroxycarbonylations of 2-vinyl-6-methoxynaphtalene and *p-iso*butylstyrene.[18d] This unusual catalyst yielded 64% of pure branched product with a high optical yield of 91%, with the disadvantage that over 10% catalyst loading was required. However, other research groups have been unable to reproduce these reactions. It is noted that the optical rotation was used to measure the e.e. of the carboxylic acid and binaphtyl ligands have unusually high values of $[\alpha]_D$, so the phosphonic acid catalyst may have contaminated the result.

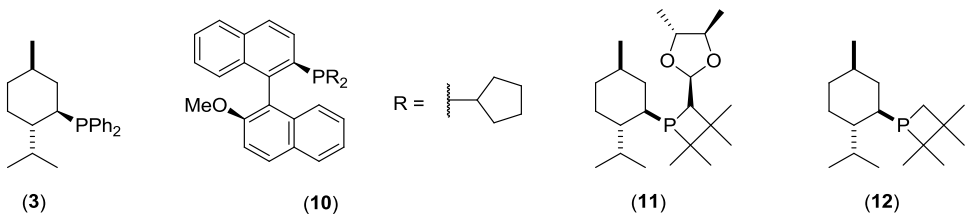
1.2.2 Asymmetric alkoxycarbonylation reaction of vinylarenes

Even though alkoxycarbonylation reactions have been studied in much greater detail compared to the related hydroxycarbonylation reactions, simultaneous control of regio- and enantio-selectivity still continues to pose a major challenge. The alkoxycarbonylation is closely related to the aforementioned hydroxycarbonylation, using CO and alcohol as the nucleophile, towards optically active compounds (Scheme 7).



Scheme 7 Asymmetric alkoxycarbonylation of styrene and derivatives.

In the palladium catalysed alkoxycarbonylation of styrene, attempts have been made to achieve regio- and stereo-selectivity but catalytic systems providing both excellent regio- and enantio-selectivity have not yet been realised.



(**3**) (**10**) (**11**) (**12**)

Figure 4 Chiral monophoshine ligands used in asymmetric methoxycarbonylation of styrene.

Potentially useful catalytic systems have been found using bulky chiral monophosphines as monodentate ligands. As early as 1982 Cometti and Chiusoli demonstrated that the use of NMDP (**3**) introduces stereoselectivity in Pd catalysed methoxycarbonylation of styrene, with a B/L ratio of 15.6 and an enantioselectivity of 52 % (Figure 4).[22]

About 20 years later Nozaki and coworkers reported a chiral binapthol derived ligand (*S*)-2-dicyclopentylphosphino-2'-methoxy-1,1'-binapthyl (**10**) for the methoxycarbonylation of 2-methoxy-6-vinylnapthalene, giving 53 % e.e. with branched 2-arylpropionic esters as the only product.[23] This result represents so far the best reported combination of enantio- and regio-selectivity achieved using monophosphine ligands.

Later studies on monodentate phosphetane ligands by Claver and coworkers found highly hindered chiral four membered ring system to give a great B/L ratio of 32 as well as a moderate e.e. of 29 % using ligand (**11**) for the methoxycarbonylation of styrene.[24] Slightly changing the nature of the substrate, the e.e. for 4-methoxystyrene could be improved up to 50 % with ligand (**12**) although chemoselectivity was poor of 71 % conversion, only 21 % was ester formation (Figure 4). More details of the individual catalysis conditions of monophosphine ligand (**3**), (**11**) und (**12**) are displayed in Table 2.

Table 2 Methoxycarbonylation of styrene derivatives using monophosphine ligands.[a]

Phosphine (P)	Pd (mol%)	P/Pd	Acid (mol%)	Promotor (mol%)	Time (h)	Temp (°C)	Conv. (%)[25]	B/L
(**3**)	0.5	3	56	-	4	50	>99{>99}	15.6
(**11**)	0.5	2	30	-	24	70	26{94}	32
(**12**)	0.5	2	10	-	24	60	71{21}	16

[a] The reactions were carried out under 30 bar CO and *p*-TsOH was the acid, unless otherwise stated. (**3**) CF_3CO_2H and 1bar CO pressure. (**12**) Pressur of CO was 35 bar.

Generally diphosphines have been found to allow better control of stereoselectivity than monophosphines. They are expected to have more restricted conformational flexibility and therefore believed to be more successfully employed in asymmetric reactions. Tuning of these steric and electronic properties might lead to optimised enantio- and regio-selectivity.

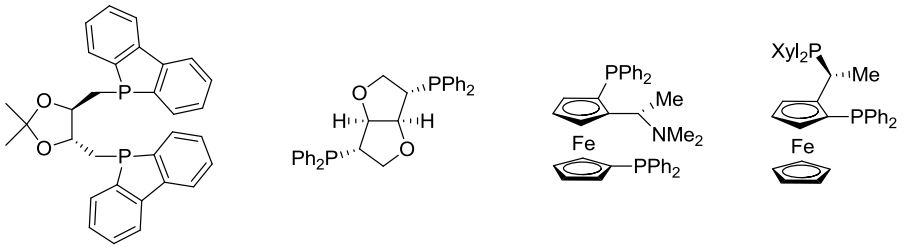
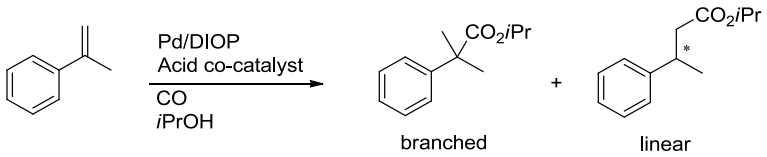


Figure 5 Various chiral diphosphine ligands which were examined in asymmetric alkoxycarbonylation reactions of styrene and derivatives.

A few successful chiral systems have been reported for the asymmetric alkoxycarbonylation of styrene and its derivatives, the greatest obtained results in regioselectivity combined with enantioselectivity are described below.

One of the first results inducing chirality by diphosphine ligands was reported by Hayashi and coworkers for *iso*-propoxycarbonylation of α-methylstyrene (Scheme 8).[26] By using an analogue of the well known (*S*,*S*)-DIOP ligand (**13**), the linear isomer was obtained with low selectivity of a B/L ratio of 8.1, however in this example the linear isomer is the chiral molecule, with an enantiomeric excess of 44 % (Figure 5).



Scheme 8 Asymmetric *iso*-propoxycarbonylation of α-methylstyrene.

Excellent asymmetric induction and good regioselectivity has been obtained using a $PdCl_2$-$CuCl_2$ system with chiral phosphines, 1,4:3,6-dianhydro-2,5-dideoxy-2,5-bis(diphenylphosphino)-L-iditol (**14**). Conversions of up to 96 % in 24 h were obtained for the methoxycarbonylation of styrene, with a B/L ratio of 26.6 and an exceptional optical yield of 99 %.[27] Achieving such great overall results, it is surprising that no further research concerning this catalyst has been undertaken. In the related alkoxycarbonylations of norbornene, good results were also claimed with this ligand that could not be repeated in a recent study by Claver and co-workers.[28] More experimental data of ligand (**14**)-(**16**) is summarised in more detail in Table 3.

Investigating stereocontrol by testing different types of chirality, such as central, axial and planar chirality (according to Cahn Ingold Prelog), the asymmetric ferrocenyl derived diphosphine ligand, (*R*)-*N*,*N*-dimethyl-1-[(*S*)-1',2-

bis(diphenylphosphine)ferrocenyl]ethylamine ((*R*, *S*)-BPPFA) (**15**) was reported to induce a promising e.e. of 87 %. (Figure 5) However, poor B/L ratio 0.8 and conversions were achieved with this catalyst system.

Slightly worse results in stereoselectivity could be obtained by Inoue and coworkers using the same chiral ligand (**15**), with a decrease in B/L ratio to 0.4 and lower optical yield of 63 %.[29]

Another chiral ferrocenyl phosphine ligand, Josiphos (**16**)**,** has been tested in asymmetric methoxycarbonylation. This ligand combines planar and central chirality in one diphosphine. This palladium catalyst system provides high enantioselectivity (86 % e.e.) and improved conversions (75 %), with main drawback of low selectivity towards the branched isomer (B/L = 0.2).[18b]

Table 3 Summary of asymmetric alkoxycarbonylations of styrene and derivatives carried out with various chiral diphosphine ligands.

Phosphine (P)	Pd (mol%)	P/Pd	Acid (mol%)	Promotor (mol%)	Time (h)	Temp (°C)	Conv. (%)	B/L
(**14**)	1.8	3	-	2.3 $CuCl_2$	24	80	96{96}	26.6
(**15**)	5	1	10	-	20	80	>99{>99}	0.4
(**16**)	1	1.1	100	-	24	150	78{75}	0.2

The reactions were carried out under 30 bar CO and *p*-TsOH was the acid, unless otherwise stated. (**14**) 50 bar CO. (**15**) 125 bar CO.

The catalysis conditions of different mono- and di-phosphine ligands for hydroxy- and methoxy-carbonylations are displayed in Table 1-3. In almost all cases high percentages of catalyst loading and acid promoters are necessary. When diphosphine ligands are used high temperatures and long reaction hours are often required to give reasonable activity. Thus, there is a strong need for catalytic systems that use lower or no added co-catalysts at all and would have the advantage for recycling.

1.2.3 Mechanism

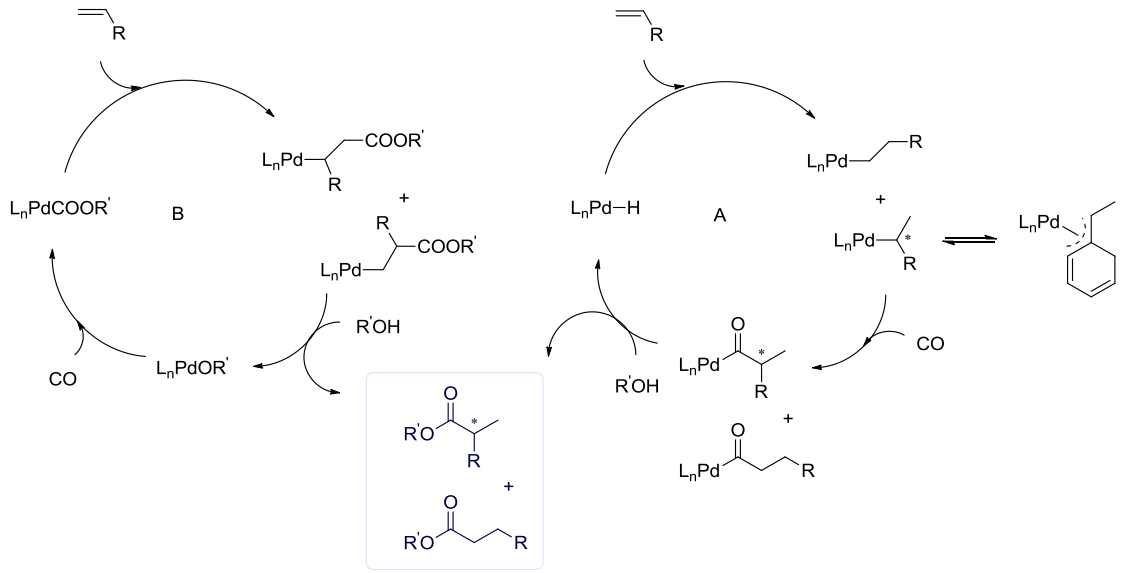
1.2.3.1 Alkoxycarbonylation mechanism

The mechanism for alkoxycarbonylation of styrene has been proposed to proceed via two possible cycles. The catalytic cycle are considered to either start from a “hydride” or “alkoxide” species, although data for either cycle has been reported using kinetic studies, ab intio calculations, deuterium labeling experiments, X-ray diffraction and NMR studies

and characterizing significant intermediates, the "hydride" mechanism is generally more accepted for styrene carbonylation reactions.[13, 30]

In the "hydride" pathway the alkene inserts into a Pd-H bond, forming the palladium-alkyl complex, coordination and migratory insertion of CO produces a metal-acyl species. Alcoholysis of the Pd-acyl complex leads then to the ester formation regenerating the Pd-H species (Scheme 9, Cycle A). Alternatively, in the "alkoxide" mechanism insertion of the alkene into the "Pd-COOR" takes place, followed by alcoholysis for ester formation, regenerating the alkoxy-metal species by CO insertion (Scheme 9, Cycle B).

Even though most researchers agree that the "hydride" is the operating mechanism, the individual catalytic species found did so far not exclude the "alkoxide" mechanism, since it is only in ethene carbonylations that detailed studies have been done.[9b, 11b, 31]



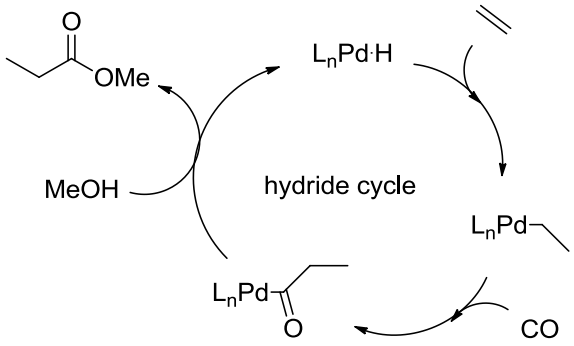
Scheme 9 Proposed mechanism for alkoxycarbonylation: A) "hydride" mechanism B) "alkoxide mechanism.

When the substrate is a vinylarene, a very important aspect of this cycle is the thermodynamic stability of the transition metal benzylic complex, which might be one of the main factors deciding regioselectivity (Scheme 9, Cycle A).[32]

Musco and coworkers have determined the structure of such a palladium η^3-benzyl complex by X-ray diffraction and have shown by NMR studies a dynamic rearrangement between η^3-η^1 coordination of the benzyl group, stabilising the branched alkyl-metal intermediate.[33]

For other alkene substrates, such as ethene, the mechanism for methoxycarbonylation reaction to methyl propanoate (MeP) was established to operate

by the "hydride" cycle.[34] When ethene methoxycarbonylation was carried out by Pd/PPh_3 system, the hydride mechanism was observed to be the operating cycle.[35] Also for the Pd(0)/DBPMB (**1**) system multinuclear NMR spectroscopy and ^{13}C-labelling study could observe and identify all occuring intermediates.[36] The observed intermediates strongly suggest the "hydride cycle" to be the operating mechanism. Furthermore, Cole-Hamilton and co-workers carried out labelling studies for the carbonylation of methyl propanoate from ethene and CO in MeOD, using Pd(0)/DBPMB (**1**) catalyst and $MeSO_3H$.[37] The results conclude that the palladium-hydride cycle is the operating mechanism for ethene methoxycarbonylation, excluding the "carbomethoxy" mechanism. All these studies showing the elementary steps of the "hydride" cycle have therefore established this cycle well.



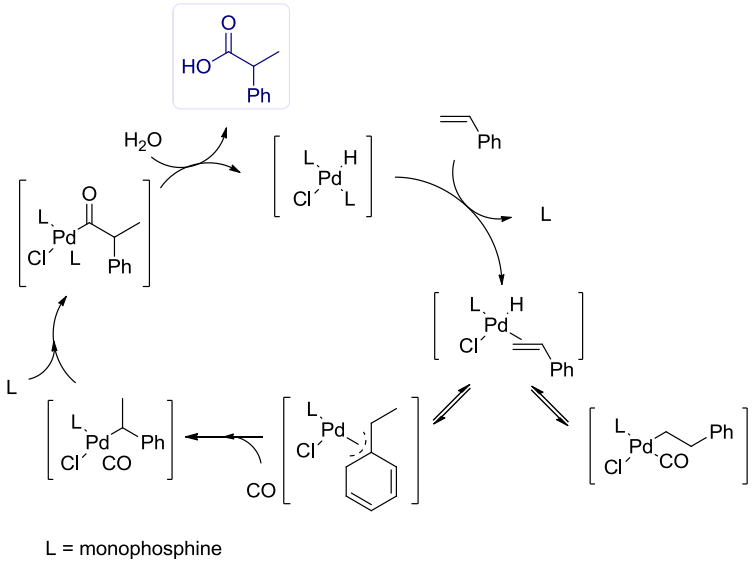
Scheme 10 Hydride mechanism for the methoxcarbonylation of ethene for the preparation of methyl propanoate.

1.2.3.2 Hydroxycarbonylation mechanism

Another objective is the need to distinguish between the hydroxy- and alkoxy-carbonylation catalysis mechanisms, as they may be different. For hydroxycarbonylation, two simplified catalytic cycles have been proposed by Claver and co-workers, suggesting two separate catalytic cycles for diphosphine and monophosphines ligands, both starting from the same palladium-hydrido intermediate.[18a] Insertion of vinylarene into the Pd-H bond leads to two intermediates, the branched and linear Pd alkyls. Catalytic experiments and deuterium labeling studies support the occurrence of β-elimination, and depending on the reaction conditions, the formation of the linear palladium-alkyl isomer was found likely to be irreversible.[13]

According to NMR spectroscopy and X-ray crystallographic data, monophosphines prefer *trans* orientation for steric reasons.[38] The displacement of one phosphine ligand will provide a coordination site for the alkene (Scheme 11). The key intermediate in this

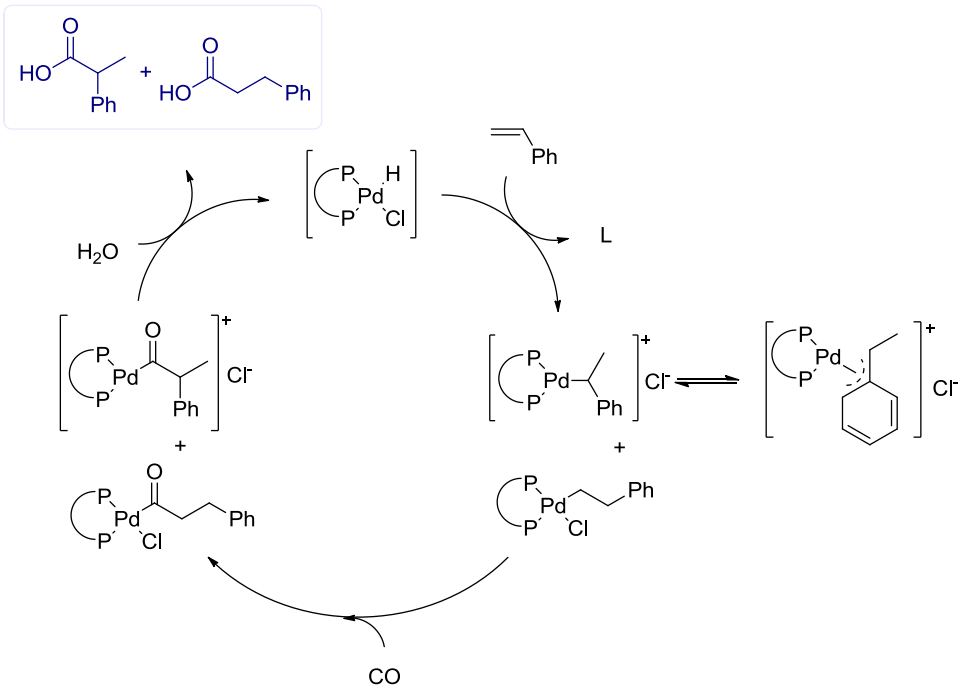
cycle contains only one phosphine ligand, which reduces steric hindrance and therefore stabilises the π-benzylic species for vinylarenes, favoring the formation of the branched acid. After CO coordination and migratory insertion another monophosphine coordinates back on the palladium-acyl complex and hydrolysis leads to the carboxylic acid formation and regenerates the Pd-H species.



Scheme 11 Proposed catalytic mechanism for hydroxycarbonylation of styrene with monophosphines (*trans* key intermediate species).

Diphosphines were found to form stable *cis* coordinated complexes, and require displacing of the chloride anion before the alkene coordination can takes place (Scheme 12). This is an important difference between the mono- and di-phosphine systems and would explain the more severe reaction conditions required for diphosphine systems than for monophosphines. Coordination and migratory insertion then results in a palladium-acyl species, following hydrolysis to form the carboxylic acid and regenerate the Pd-H complex.

Equilibrium between the Pd-H and Pd-acyl species in the catalytic cycle has been proposed and verified by several catalytic experiments, reconciling the reversibility of the CO insertion in the palladium alkyl bond. It was also suggested that depending on the reaction conditions the linear alkyl formation seems more likely to be irreversible.[39]



Scheme 12 Proposed catalytic mechanism for hydroxycarbonylation of styrene with diphosphines (*cis* key intermediate species).

An interesting observation was that diphosphines were found, depending on their exact features, to form *cis* or *trans* complexes with palladium during their resting state and based on their counteranion could also become mono-coordinated (Figure 6). It is also conceivable that they may bridge two different palladium centers, building a dimeric palladium complex, so that two diphosphine ligands form a dinuclear species.[40]

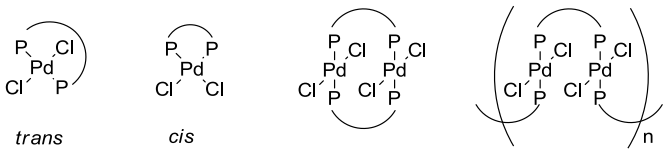


Figure 6 Various co-ordination modes for diphosphines with Pd(II) monomeric, dimeric and oligomeric formations.

Larger bite angle diphosphines with more flexible backbone structures have been proposed to form a more open active species. Some palladium diphospine systems have even been speculated to change their coordination modes during catalysis and perform as monophosphines rather than diphosphines.[40]

1.2.4 Acidic Medium and Counter Anion

Acids and counter anions are essential for hydroxy- and alkoxy-carbonylation reactions. Intensive research has been done to understand the role of counter anions, and use their influence to improve selectivity and productivity. Although their role is not yet fully understood, it has been reported to affect the rate and regioselectivity, depending on the nature of the acid and counter anion. [22, 41]

In the early 80's Cometti and Chiusoli reported the asymmetric methoxycarbonylation of styrene with $Pd(dba)_2$/NMDP (**3**) using CF_3COOH as the acid to give 52 % e.e, good B/L ratio of 16 and high yield. Changing towards different acids such as MeCOOH, HCOOH, HCl, HBr they found the conversions and asymmetric induction very low.[22]

Claver and coworkers carried out a study with the monophosphine triphenylphosphine (PPh_3) (**17**) and the diphosphine 1,4-bis(diphenylphosphino)butane (dppb) (**18**) in hydroxycarbonylation of styrene, testing the effect of different acids and counteranions on the reaction outcome.[42] The palladium precursor of choice was $Pd(dba)_2$, to prevent other counter anions to be involved. Interestingly, when the monophophine (**17**) and non-coordinating anion such as *p*-TsOH was used the favored isomer was the linear, whereas when using strongly coordinating anions, such as halides, the reaction was found to support the branched acid (Figure 7).

When using the diphosphine ligand (**18**), it was observed that higher pressures and temperatures were necessary. When H_2O and $H_2C_2O_4$ were used as the acid, good conversions could be achieved, although with poor regioselectivity. A significant drop in chemoselectivitiy was observed when *p*-TsOH or hydrogen halides were applied. When using $MeSO_3H$ and perchloric acid no conversion to the acid could be observed, only oligomerisation was detected. Concerning regioselectivity, hydrogen halides were reported to give quite different results, HCl was found to give mainly the linear isomer, whereas HI was found to produce mainly the branched acid (Figure 7).

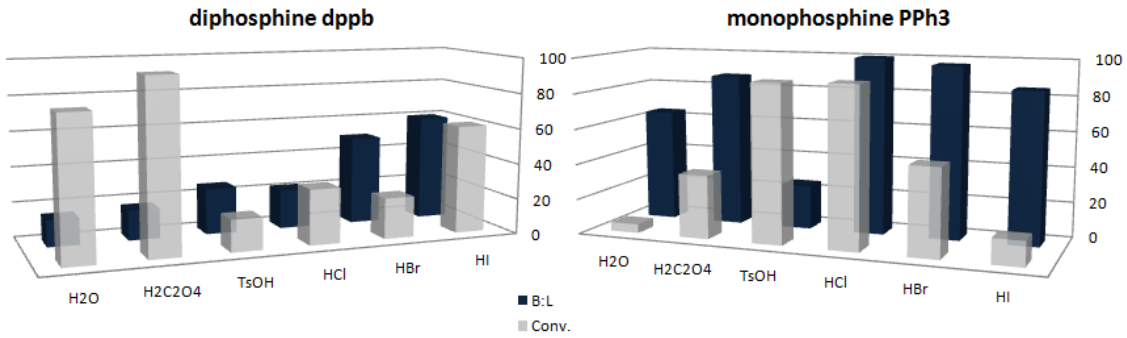


Figure 7 Hydroxycarbonylation of styrene using different acid co-catalyts (B in %).

Some coordinating anions were found to favour the formation of branched acids, whereas weakly coordinating anions, such as sulfonic acids, show a higher affinity towards the formation of linear acids. Other systems work better with non-coordinating anions. A diphosphine/palladium(II) system in alkoxycarbonylation of vinyl aromatic compounds was not only found to be more active using non-coordinating anions, such as *p*-TsO^-, but did also achieve better enantioselectivity for branched esters, than with the coordinating anions like Cl^-.[25]

Lee and coworkers reported the hydroxycarbonylation of 4-methylstyrene after a halogen compound had been added. They observed that the addition of chloride anions improved the reaction rate significantly, with the catalyst system $PdCl_2$-$CuCl_2$-HCl-(**17**).[43]

The combination of *p*-TsOH and LiCl as promoters was utilised by Chaudari and coworkers on carbonylation reactions with a Pd/(**17**) system, resulting in high activity and significant improvement in selectivity allowing milder reaction conditions.[9b, 11b, 31] Further studies did show that in the absence of LiCl the reaction was slow and unselective.[44]

Unpublished results in the M. L. Clarke group using different acids and counter anions using a fluorinated diphosphine ligand (**6**) made it apparent that the use of *p*-TsOH and LiCl are essential for the best activity and selectivity (Figure 8). All reactions were carried out under the same reaction conditions using diphosphine ligand (**6**), the results are displayed in Figure 8.

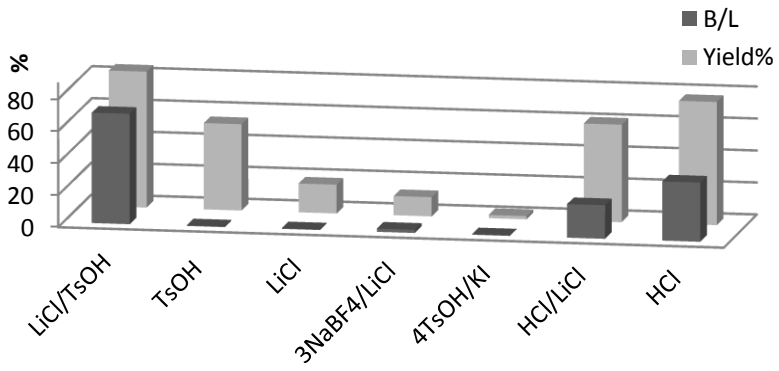
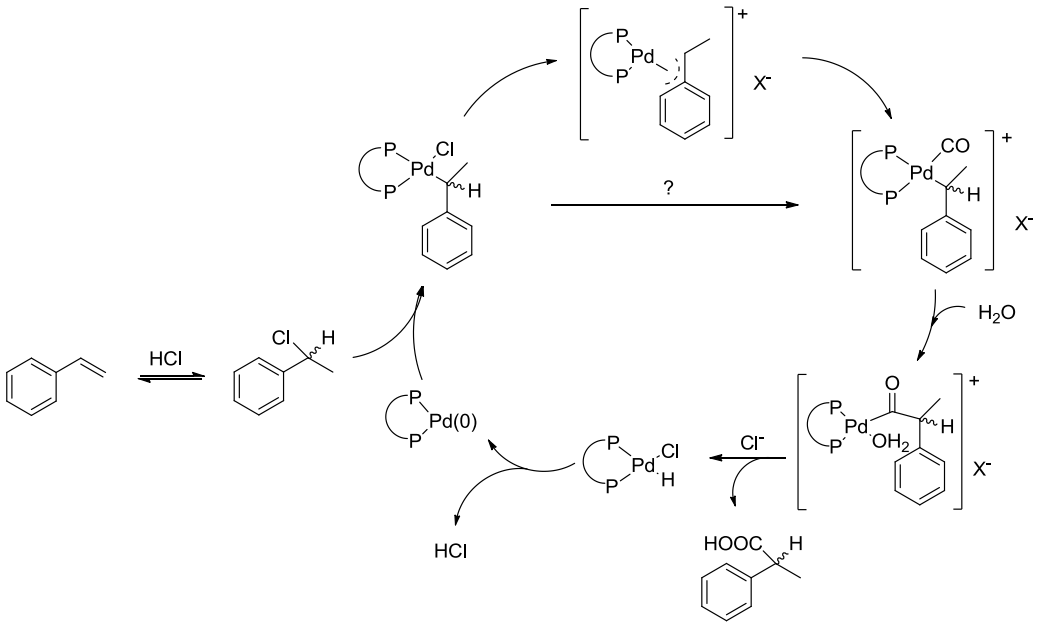


Figure 8 Comparison of different promoters using a fluorinated diphosphine catalyst in styrene hydroxycarbonylation.

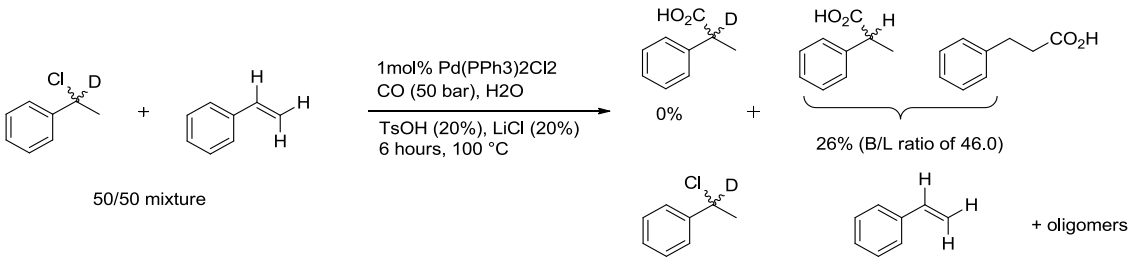
Another interesting study by Chaudhari and coworkers suggested the formation of a phenethyl chloride as the operating key intermediate in the catalytic pathway, proceeding by oxidative addition, forming a palladium(II) alkylchloride species.[9b, 11b, 31, 44] Their main evidence for this was indirect; phenethyl chloride was detected by GC-MS during styrene hydroxycarbonylation and that hydroxycarbonylation of phenethyl chloride can occur without a promoter at a very slow rate (Scheme 13).



Scheme 13 Proposed mechanism by Chaudhari and co-workers, suggesting the phenethyl chloride as the key intermediate.

Frew *et al.* published a deuterium labeling study in 2009 questioning the proposed mechanism by Chaudhari and co-workers.[45] In order to distinguish the phenethylchloride as the key intermediate in the reaction, hydroxycarbonylation

reactions were carried out using an equimolar mixture of deuterated phenylethyl chloride and styrene (Scheme 14). Stopping the reaction at an early stage showed large amounts of carbonylated styrene, small amounts of deuterated styrene (produced via elimination reactions from the d-phenethyl chloride), but no product formed showed any deuterium label, suggesting the proposed mechanism from Chaudhari and co-workers to be unlikely. More likely the results explained by Chaudhari can be interpreted as the elimination of styrene and HCl, the real substrate and promoter. In agreement with this, deuterated phenethyl chloride can act as a promoter for styrene hydroxycarbonylation.



Scheme 14 Deuterium labelling study carried out in hydroxycarbonylation of styrene.

Although much progress has been made to overcome activity, enantio- and regio-selectivity problems for asymmetric hydroxy- and alkoxy-carbonylation reactions still require great improvements. Although these reactions show high potential and would provide atom efficient routes towards valuable chiral carboxylic acid derivatives, the current processes need to become easier to operate. Present processes do need high pressure of carbon monoxide, high temperatures and high concentrations of inorganic acids, salts and co-catalysts in order to facilitate the reaction. Also a main drawback of these reactions is the combination of high B/L ratio with high e.e., which has until recently not been realised. Particularly regioselectivity control is of great importance for asymmetric carbonylation reactions, as only the branched isomer can be chiral.

The main aim of this thesis is to improve this type of reaction and to develop catalysts able to improve catalytic activity, regio- and enantio-selectivity, in order to make them potentially more valuable and an environmentally friendlier application.

1.3 Heterogeneous molecular catalysts

1.3.1 Introduction

A heterogeneous catalyst is, as "heterogeneous" already indicates, in a different phase to the reactants. Although heterogeneous catalysts have been/are key in chemical industry, their low flexibility in process development and chemical modifications has led researchers to investigate more supple methods such as heterogenisation of homogeneous catalysts.[46] To make sustainable improvements in reduction of energy use, environmental impact and production costs, more flexible processes would be certainly of advantage and heterogenising homogeneous catalysts could be the solution.

Over the years different methods for recycling homogeneous catalysts from product mixtures have been studied and can roughly be divided into 3 subcategories:

- biphasic catalytic systems,[5a, 47]
- soluble support systems (catalyst is molecular weight enlarged (MWE))[5b, 48] and
- insoluble supports (heterogenisation).[46d, 49]

This thesis focuses largely on insoluble supports, in particular using ion exchange as the immobilization method of choice. In the *appendix* soluble molecular enlarged supports will be briefly introduced, that are homogeneous catalysts that can be separated by relatively simple means.

Heterogenised catalysts can be sectioned into their different methodologies and type of anchoring using various support materials. Table 4 roughly summarises the foremost methods used. In this *chapter*, due to the amount of different immobilisation techniques and materials available, only ion-exchange onto polymeric supports will be reviewed in more detail. Throughout *chapter III* also supported ionic liquid phase systems on silica will be briefly discussed, highlighting their application in continuous $scCO_2$ flow.

Further information about different types of immobilisation are listed in Table 4 and examples can be checked in their references.

Table 4 Summary of key methodologies for the preparation of heterogenised catalysts (Figure 9).

Type of attachment	Type of anchoring	Advantage(+)/Disadvantage(-)
Covalent bonding[50]		+ stable linkage
a)metal centre	Chemisorptions	- can change nature of catalyst
b)ligand	Covalent anchoring onto e.g. : inorganic supports (e.g. Si-O) polymer supports (Merrifield) dendrimers [51]	+distance between complex to surface controllable -laborious synthesis effort +easy filtration
Ionic bonding[52]	Electrostatic attraction onto either	+ easy prepared
a)ionically bound metal	-inorganic supports -polymeric support	- catalyst must stay charged throughout catalysis
b)ionically bound ligand	-supported ionic liquid phase (SILP)	+catalyst does not need to stay charged all the time
Encapsulating[53] (Ship in the bottle SIB)	Physically constraint, catalyst trapped inside cage-like pore	+stable immobilization - approaching catalyst difficult
Entanglement	Physical restriction	+simple preparation
a)Polymer network[54]	catalyst entrapped in polymer network	+ entrapment adjustable -thermal stability limited
b)Supported liquid phase catalyst (SLPC)[55]	Thin film of liquid (+catalyst) on surface and pores of solid (silica, alumina)	+catalyst simply dissolved in liquid phase - modification of catalyst
Physical adsorption[56]	Physisorption: Van der Waals force, dipole-dipole interaction π-π stacking hydrogen bonding	+easy preparation -catalyst easily re-dissolved in reaction medium due to weak interaction

Heterogenised catalysts could not only benefit from easy separation and recyclability, but potentially can also contribute advantageous effects of the support, such as stabilising the active species of the catalyst, and therefore preventing cluster formations which would result in deactivation of the catalytic species.

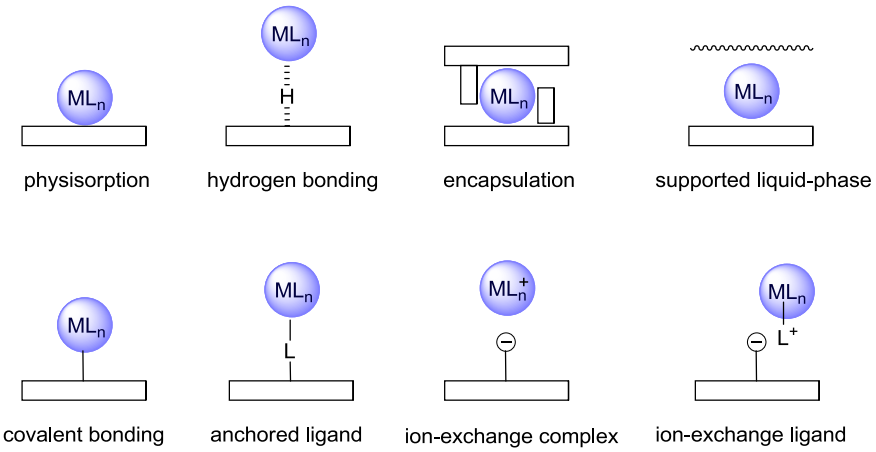


Figure 9 Methods for immobilising a catalyst, *via* different approaches.

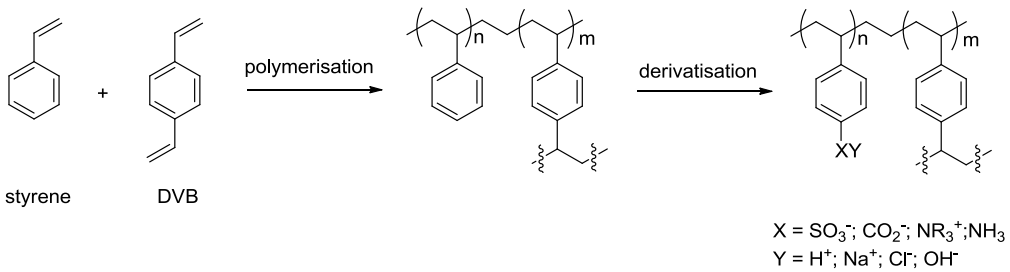
Heterogenisation by ion exchange offers an easy way for immobilisation. By simple ion-exchange the homogeneous catalyst can be heterogenised onto a solid support. For this approach the metal complex and the support must be ionic compounds. As shown in Table 4 the charge can be located either on the metal centre or the ligand, depending where the ionic charge is located. When the metal centre is the source of immobilisation, all possible oxidation states of the catalyst during catalysis have to be considered, before starting an ionic immobilisation. Possible materials as supports for ion-exchange are inorganic solids (silica, alumina, clays, zeolites, heteropolyacids etc.) and organic carriers (polymers, dendrimers, carbon, etc.).[46e] The molecular homogeneous catalyst is preformed in the homogeneous phase and then anchored to the support by ion-exchange. Benefits of this approach are 1) simple preparation route 2) catalyst is known and so is its activity and selectivity; 3) no need for further chemical modifications to the support prior to immobilisation; 4) design of catalyst is straightforward and 5) this methodology allows a great amount of different organometallic catalysts to be immobilised.

1.3.2 Ion-exchange resin as the support material

Ion exchange resins meet most requirements for the “ideal” catalyst support. Resins are widely used in all kind of areas, e.g. for water softening, water purification of heavy metals, catalysis and pharmaceuticals. Most resins are commercially available, due to their simple preparation, their ease in control of cross linkage and amount/type of functional groups. Functional groups are divided into -cationic exchange resins, with anionic functionalities and positively charged mobile ions (strong or weak acid groups) and anionic exchange resins, with cationic functionalities (strong or weak basic groups). Most resin types were designed to work well in water and, due to their application

potential, resin types with a lower degree of functionalisation were synthesised to make them useful also in organic medium (Scheme 15).

The porosity of the resin is controlled by its cross linkage and can vary from well defined pore systems, obtained by higher cross linkage (up to 16 %) resulting in so called macroreticular (rigid) resins, to less distinct pore systems. The lower degrees of cross linkage (down to 2 %) results in a more gel-like resins (microreticular) that lacks a distinct pore system. Slight changes in the cross linkage also affect the size of the resin in solvents and its solvent content, e.g. the lower the cross linkage the better the swelling of the resin, but this also leaves the resin more fragile to mechanical destruction. Typical bulk properties, which can be modified to individual preferences, are bead size (beads diameter 16-400mesh), ionic form, capacity of resin (between 1.5-10 meg/g), swelling (up to 800% was found possible), physical stability, equilibration rate and selectivity.



Scheme 15 Preparation of polymeric ionic exchange resins, by polymerization of styrene and divinylbenzene (DVB), followed by functionalisation of the resin.

A good swelling and capacity of the resin is crucial for good mass transfer into the resin and efficient catalyst anchoring. Mostly gel-type resins with low cross linkage have been found more useful, since problems with the substrate diffusion was alleviated and higher catalyst loading was possible.

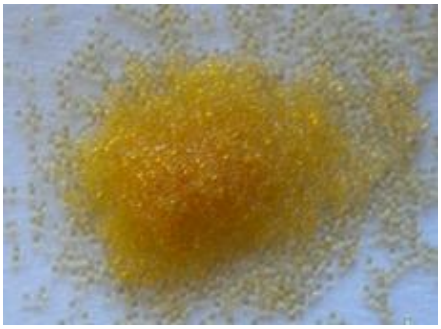


Image 1 Polymeric ion-exchange resin.

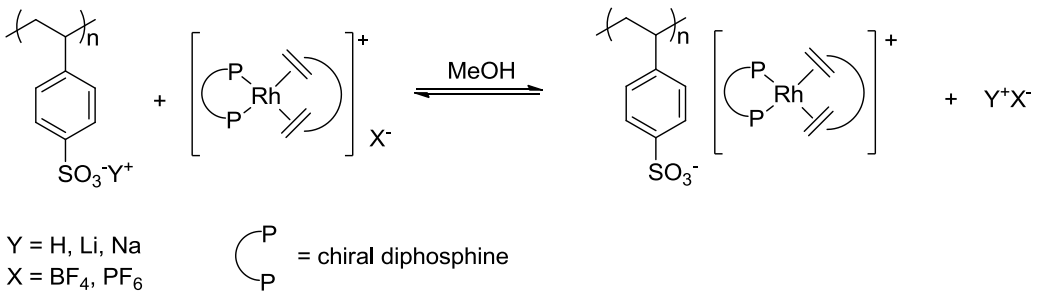
1.3.3 Catalysis

Asymmetric hydrogenation reactions of prochiral olefins are the most studied enantioselective transformation for immobilised catalysts. An immense amount of homogeneous catalysts have been reported in the literature providing excellent selectivity and activity. Unfortunately up to date there is no economically valuable process for recovering these expensive and mostly sensitive catalysts. While many industrial asymmetric hydrogenation processes have been developed in homogeneous phase, in cases where very low catalyst loadings are not possible, the ability to recycle the catalyst could enable new processes.

The heterogenised complex can be obtained by simply adding the ion-exchange support to the solution with the preformed ionic transition metal complexes (homogeneous phase) and stirring. Due to the preparation of the catalyst prior to attachment, these catalysts are still considered single site catalysts, once they are immobilised. Commonly rhodium complexes are anchored to the support through ionic bonding of the metal centre. Only a few reports are published about attaching the catalyst via ion exchange on the ligand.[46d]

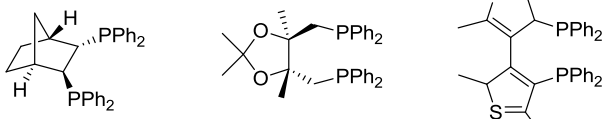
1.3.4 Transition metal complexes with non-functionalised chiral ligands

Rhodium(I) complexes are among the most applied homogeneous catalysts for alkene hydrogenation. Anchoring a cationic complex onto anionic exchange resins is a simple task of stirring of the resin in a homogeneous catalyst solution, followed by filtration, washing and drying. Immobilisation is achieved by ion-exchange of the catalyst counter-anion and the counter-cation of the support material (Scheme 16).



Scheme 16 Immobilisation by ion-exchange of a homogeneous chiral rhodium catalyst onto a polymeric ion exchange.

A variety of chiral diphosphine Rh complexes were synthesised using diphosphine ligands, such as (2*R*,3*R*)-(-)-2,3-bis(diphenylphosphino)-bicyclo-[2.2.1]-hept-5-ene (NORPHOS (**19**)), (4*R*,5*R*)-(-)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolan (DIOP (**20**)) and 2,2´,5,5´-tetramethyl-3,3´bis(diphenylphosphino)-4,4´-bithiophen (TMBTP (**21**)) and heterogenised onto ion-exchange resins (Figure 10). Typical numbers of metal loadings on the resin vary depending on the type of resin between 0.3-1.5 %. Furthermore were these resins investigated in asymmetric hydrogenation reactions of prochiral alkenes and compared to their homogeneous analogues.



(**19**) (**20**) (**21**)

Figure 10 Chiral biphosphine ligands applied as immobilised catalysts in asymmetric hydrogenation reactions.

In 1990, Brunner and Bielmeier reported about their catalytic observation when using strong (-SO_3H, DOWEX HCR-S; -$SO_3^-Na^+$, DOWEX MSC-1) or weak (-CO_2H, SERDOLIT-CW18) functionalised acidic ion-exchange resins in asymmetric hydrogenations of (*Z*)-α-acetamidocinnamic acid (ACA). Chiral rhodium complexes of the type [Rh(COD)(diphosphine)]PF_4 with (-)-NORPHOS (**19**) and (-)-DIOP (**20**), respectively were immobilised onto the different resins.[57] When weak acidic ion-exchange resins were used, the activity and optical induction was found much lower, than when strong acidic ion-exchange resins were used. Generally very long reaction times were necessary to achieve reasonable conversions and also the e.e. was observed lower than found for the homogeneous phase catalysts (Table 5).

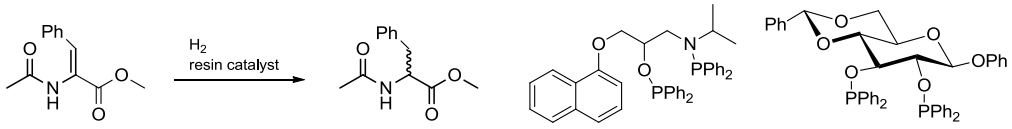
Table 5 Asymmetric hydrogenation of ACA using [Rh(COD)(**19**)]PF_6 immobilised on the strong acidic ion-exchange resin DOWEX HCR-S and DOWEX MSC-1.

Entry[a]	Ionic form	Resin catalyst	Cycle	Time (h)	Conversion (%)	E.e. (%)
1[b]	H^+	DOWEX HCR-S	1	42	100	68
2			2	46	95	65
3			3	58	90	68
4			4	49	82	66
5			5	52	67	61
6[c]	Na^+	DOWEX MSC-1	1	40	100	69
7			2	43	98	79
8			3	70	100	76
9			4	65	100	70
10			5	67	95	61

[a] Reactions were carried out in MeOH/H_2O 1:1. [b] H_2 pressure 20 bar, reaction temperature 50 °C. [c] H_2 pressure 25 bar, reaction temperature 50 °C.

Barbaro and co-workers heterogenised homogeneous [Rh(NBD)(**20**)]PF_6 and [Rh(NBD)(**21**)]PF_6 complexes onto the commercially available DOWEX 50WX2-100 (–$SO_3^-Li^+$) resin. Previous studies reported that using the ionic form of Li^+ instead of H^+, the effect of anchoring homogeneous cationic catalyst onto the resin could be improved and the metal uptake of the resin was enhanced (Rh loading between 0.93-1.04 %).[58] The immobilised resins were tested in asymmetric hydrogenations of methyl-2 acetamidoacrylate (MAA) in MeOH at 5 bar H_2. Each complex gave comparable results in the first cycle to its homogeneous analogue, although already in the second cycle 5 times longer reactions times were necessary to achieve full conversion.

One of the most active and earliest examples for heterogenised ion-exchange resins was reported by Selke *et al*.[58] Rhodium complexes were prepared with the chiral bidentate phosphinite ligands (*S*)-2,3-*O*,*N*-bis(diphenylphosphino)-1-(α-naphtyloxy)-2-hydroxy-3-isopropylaminopropane (PROPRAPHOS (**22**)) and phenyl (*R*)-4,6-*O*-benzylidene-2,3-*O*-bis(diphenylphosphino)-β-D-glucopyranoside (Ph-β-glup (**23**)).



(**22**) (**23**)

Scheme 17 Asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate with cationic Rh phosphinite complexes.

Their Rh complexes were immobilized onto sulfonated polymeric resins (-SO_3H) and the catalytic activity examined in enantioselective hydrogenation reactions of methyl (*Z*)-α-acetamidocinnamate (MAC) (Scheme 17). The heterogeneous catalyst could be recycled and reused up to 15 times, with the catalyst activity slightly decreasing after each cycle (Table 6).

Table 6 Summary of recycling experiment of immobilised Rh catalyst attached onto a 0.5% crosslinked sulfonated styrene/divinylbenzene resin for hydrogenation reactions.

Cycle	Time (t/2)	E.e. (%)	Time (t/2)	E.e. (%)
Catalyst	[Rh(COD)(*S*)-(**22**)]BF_4		[Rh(COD)(*S*)-(**23**)]BF_4	
Homogeneous	1	84(*S*)	6	91(*S*)
1	22	80	24	93
2	24	79	23	93
3	32	76	27	93
4	34	76	28	93
5	43	73	28	93
6	55	71	30	93
7	75	62	34	93
8	125	43	38	93
9	227	25	40	93
10	-	-	42	94
11	-	-	52	94
12	-	-	55	94
13	-	-	66	94
14	-	-	108	94
15	-	-	150	94

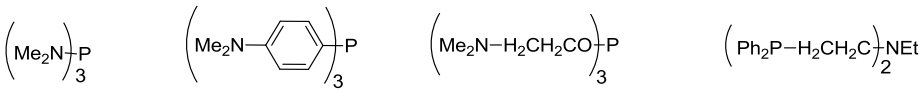
Furthermore different ionic forms of resins, such as H^+, Li^+, Na^+, K^+, NH_4^+, NMe_2^+ and others, were examined in hydrogenation reactions of AAC with catalyst [Rh(COD)(*S*)-

(**22**)]BF_4. The lithiated resin gave the best activity and e.e. although Rh leaching was observed much higher, >70 % than with H^+ resins, where the leaching was observed <10 %.

Heterogenised catalysts by ion exchange *via* the catalyst charge were generally found to be less active but comparable in terms of stereoselectivity with their homogeneous analogues. All immobilised catalytic systems reported showed a loss of activity and selectivity already after the first cycle.[59] Lengthening of the reaction times allowed achieving full conversions for second or more cycles, although in some cases the enantiomeric excess was observed decreased.

1.3.5 Transition metal complexes with functionalised chiral ligands

Immobilisations through ionic interactions onto ion-exchange resin with functionalised ligands, such as monophosphine ligands with a tertiary amine, were reported in the 1980s for the first time.[60] Various aminophosphine ligands (**24**-**27**) (Figure 11) were immobilised onto sulfonated styrene-divinylbenzene resins (-SO_3H). These aminophosphine functionalised resins were further treated with various Pt and Co precursors and their catalytic activity tested. Hydroformylation reactions of 1-hexene were carried out using Pt and Co resins. Although these immobilised catalysts showed low activity, high selectivity was achieved and no detectable leaching in the first 2 cycles was observed.



(**24**) (**25**) (**26**) (**27**)

Figure 11 Nitrogen functionalised monophosphines.

Protonation or quaternisation of the phosphorus compound can be avoided by simple protection of the phosphine by complexation prior to heterogenisation onto the solid support.

Immobilisation of a nitrogen functionalised diphosphine rhodium complex was reported by Tóth and Hanson using Nafion resins (perfluorinated polymeric backbone -SO_3H) and (*S*,*S*)-BDPP-(*p*-NMe_2)$_4$ (**28**) and (*S*,*S*)-chiraphos-(*p*-NMe_2)$_4$ (**29**).[61] By simple acid-base exchange equilibrium with the *N*-functionality of the amines, the catalyst stayed attached to the support.

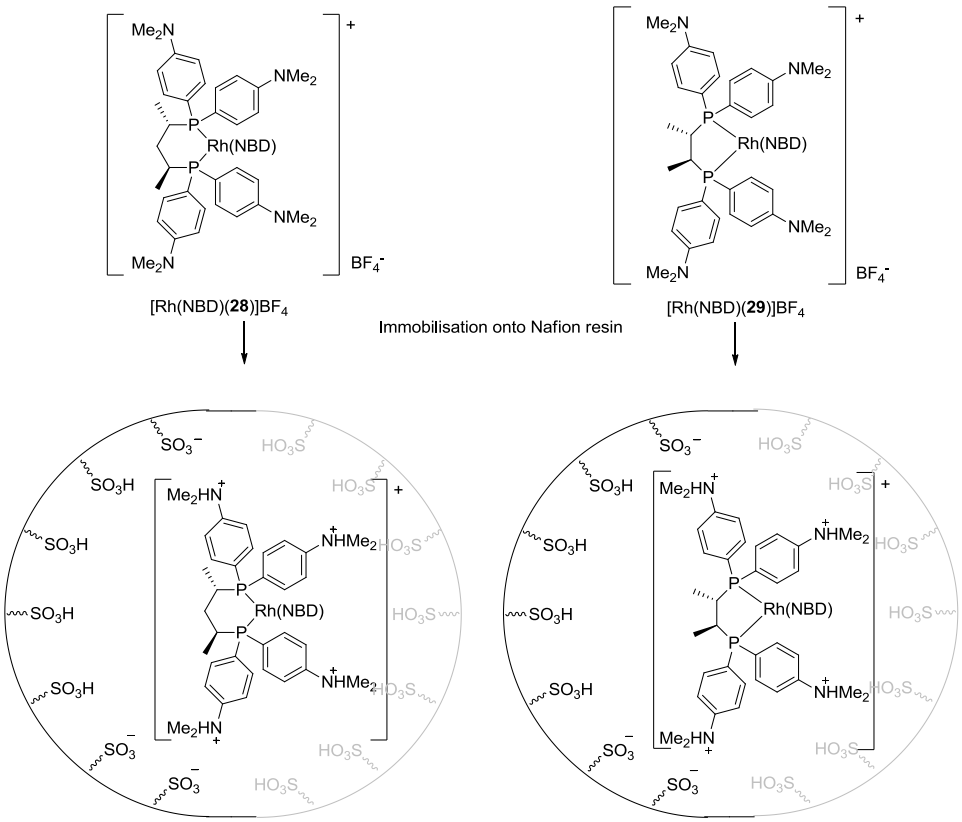


Figure 12 Immobilisation by *N*-functionalised chiral ligands.

These resins were then used for the asymmetric hydrogenation of methyl (*Z*)-*N*-acetylaminocinnamate (MAC) and the resin catalysts were able to maintain activity and selectivity for 6 cycles. Although the catalyst could be reused, the rate of hydrogenation of the heterogenised catalysts was very slow, in comparision to their homogeneous analogues, but comparable to other polymer supported hydrogenation catalysts.[62] The rhodium leaching observed for the immobilized catalysts was < 0.1 ppm, for every cycle. Table 7 summarises the heterogeneous catalysis cycles (Entry 3-8) and the homogeneous results, which are displayed in Entry 1 and 2. This is therefore an interesting approach with some drawbacks; however a comparison of the ion exchange at the metal and the ligand has not been made.

Table 7 Hydrogenation of dehydroaminoacid derivatives with immobilised catalyst [Rh(NBD)(**28**)]BF_4 and [Rh(NBD)(**29**)]BF_4 with a substrate/catalyst ratio of 100/1.

Entry	Catalyst	Cycle	Time (h)	Conv. (%)	e.e. (%)
1[a]	[Rh(NBD)(**28**)]BF_4	-	5 min	>95	57
2[a]	[Rh(NBD)(**29**)]BF_4	-	1	>95	53
3[b]	[Rh(NBD)(**29**)]BF_4	1	36	98	73
4		2	36	98	72
5		3	36	98	73
6		4	36	92	67
7		5	36	96	64
8		6	36	97	63

[a] Reaction carried out at 1 bar H_2 pressure at room temperature. [b] Reaction carried out at 14 bar H_2 pressure.

Two years later another article by Tóth and Hansen reported the change from ion-exchange Nafion beads to a soluble form of Nafion, using a 5wt% Nafion-H gel.[61b] This Nafion gel enabled the heterogenised catalyst to overcome the activity slowdown and esterification side reaction when using (*Z*)-α-acetamidocinnamic acid (ACA) as substrate. The same catalyst precursors were used and conditions applied as for the Nafion resin (Table 8). When using the Nafion-H gel as solid support, immobilisation of the homogeneous catalyst resulted in an orange gel-like precipitate, which could be separated by filtration from the solvent mixture. Interactions of the phosphorus by protonation with the resin are excluded due to ^{31}P {^1H} NMR spectrometry doublet at 29 ppm, the signal for Rh diphosphine complex. It was observed that after reusing this Nafion gel for several times, the gel started to form smaller particles and it became impossible to filter them by normal methods such as sintered glass filter techniques or centrifuge. Special filtration techniques were required (membrane filtration) for separating the Nafion-H gel particles from the solution. Results of the asymmetric hydrogenation of MAC are summarised in Table 8.

Table 8 Nafion-H supported complexes for asymmetric hydrogenation reactions with [Rh(NBD)(**28**)]BF_4 and [Rh(NBD)(**29**)]BF_4 using a substrate/catalyst ratio of 100/1.

Catalyst	Cycle	Time (min)	Conv. (%)	e.e. (%)
[Rh(NBD)(**28**)]BF_4[a]	1	10	100	47
	2	15	100	46
	3	25	100	43
	4	20	100	42
	5	20	100	43
	6	28	100	44
[Rh(NBD)(**29**)]BF_4[b]	1	8 (h)	100	80
	2	6(h)	100	73
	3	5(h)	100	74
	4	8(h)	100	75
	5	6(h)	100	78
	6	6(h)	100	77

[a] Hydrogenation reaction of methyl-(*Z*)-α-benzamidocinnamate. [b] Hydrogenation reaction of (*Z*)-*α*-acetamido cinnamic acid.

A detailed comparison study with four different anionic support materials, such as silicate based material (AITUD), phosphortungstic acid on alumina (PWTUD), a Nafion silica composite (SAC-13) and Nafion as ion-exchange resin (-$SO_3^-Na^+$, NafionC1) was carried out with a cationic Rh complex with the chiral monodentate ligand MONOPHOS (**30**).[63] The anchoring of the catalyst onto the resin was by ion exchange with the cationic complex and anionic support (Figure 13). Initial experiments showed that when using the acidic sites had a negative effect onto the reaction outcome and therefore only the sodium treated resin was used.

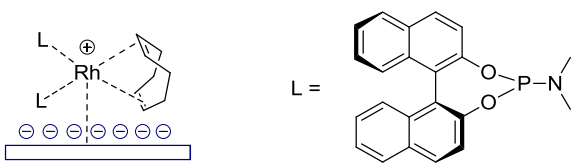


Figure 13 Immobilised Rh complex by ion-exchange onto solid supports.

All supports were investigated in asymmetric hydrogenation of MAA. Each support material did retain activity and selectivity for up to 4 cycles, the conversions and e.e. of Nafion SAC-13 and NafionC1 are presented in Figure 14. From all the support materials examined, the NafionC1 resin was reported to be the least active, due to its low surface

area. With the Nafion silica composite the drawback of the surface area restriction could be overcome and high conversions (~98 %) and e.e. (~99 %) was obtained, similar to the results achieved with AITUD and PWTUD.

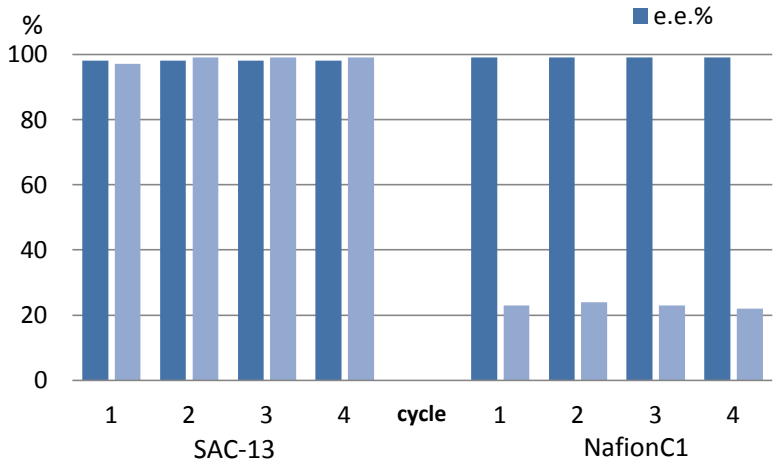


Figure 14 Conversions and e.e. for 4 cycles with SAC-13 and NafionC1.

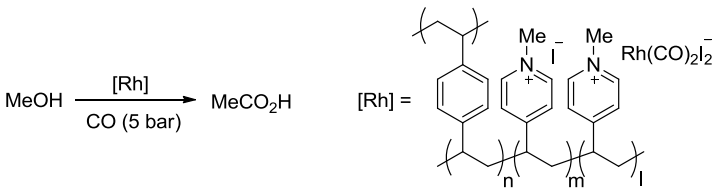
Renaud and Baird reported the use of a cationic $[Rh(NBD)(Ph_2P(CH_2)_nPMe_3^+\}_2]^+[NO_3]^-$ (n=2,3,6,10), by changing the length of the alkyl spacer the immobilized catalyst was found to influence activity.[64] The catalyst is immobilized onto the resin by the tetraalkylphosphonium groups $Ph_2P(CH_2)_nPMe_3^+$. The catalyst activity in hydrogenations of 1-hexene was found to give higher conversions when the catalytically active centre was located in some distance to the resin surface, such as when the chain length was observed with n = 6 or 10 $[Rh(NBD)(Ph_2P(CH_2)_nPMe_3^+\}_2]^+[NO_3]^-$, for most alkene hydrogenation substrates the catalyst was observed more active. Catalyst activity could be improved by increasing the accessibility of the active centre.

Testing the catalysts true heterogeneity can be done by a "filtration-test". Removing the support from the solution and continuing the reaction, no further conversion indicates the catalyst is heterogeneous.

1.3.6 Resins applied in carbonylation reactions

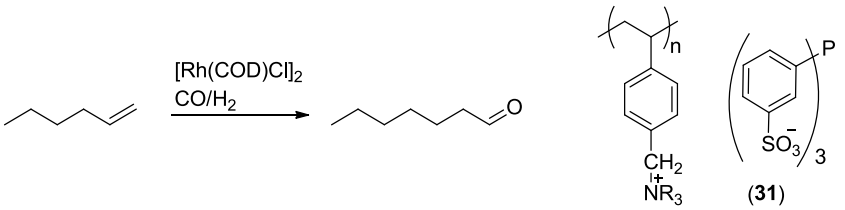
Research for the use of ion exchange resins in methanol carbonylations was carried out and Rh supported catalysts were found highly active. This process makes use of the fact that the Rh complex is anionic throughout all the catalytic cycle, making it an ideal candidate for ion-exchange heterogenisation. The anionic $[Rh(CO)_2I_2]^-$ complex was

immoblised onto the macroporous, Reillex 425, 33% w/w cross-linked 4-vinylpyridine/divinylbenzene polymeric resin by simple ion exchange.[65] The heterogenised catalyst was investigated in methanol carbonylation reaction of acetic acid (Scheme 18). Interestingly the resin was observed to provide the same activity and chemoselectivity as its homogeneous analogue. This heterogeneous catalyst was even applied industrially for methanol carbonylation, as "the acetic process" by Chiyoda/UOP in a continuous recycle pilot plant in 1997. The process was operated at moderate temperatures (160-200 °C) and pressures (30-60 bar) with no additives necessary. Furthermore it was reported that no deactivation of the catalyst was observed after more than 7000 hours continuous operation.[66] Kinetic measurements demonstrated that this heterogeneous catalyst undergoes the same analogue quantitative reaction rates as the homogeneous catalyst.[67] The Reillex resin showed excellent swell ability in water/methanol/acetic acid mixtures after iodomethylation, thus no mass transfer limitation into the resins occurred. Immobilisation not only overcomes Rh loss and solubility problems of the homogeneous catalyst but also limited corrosion of the process environment in the reactor was observed due to reduced water content necessary with resins.



Scheme 18 Methanol carbonylation using Reillex polymeric resin.

Supported catalysts have also been studied in hydroformylation reactions, examining various types of supports.[68] Hydroformylation of 1-hexene was reported using Rh(I)/ TPPTS (**31**) (=sodium triphenylphosphine trisulfonate) supported onto macroporous anion-exchange resins (Scheme 19). The heterogenised catalyst could be recycled up to 5 times with almost no changes in activity, chemo- and regio-selectivity. Turnover frequencies (TOF) of 3000 h^{-1} were observed, which are comparable to its homogeneous analogue. The Rh leaching for the cycles was reported > 0.1 ppm.



Scheme 19 Hydroformylation of 1-hexene using Rh/(**31**) immobilised on anion exchange resin.

Many more applications for ion-exchange resin have also reported for different catalytic reactions but will not be further discussed in this thesis, further information can be found in the literature.[46d]

Chiral catalysts with functionalisation would evidently be better candidates for heterogenisation onto ionic supports, by preventing leaching through the formation of neutral or zerovalent species. Although their availability is more limited than unfunctionalised ligands, most water soluble ligands could be appropriate candidates for non-covalent immobilization.

1.4 Project aims and Thesis outline

1.4.1 Project aims

Pd-catalysed hydroxy- and methoxy-carbonylation of aryl alkenes is potentially the most efficient route to 2-aryl-propanoic acids/esters, and has attracted great industrial interest, as they form important products for pharmaceutical and chiral building blocks for organic synthesis.

Until recently there have been no truly efficient chiral catalysts for regio- and enantioselective hydroxy- and methoxy-carbonylation of styrene derivatives, perhaps partly due to the regioselectivity and activity problems that bidentate phosphine based catalysts have. Therefore, the need of new Pd-diphosphine based catalyst systems are of great interest, which not only gives unprecedented selectivity and activity but also provides enantioselectivity. Due to the intensive studies of different working groups, we focused on the preparation of bulky chiral diphosphine palladium systems, to combine regio- and stereo-selectivity. We envisaged that desirable properties for a new system could be a chiral backbone, larger bite angle and (for activity) possibly steric bulk at the phosphorus atom, since these characteristics have been reported of having a positive influence on the B/L ratio.

Pd catalysed asymmetric carbonylations require relatively high catalyst loadings, meaning that it is of great environmental and immense scientific interest to recycle these

palladium catalysts, since this might be required for cost-effective commercial applications. A major disadvantage of homogeneous catalysts is that often difficulties for separating and recycling the catalyst from the reaction products can sometimes preclude industrial applications, especially in reactions that need significant catalyst loadings. Therefore there is a need for appropriate catalyst systems, which do not only allow the control of regio- and stereo-selectivity but also give an easier access to catalyst recovery. Chiral diphosphines functionalised with tertiary amines could hold the key to this. The general idea is that by simply protonating the nitrogen substituent the catalyst becomes cationic and can therefore be immobilised via ion exchange onto charged supports.

1.4.2 Thesis outline

This review *chapter* has evaluated the literature on alkoxy- and hydroxy-carbonylation of alkenes with the conclusions that chiral diphosphines with bulky substituents would be of considerable interest to study in these Pd-catalysed carbonylations, due to excellent B/L ratios obtained with catalyst (**6**).

In *chapter II* the synthesis of chiral diphosphine phanephos derived ligands is described and the coordination chemistry for novel mono- and di-palladium complexes investigated. Furthermore these complexes were examined in homogeneous asymmetric hydroxy- and methoxy-carbonylation catalysis, achieving the most enantioselective catalyst to date, by using a new dipalladium catalyst system. These dipalladium catalysts turned out to improve selectivity immensely in carbonylation reaction of various prochiral alkenes. This *chapter* also includes the development of other ligands changing the electronic and steric properties and their influence on regio- and enantio-selectivity upon different prochiral alkenes.

Chapter III summarises the immobilization of chiral homogeneous rhodium and palladium catalysts with and without *N*-functionality onto acidic ion-exchange resins and acidic SILP (supported ionic liquid phase) systems. Furthermore these polymeric resins were characterised by EDX (energy dispersive X-ray spectroscopy) and their recyclability in catalysis investigated. The immobilized Rh(I) complexes were tested in asymmetric hydrogenation reactions of MAA (methyl-2 acetamidoacrylate) and the immobilised neutral Pd (II) complexes studied in asymmetric methoxycarbonylation reactions. Differences in catalysis between catalysts immobilized *via N*-functionality on the resin and catalysts with no functionality are discussed.

In the *appendix* a brief outlook is given into homogeneous molecular weight enlarged catalysts and first attempts in nano-filtration continuous flow reactors. This *chapter* mainly highlights other potentially interesting approaches for expensive catalyst recycling.

1.5 References

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CHAPTER II

Homogeneous Catalysis: Preparation of chiral diphosphine ligands and novel Pd complexes and their application in asymmetric hydroxy- and alkoxy-carbonylations.

Abstract The synthesis of new chiral bidentate phanephos derived ligands is described. Pd complexes of the type $[PdCl_2(P\text{-}P)]$ were prepared, and a new class of dipalladium catalysts $[Pd_2Cl_2(\mu\text{-}Cl)_2(\mu\text{-}P\text{-}P)]$ were developed. All complexes were evaluated in asymmetric hydroxy- and alkoxy-carbonylations of prochiral alkenes. The dipalladium catalysts were observed to result in most reactions enhanced activity, regio- and enantio-selectivity, in comparison to their monopalladium analogues. Furthermore, due to an intensive study of various electronically and sterically different diphosphine ligands the catalyst selectivity and activity could be improved to the best catalytic system reported so far in literature for asymmetric hydroxy- and alkoxy-carbonylations of styrene and styrene derivatives.

2.1 Introduction Phosphine ligands

Phosphine ligands are used in many homogeneous catalytic reactions involving precious metals. Their ability to influence the reaction outcome in different ways by makin simple structural modifications, such as controlling the electron density at the metal or changing steric properties has made them indispensable in homogeneous catalysis. Furthermore enantiomerically pure ligands can induce enantioselectivity.

The *cone angle* θ was introduced by Tolman in order to indicate the steric bulk properties that the phosphine ligand occupies around the metal.[1] This angle is defined by the cone of the substituents on the phosphorus, as the apex angle of a cylindric cone centered 2.28 Å from the Rh to the P atom (Figure 15). Sometimes X-ray crystal structures are available in order to determine this angle, but if this is not the case various modeling studies can establish the *cone angle*.

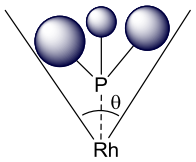


Figure 15 Illustration of the cone angle θ.

Phosphine ligands are known to be σ-donors and π-acceptors, and the strength of the individual bond is dependent on the other groups on the phosphines. In 1967 Strohman and Müller published a ranking of different phosphorus ligands based on their CO stretching frequencies.[2] Tolman expanded this work by measuring the stretching frequency of the carbonyl complex $NiL(CO)_3$ with different phosphine ligands (L).[3] These carbonyl stretching frequencies caused by the different bond strengths between the metal and CO ligands, was defined by Tolman as the *electronic parameter* χ, with the $Ni(P^tBu_3)(CO)_3$ as the reference. Generally alkylphosphines are strong σ-donors, donating electron density towards the metal, whereas organophosphites are stronger π-acceptors, competing for backbonding with carbon monoxide. This parameter, that describe σ-basicity and π-acidity of phosphines is today known for many phosphine ligands.[4]

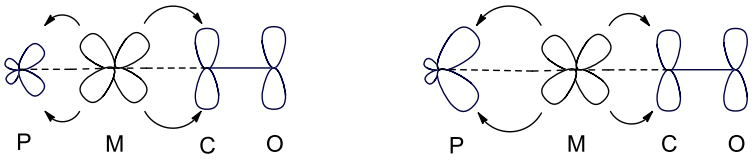


Figure 16 Effect on CO bonding by strong or weak back donation of the phosphorus ligand.

Over the years, tertiary phosphines with a variety of substituents have been synthesised and their electronic properties have been investigated. The first chiral phosphines were more intensely investigated in the early 70's in asymmetric hydrogenation reactions, such as DIPAMP[5] (**32**), DIOP[6] (**33**), CHIRAPHOS[7] (**34**), and BPPFA[8] (**35**); the first planar chiral diphosphine ligand (Figure 17). Chirality of diphosphine ligands for asymmetric reactions gained further importance over the years. Developing ligands with the stereogenic centre in the backbone using chiral centres, axial chirality, helical and planar chirality soon started to become equally important. Axial stereogeneity, in particular, gained interest when Noyori and Takaya synthesised the BINAP[9] ligand, which turned out to be one of the most famous diphosphine ligands in asymmetric catalysis. Many other groups added further biaryl diphosphine ligands, achieving great results in asymmetric hydrogenations.[10],[11]

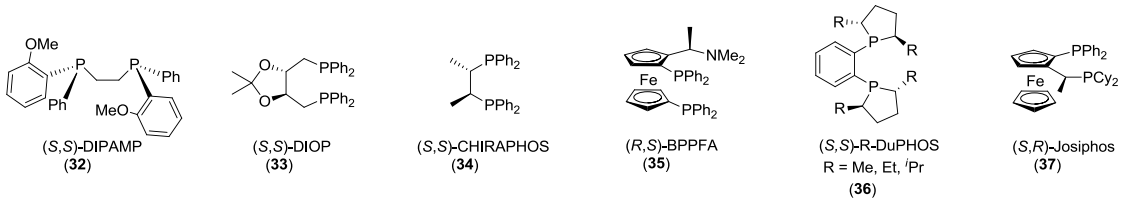


Figure 17 Various chiral diphosphine ligands developed over the last 40 years.

In the early 90's phospholane diphosphine ligands and DuPHOS[12] (**36**)were introduced by Burck *et al.* Also ferrocene derived diphosphines, such as Josiphos[13] (**37**), were investigated more intensively. In 1997, Pye and Rossen synthesised the chiral cyclophane containing diphosphine 4,12-bis(diphenylphosphino)[2.2]-*para*cyclophane (PhanePhos)(**38**)[14], which is nowadays a well established ligand in asymmetric hydrogenation. The chiral moiety of phanephos arises from its *para*-cyclophane backbone. The most known representatives of bis-phosphino-cyclophanes are in fact Ph-phanephos (**38**) and Xyl-phanephos (**39**). (Figure 18) These ligands are well established

in asymmetric hydrogenation reactions, showing extraordinary activity and steroselectivity. The impressive success of this chiral planar diphosphine ligand, comprises rhodium catalysed hydrogenation of dehydroamino acids[14], allylic acids[15], ruthenium catalysed hydrogenations of *β*-ketoesters[16], ruthenium hydrogenation of unfunctionalised ketones[17] and palladium catalysed aminations[18].

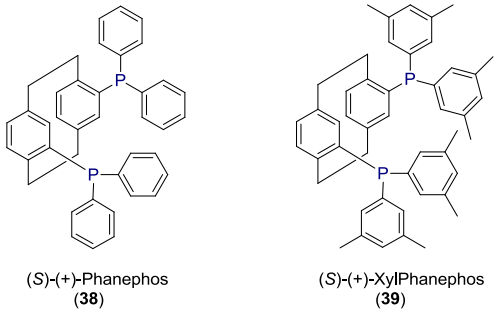


Figure 18 The well established chiral diphophine cyclophane ligands Phanephos (**38**) and XylPhanephos (**39**).

Despite the impressive results using this ligand, it is still relatively unknown in other homogeneous catalysed reactions, such as C-C bond forming reactions. Even the simplest phanephos[14] (R^1=R^2=Ph) ligands have not been investigated in Pd catalysed carbonylation, and were therefore studied in this thesis.

Subsequently, we became interested in studying the catalytic activity of palladium complexes derived from a range of different Phanephos derivatives. Herein we report the synthesis and characterisation of palladium complexes with ligands containing a *para*cyclophane backbone and their performance in asymmetric hydroxy- and alkoxy-carbonylation.

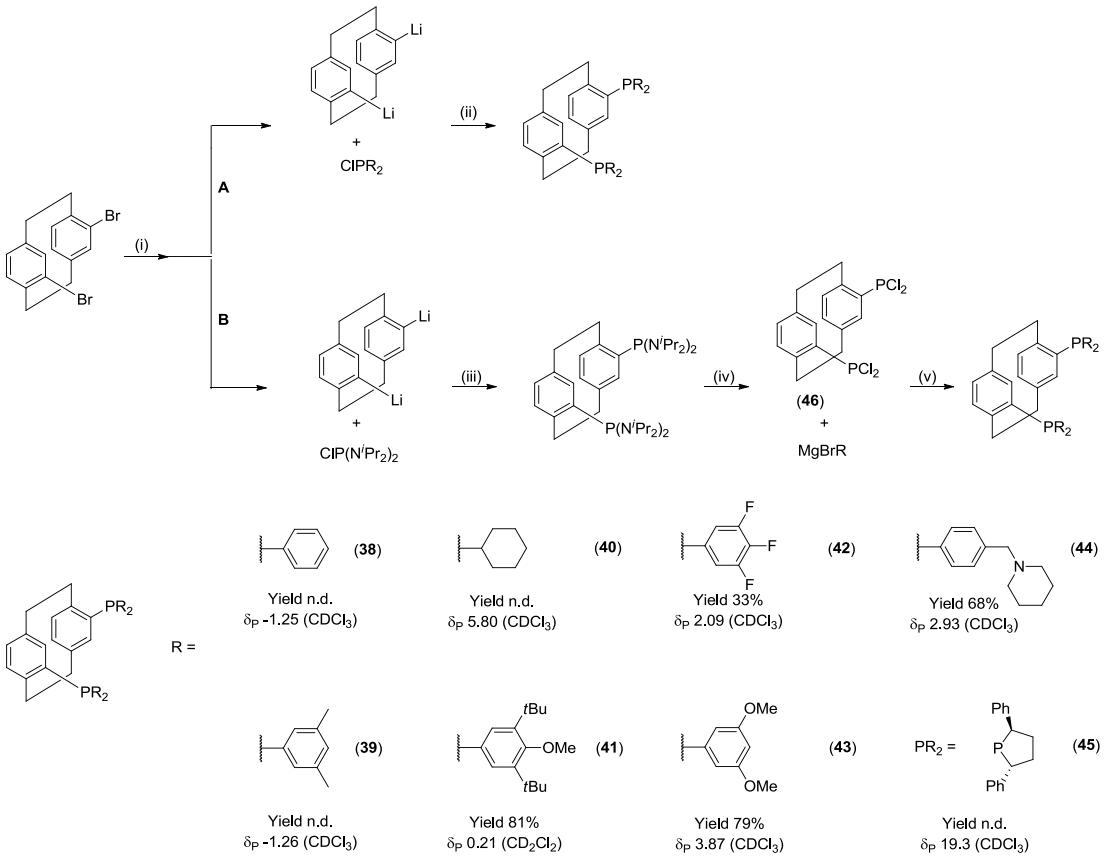
2.2 Results and Discussion

2.2.1 Ligand Preparation

Lithiation of the 4,12-*ortho*-dibromo[2.2]*para*cyclophane is already reported in literature using *t*-BuLi in tetrahydrofuran (THF), however attempts using this method as reported in literature resulted in an incomplete lithiation.[19] Therefore lithiation was conducted slightly differently from the method reported. The (*R*)-(-) or (*S*)-(+) enantiomer of 4,12-*ortho*-dibromo[2.2]*para*cyclophane was dissolved in diethyl ether and halogen metal exchange was possible by either route: The aryl halide was partially dissolved in Et_2O and then either

- cooled to –78 °C in a dry ice/acetone bath. Adding 2 equiv. of *t*-BuLi (1.6 M in pentane) and stirred for 2-3 hours at -78 °C before reactions, or
- 2 equiv. *n*-BuLi (2.5 M in hexane) was added at room temperature (between 10-18 °C) and the solution stirred for 2-3 hours.

Both organolithium reagents result in the same lithiated 4,12-dilithium-[2.2]-*para*cyclophane, but due to the extreme reactivity and pyrophoric nature of the *t*-BuLi solution, the less flammable *n*-BuLi solution was applied in most preparations. Lithiation was followed by either pathway **A** or **B** presented in Scheme 20. Due to the limited availability of R_2PCl, the Grignard of different aryl derivatives was used for the preparation of the diphosphine ligands (**42**), (**43**) and (**44**) (pathway B). Pathway **A** represents a simple metathesis reaction with addition of 2.0 equiv. of the desired Ar_2PCl to the lithiated intermediate and stirring over night providing a clean, high-yielding and convenient method for preparing various diaryl phosphine cyclophanes. After lithiation in route **B** the known compound 4-12-bis[bis(di-*iso*-propylamino)phosphino][2.2]-*para*cyclophane was formed, which was then reacted with an HCl solution in ether to give the 4,12-bis(dichlorophophino)[2.2]-*para*cyclophane.[20] Further reaction with an individual aryl Grignard reagent yielded the desire diphosphine compounds. Conversions of all ligands can be found in the *experimental II*.



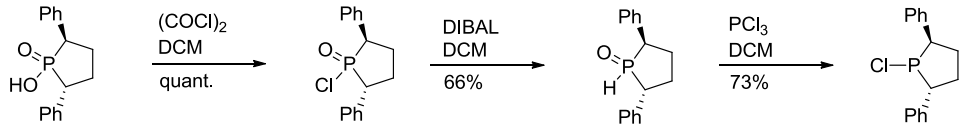
Scheme 20 Synthesis route **A** and **B** for diphosphine ligand (**38**)-(**45**). Reaction condition: (i) *n*-BuLi (2 equiv.) in Et_2O for 2-3 h at r.t.; **A** (ii) $ClPR_2$ (2 equiv.) added at r.t. overnight; **B** (iii) $ClP(N^iPr_2)_2$ (2.3 equiv.) added; (iv) HCl*Et_2O (28 equiv.) in Et_2O for 24 h; (v) MgBrR (5 equiv.) in Et_2O overnight.

The reactions presented in Scheme 20 are already known and were applied with slight alterations to the reported synthesis method.[21] In Scheme 20 the synthetic pathways for compounds (**40**)-(**45**) are summarised. All ligands, except ligands (**38**) and (**39**), were prepared from the commercially available compounds (*R*)-(-)-4,12-*ortho*-dibromo[2.2]-*para*cyclophane or (*S*)-(+)-4,12-*ortho*-dibromo[2.2]-*para*cyclophane.[20] Ligand (**40**) is a known compound but its reported synthetic route differs from the one described in this thesis.[20] The ^{31}P $\{^1H\}$39 NMR spectrum in C_6D_6 displays a single resonance signal at δ_P 5.80 ppm.

Ph-phanephos (**38**) and Xyl-phanephos (**39**) were obtained commercially or was kindly donated by Dr. Reddy's (formerly Chirotech). It was found that ligands (**38**), (**39**) and (**41**) are air stable in the solid state, whereas ligands (**40**), (**42**), (**43**) and (**44**) are air-sensitive.

Ligand (**45**) was prepared using Route A in Scheme 20. The chlorophosphine, (2*R*,5*R*)-1-chloro-2,5-diphenylphospholane, was prepared from (2*R*,5*R*)-1-hydroxy-1-

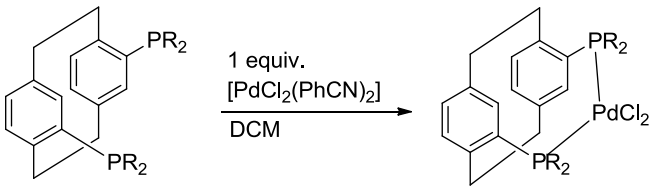
oxo-2,5-*trans*-diphenylphospholane by adapting a literature procedure (Scheme 21).[22] The ^{31}P {^{1}H} NMR spectrum of (**45**) showed a single resonance signal at δ_P 19.3 ppm, which is ascribed to the identical phosphine groups. Since (**45**) did not give a useful asymmetric carbonylation results, and by then other ligands had been discovered to give very exciting results, only one (*S*)-(+)-4,12-Bis((2*R*,5*R*)-2,5-diphenylphospholane)-[2.2]-*para*cyclophane of this ligand was prepared and very briefly investigated.



Scheme 21 Preparation of chlorophosphinephospholane for the synthesis of ligand (**45**).

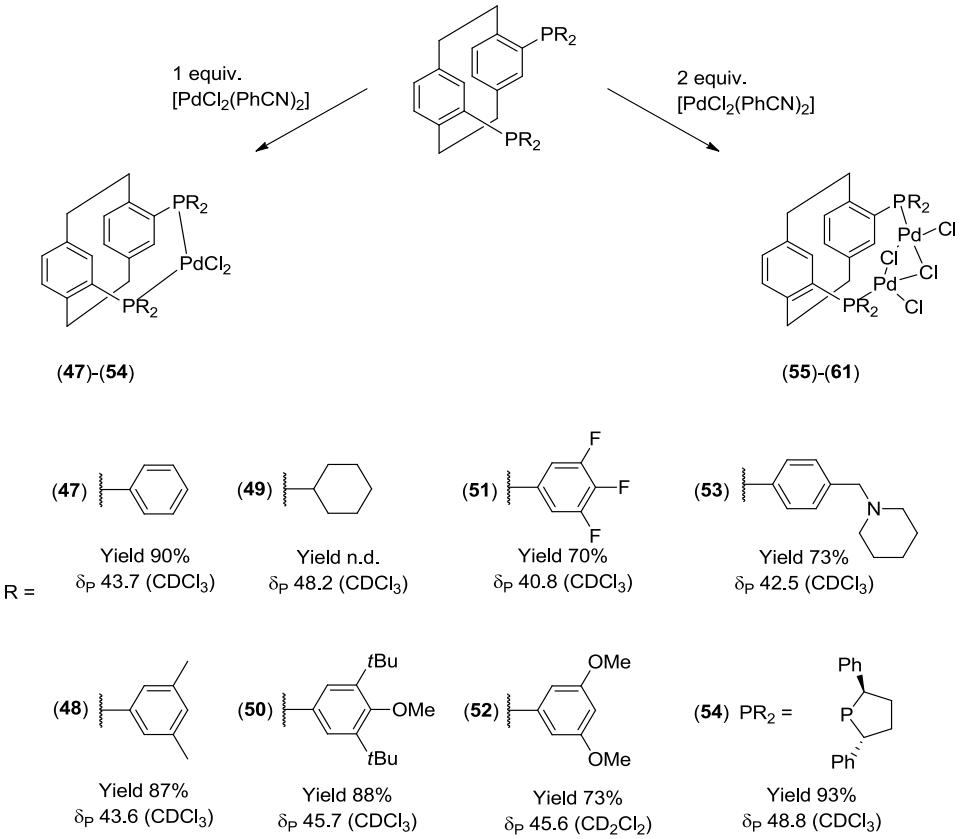
2.2.2 Preparation of the Palladium Complexes

All palladium complexes were prepared as presented in Scheme 22. Dissolving the ligand in dichloromethane (CH_2Cl_2) and adding the palladium precursor [$PdCl_2(PhCN)_2$], resulted over night in the formation of the desired complexes (**47**)-(**54**).



Scheme 22 Preparation of the palladium complexes (**47**)-(**54**). The ligands were dissolved in CH_2Cl_2 and 1 equiv. palladium precursor added.

Ligands (**40**) and (**45**) were used without any further characterisation and the monopalladium complexes formed, as shown in Scheme 23, by adding stoichiometric amounts of [$PdCl_2(PhCN)_2$] in CH_2Cl_2 at room temperature. Ligand (**45**) resulted in the expected monopalladium complex (**54**) in 34% yield, with the ^{31}P {^{1}H} NMR spectrum showing a single peak at δ_P 48.8 ppm.



Scheme 23 Preparation of the mono-Pd(II) and di-Pd(II) complexes. The monopalladium complexes could be prepared by addition of 1 equiv. of palladium precursor, whereas addition of 2 equiv. forms novel di-palladium complexes.

The preparation of the monopalladium complex (**49**) was found to be more complicated. When adding 1 equiv. of palladium precursor $[PdCl_2(PhCN)_2]$ to a CH_2Cl_2 solution of 1 equiv. (**40**), the ligand peak at δ_P 5.2 ppm in the ^{31}P $\{^1H\}$ NMR spectrum disappears and yellow precipitate together with several unidentified peaks formed. This shift was during later investigations found to be a bimetallic complex, resulting in a rare halogen bridged dipalladium arrangement possessing a Pd_2Cl_4 core. (Scheme 23) These complexes are discussed in more detail in *section 2.2.3*. Another attempt to prepare (**49**) was carried out by addition of less than 1 equiv. of $[PdCl_2(PhCN)_2]$ and slow addition of more palladium precursor until 1 equiv. was reached. This too resulted in the formation of yellow precipitate and several unidentified peaks in the ^{31}P $\{^1H\}$ NMR spectrum. Most of these peaks were observed before in the ^{31}P $\{^1H\}$ NMR, as less than 1% impurity in comparison to the ligand signal at 5.2 ppm. Attempts of dissolving the precipitate were unsuccessful. This is unusual, since all other monopalladium complex formations (**47**)-(**48**) and (**50**)-(**54**) could be prepared easily and provided clean complexes after thorough washing with hexane.

Due to difficulties obtaining a clean ^{31}P $\{^{1}H\}$ NMR spectrum, 1 equiv. of $[PdCl_2(PhCN)_2]$ and 1 equiv. of (**40**) where dissolved in CH_2Cl_2 and stirred for ~3 hours. Nevertheless, the ^{31}P $\{^{1}H\}$ NMR spectrum showed several signals and precipitate was present in solution, the solution was removed and the compound was washed thoroughly with hexane and dried under vacuum. Elemental analysis is in excellent agreement for the monopalladium (**49**). Mass spectrometry also confirmed the existence of the monopalladium structure (**49**); however, although the analysed samples yielded possible fragment ions that correlate with the ligand monopalladium structure, high molecular weight structures, that correspond to the presence of 2 ligands forming a complex with >1 Pd atom and higher were observed (*experimental II*). Therefore, while it is possible that the form in the mass spectrometer or that the monopalladium compound is not the only compound formed, supporting the likelihood of many different structures of $[PdCl_2(\mathbf{40})]_n$ present in the sample.

To confirm that the catalytic performance in hydroxy- and methoxy-carbonylation of styrene is not negatively influenced by various isomers of $[Pd_nCl_{2n}(\mathbf{40})]_n$, the catalytic activity and selectivity was compared to catalyst systems prepared *in-situ*, by simply adding 1 equiv. ligand (**40**) and $[PdCl_2(PhCN)_2]$, respectively, providing the same activity and selectivity.

The characterisation for the dipalladium complex (**57**) was also difficult. Addition of 2 equiv. $[PdCl_2(PhCN)_2]$ and 1 equiv. (**40**) in CH_2Cl_2 resulted in yellow precipitate in solution and several unidentified signals in the ^{31}P $\{^{1}H\}$ NMR spectrum. After work up and thorough washing, the ^{31}P $\{^{1}H\}$ NMR spectrum still displayed three single resonance peaks with frequencies at 38.2 ppm and 54.7 ppm and 55.9 ppm. The first value was assigned as the dipalladium complex (**57**), due to fact that all other dipalladium structures were also observed in this particular area (Table 13). It was possible to grow crystals of the bimetallic complex (**57**). The crystals were obtained by slow diffusion (~1 month) in a Schlenk flask under inert conditions. Attempts to separate the crystals from the by-products proved not possible.

An explanation for the difficulties of obtaining a clean sample may lie in the formation of several species such as dimeric or oligomeric structures as already discussed earlier on in *chapter I*. For a definite explanation further investigations would be necessary, but are outside of the scope of this work, since (**40**) did not deliver the best catalysts.

Complexes (**47**) and (**48**), and (**50**)–(**54**) were obtained by reaction of ligand (**38**) and (**39**), and (**41**)-(**45**) with stoichiometric amounts of $[PdCl_2(PhCN)_2]$ in CH_2Cl_2 at room

temperature, yielding (**47**) and (**48**) in 92 % and 87 % yield, respectively, and (**50**)–(**54**) in 70-88 % yield. In contrast to the complex formation with (**40**), all other ligands prepared formed the Pd complexes in a clean reaction.

Complex (**47**) was previously reported in literature but was prepared by a different synthetic route.[23] The ^{31}P {^{1}H} NMR spectrum of (**47**) displayed a sharp singlet at 43.7ppm. Generally for monopalladium complexes, a single signal was displayed between 40-48 ppm, even in the crude ^{31}P {^{1}H} NMR. Complexes (**47**)-(**53**) and (**55**)-(**61**), were characterised by elemental analysis, mass spectrometry, ^{1}H, ^{31}P {^{1}H} and ^{13}C {^{1}H} NMR spectroscopy, as well as optical rotation and melting points. Due to the poor performance in catalysis for (**54**), which will be discussed in more detail later, and its more complicated synthesis route, only mass spectrometry and ^{31}P {^{1}H} NMR was carried out.

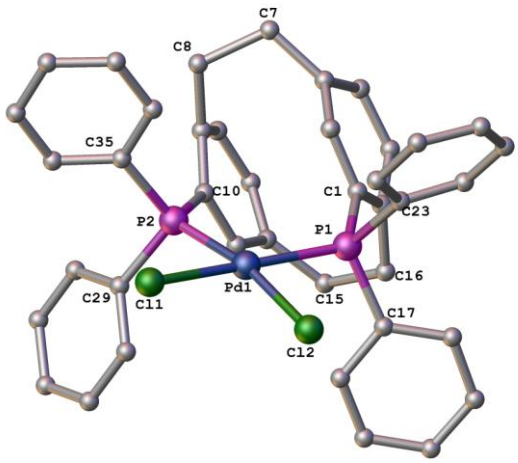


Figure 19 Monopalladium (*R*)-(**47**) crystal structure (protons removed for clarity).

Table 9 Selected bond lengths (Å) and angels (°) for complex (**47**).

Pd(1)—P(1) 2.293(8))	Pd(1)—P(2) 2.284(1)	Pd(1)—Cl(1) 2.356(6)
Pd(1)—Cl(2) 2.374(9)	P(1)—C(1) 1.835(4)	P(2)—C(10) 1.839(3)
P(1)—C(17) 1.824(4)	P(1)—C(23) 1.828(3)	P(2)—C(35) 1.819(4)
P(2)—C(29) 1.839(4)	C(7)—C(8) 1.593(6)	C(15)—C(16) 1.583(5)
Cl(1)-Pd(1)-Cl(2) 90.46(3)	P(1)-Pd(1)-P(2) 102.98(3)	Pd(1)-P(1)-C(1) 122.13(10)
Pd(1)-P(2)-C(10) 119.68(10)	P(1)-Pd(1)-Cl(1) 171.59(3)	P(2)-Pd(1)-Cl(2) 169.39(3)
P(1)-Pd(1)-Cl(2) 83.37(3)	P(2)-Pd(1)-Cl(1) 83.99(3)	

Single crystals suitable for X-ray analysis for complex (**47**), (**48**), (**50**) and (**51**) were successfully obtained *via* slow diffusion from a CH_2Cl_2/hexane solution. The crystal structure for (**47**) is already known and published.[23] For an easier comparison the crystal structure and selected bond lengths are displayed from our diffraction study.

The crystal structure of (**48**), (**50**) and (**51**) are displayed in Figure 20, Figure 22 and Figure 23, respectively. Relevant bond lengths and angles are listed in Table 9-12. All hydrogen atoms have been removed to enable a better view of the Pd palladium square plane, revealing the P-Pd-P arrangements of the individual crystal structures.

When comparing all 4 monopalladium crystal structure with one another, the distance between the phosphorus atoms P(1)—P(2) are observed to not vary much between (**47**), (**48**) and (**51**) 3.582, 3.616 and 3.613 Å. The slightly smaller distance of (**47**)**,** with 3.582 Å is most likely due to less steric interactions of the phenyl substituents. The complexes (**48**) and (**51**) show an almost identical distance between the P(1)—P(2) atoms.

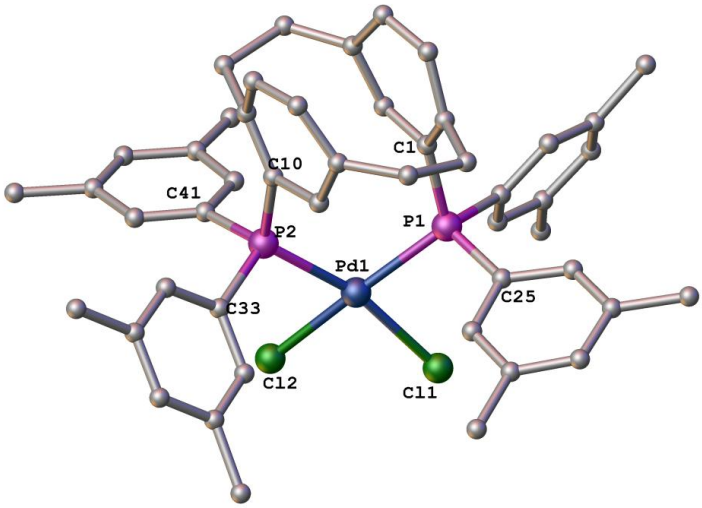


Figure 20 Monopalladium (*S*)-(**48**) crystal structure (protons removed for clarity).

Table 10 Selected bond lengths (Å) and angels (°) for complex (**48**).

Pd(1)—P(1) 2.305(3)	Pd(1)—P(2) 2.286(3)	Pd(1)—Cl(1) 2.346(3)
Pd(1)—Cl(2) 2.358(3)	P(1)—C(1) 1.829(1)	P(2)—C(10) 1.840(1)
P(1)—C(17) 1.832(1)	P(1)—C(25) 1.806(1)	P(2)—C(33) 1.856(1)
P(2)—C(41) 1.817(1)	C(7)—C(8) 1.565(2)	C(15)—C(16) 1.559(2)
Cl(1)-Pd(1)-Cl(2) 88.76(1)	P(1)-Pd(1)-P(2) 103.89(1)	Pd(1)-P(1)-C(1) 117.3(4)
Pd(1)-P(2)-C(10) 121.8(4)	P(1)-Pd(1)-Cl(1) 86.53(1)	P(2)-Pd(1)-Cl(2) 82.02(1)
P(1)-Pd(1)-Cl(2) 171.55(1)	P(2)-Pd(1)-Cl(1) 165.66(1)	

The P—Pd—P *bite angle* arises from a 10 membered metalacycle. For (**47**) this angle was observed to be 102.89(3) ° and slightly increases with more bulky substituents, up to 104.41(1) °. This bite angle is fairly large; all complexes gave the *cis* chelating isomer

rather than the *trans*. Sometimes with larger *bite angle* the *trans* isomer is the preferred species, due to steric interactions.[24] Also larger bite angle diphosphines with less sterically rigid structure, such as dpph (bis(diphenylphosphino)heptanes), have been observed to form in some cases bimetallic Pd_2Cl_4 complexes, as shown in Figure 21.[25] It is important to note that these types of Pd2 species are quite different to those that will be discussed shortly.

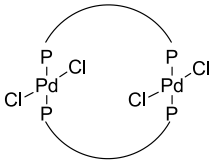


Figure 21 Bimetallic Pd_2Cl_4 complexes formed by diphosphine ligands with larger bite angles.

Comparing the *bite angle* of palladium complex (**48**) with 103.89(1) °, and the known platinum analogue complex [$PtCl_2$(**39**)] (103.75 °), the bite angle values are in good agreement.[26] The observed bond distances of Pt—P (2.2739(12) Å and 2.2749(12) Å) are slightly decreased in comparison to the Pd—P bond lengths, other bond lengths such as Pt—Cl and P—C do not differ much. Similar distortions for the square planar geometry of the Pt and Pd complex for P(1)—Pt(1)—Cl(2) and P(2)—Pt(1)—Cl(1) (164.96(24)°; 170.19(5)°) have been observed.

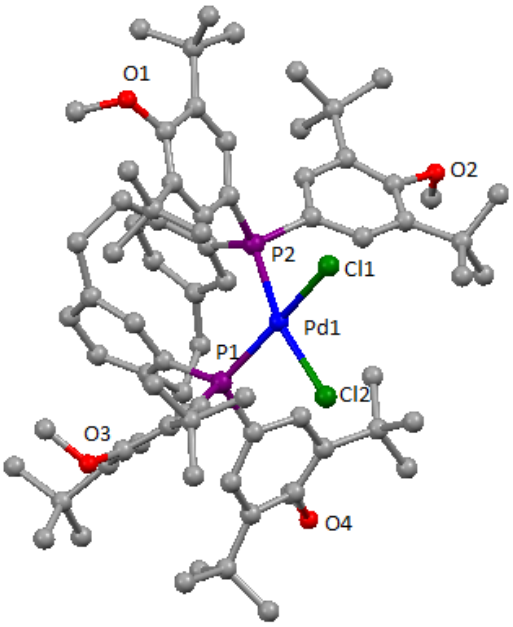


Figure 22 Monopalladium (*S*)- (**50**) crystal structure (protons removed for clarity).

Table 11 Selected bond lengths (Å) and angles (°) for complex (**50**).

Pd(1)—P(1) 2.285(3)	Pd(1)—P(2) 2.286(3)	Pd(1)—Cl(1) 2.369(3)
Pd(1)—Cl(2) 2.369(3)	P(1)—C(1) 1.792(1)	P(2)—C(10) 1.825(8)
Cl(1)-Pd(1)-P(2) 165.23(7)	Cl(1)-Pd(1)-Cl(2) 90.55(6)	P(1)-Pd(1)-P(1) 103.25(7)
P(1)-Pd(1)-Cl(1) 84.65(7)		

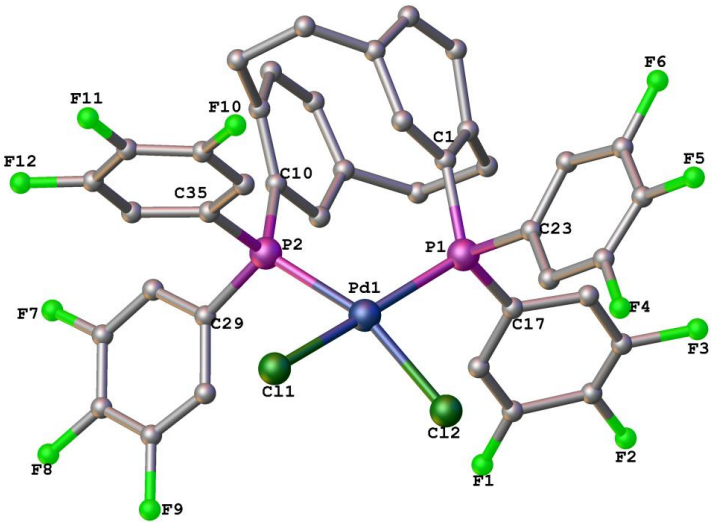


Figure 23 Monopalladium (*R*)- (**51**) crystal structure (protons removed for clarity).

Table 12 Selected bond lengths (Å) and angles (°) for complex (**51**).

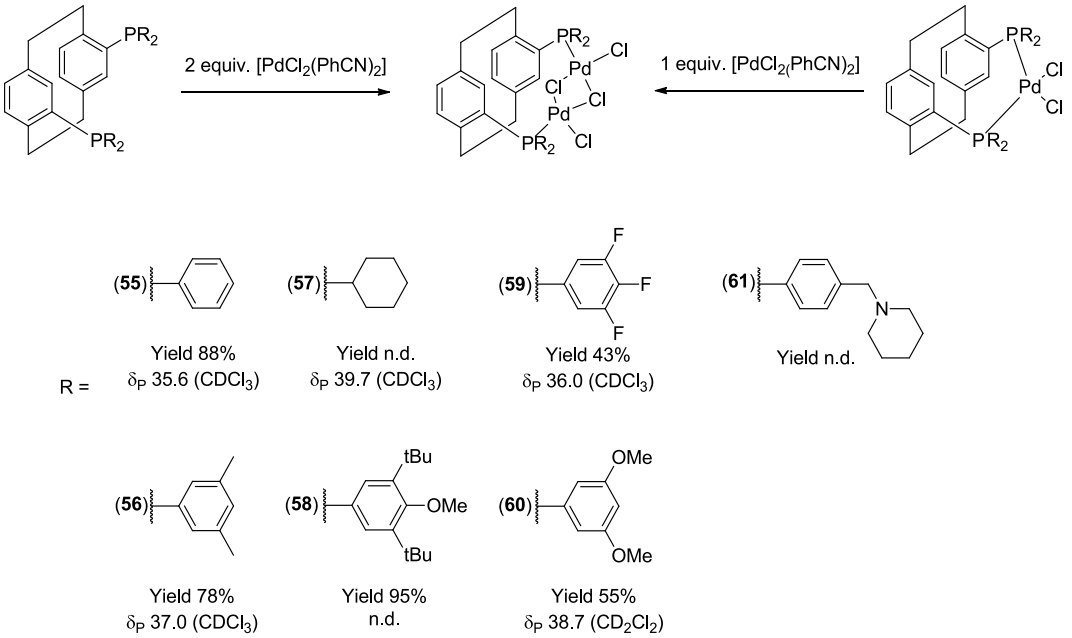
Pd(1)—P(1) 2.286(3)	Pd(1)—P(2) 2.286(4)	Pd(1)—Cl(1) 2.348(4)
Pd(1)—Cl(2) 2.348(3)	P(1)—C(1) 1.862(1)	P(2)—C(10) 1.819(1)
P(1)—C(17) 1.765(2)	P(1)—C(23) 1.833(1)	P(2)—C(35) 1.835(1)
P(2)—C(29) 1.839(2)	C(7)—C(8) 1.517(2)	C(15)—C(16) 1.660(3)
Cl(1)-Pd(1)-Cl(2) 90.54(12)	P(1)-Pd(1)-P(2) 104.41(12)	Pd(1)-P(1)-C(1) 115.8(5)
Pd(1)-P(2)-C(10) 121.0(4)	P(1)-Pd(1)-Cl(1) 166.91(1)	P(2)-Pd(1)-Cl(2) 161.38(1)
P(1)-Pd(1)-Cl(2) 86.75(1)	P(2)-Pd(1)-Cl(1) 81.75(1)	

The Pd—P and Pd—Cl bond lengths observed for all complexes are situated all within the normal ranges of diphosphine palladium dichloride compounds. The positions of the chlorides are almost equally distant from the palladium.

Palladium metals are known to form square planar complexes. All crystal structures show a strongly distortion from the square-planar geometry, the angles are summarised in the tables below the individual crystal structures. Complex (**51**) showed the strongest distortion from the square planar formation, with an angle of 166.91(1) ° for P(1)—Pd(1)—Cl(1) and 161.38(1) ° for P(2)—Pd(1)—Cl(2). Distortions from the square-planar geometry have been reported previously, similar parameters have been observed with *trans* coordinating diphosphine ligands.[27]

2.2.3 Preparation of the Bimetallic Complexes

Ligands (**38**)-(**44**) were found to also form bi-metallic complexes, resulting in a rare halogen bridged dipalladium arrangement, possessing a Pd_2Cl_4 core. This structure, with one diphosphine bridging core structure, is quite common for monophosphines but is limited to one other ligand for bridging diphosphines.[28] These binuclear complexes can be prepared by the synthetic pathways displayed in Scheme 24. Either starting from the ligand and adding 2 equiv. $[PdCl_2(PhCN)_2]$, or starting from the monopalladium complex and adding 1 equiv. of palladium precursor, leads to the dipalladium complex.



Scheme 24 Preparation of the di-Pd(II) complex. This complex can be prepared *via* two different approaches. This can be achieved by the addition of 2 equiv. of palladium precursor, or by addition of 1 equiv. of palladium precursor to a monopalladium complex.

The signals in the $^{31}P\{^1H\}$ NMR spectra for the dipalladium complexes show an upfield shift compared to the signals obtained for the monopalladium catalysts. Compound (**55**) was found to be too insoluble in common organic solvents for $^{13}C\{^1H\}$ NMR analysis, even over 19 hour's acquisition time, and no spectra could be obtained. Complex (**58**) and (**61**) also had limited solubility; however, in these cases their solubility in various deuterated organic solvents was so insufficient that not even ^1H or $^{31}P\{^1H\}$ NMR spectra could be recorded. Characterisation of compound (**58**) and (**61**) were restricted to mass spectrometry. The different $^{31}P\{^1H\}$ NMR chemical shifts of the mono- and dipalladium complexes are summarised in Table 13.

IR spectroscopy was used to investigate the M-Cl stretching vibrations of the mono- and di-Pd(II) complexes (**38**) and (**39**) only. Little infrared data on bridged palladium compounds, such as $[Pd_2Cl_4L_2]$ (L = phosphorus) has been published.[29] However, the metal halide stretches were generally found at 370-345, 310-300 and 280-250 cm^{-1}. Unfortunately, tertiary phosphine deformation modes and Pd-P modes can occur in the same region. Stronger signals than those observed for the ligand could be consistent with the symmetric and asymmetric Pd-Cl stretches, although this conclusion remains tentative. The two medium *cis* Pd-Cl stretches for the mono-Pd(II) complex (**47**) was observed at 306 and 252 cm^{-1}. In contrast complex (**48**) showed only one weak band at 312 cm^{-1} and the second Pd-Cl stretching mode might be mixed with the ligand modes in a range around 280 cm^{-1}.

In literature the Pd-Cl terminal stretching vibration for $[Pd_2Cl_4(PPh_3)_2]$ is reported at 359 cm^{-1}. For complex (**56**) the terminal chlorides were found to be in a *trans* conformation relative to each other according to the crystal structure shown below. The terminal Pd-Cl stretching vibrations for complex (**55**) and (**56**) were found at 354 and 362 cm^{-1}, respectively. The bridging M-Cl stretchings may be affected by other resonances and although Raman spectroscopy was performed to clarify this part, it did not give any conclusive information. IR spectroscopy was therefore not considered useful for this class of complex.

The consistent NMR shifts, mass spectra and the crystal structures obtained, showing the Pd_2Cl_4L species, are very strong evidence for the formation of $[Pd_2(Cl)_2(\mu\text{-}Cl)_2(\mu\text{-}P—P)]$ complexes.

Table 13 ^{31}P {^{1}H} NMR data for mono- and di-Pd(II) complexes.

Ligand	^{31}P {^{1}H} NMR (ppm) **mono-Pd-complex**	^{31}P {^{1}H} NMR (ppm) **di-Pd-complex**
(**38**)	43.7	35.6
(**39**)	43.6	37.0
(**40**)	48.2	39.7
(**41**)	45.7	No signal
(**42**)	40.8	36.1
(**43**)	46.7	38.7
(**44**)	42.5	No signal
(**45**)	48.8	n.d.

The final proof for the formation of the dipalladium structure was given by crystal structures of complexes (**56**) and (**57**) (Figure 24 and Figure 25). Suitable single crystals were grown by slow diffusion of hexane into a saturated solution of the complexes in CH_2Cl_2 at room temperature. Unfortunately, it was not possible to obtain a single crystal suitable for X-ray diffraction from the di-Pd(II) complexes (**55**), (**58**), (**60**), (**59**) and (**61**). No attempts to prepare the dipalladium complexes from ligand (**45**) were made, due to its time consuming preparation.

Selected bond lengths and angles for both crystal structures are shown in Table 14 and Table 15. The X-ray structure of compound (**56**) confirms the presence of two Pd atoms. Two Pd and 4 Cl atoms form a $Pd_2(\mu\text{-}Cl)_2\text{-}Cl_2$ unit sharing two chloride atoms. The two palladium atoms are in close contact with each other, with a Pd—Pd distance of 2.913(3) Å. Such a short Pd—Pd distance is unprecedented, compared to other di-Pd systems found in the literature.[30] The Pd—Cl bonding is far from symmetric, containing one bridging Pd—Cl bond that is slightly longer (Pd(1)—Cl(1) 2.456(4) Å) than that found for the other bridging chloride (Pd(1)—Cl(3) 2.341(4) Å). Both of these are longer than the terminal Pd-Cl bond, Pd(1)—Cl(2) 2.258(4) Å. The angles between the two more closely coordinated chloride atoms Cl—Pd—Cl are almost linear (Cl(2)—Pd(1)—Cl(3) 173.79(17) ° and Cl(1)—Pd(2)—Cl(4) 175.84(16) °). Both terminal chloride atoms (Cl(4) and Cl(2)) are located gauche to each other with a torsion angle of Cl(4)—Pd(2)—Pd(1)-Cl(2) 128.299(2) Å. This $[Pd_2(\mu\text{-}X)_2\text{-}X_2L]$ core is a very rare structure and few publications have referred to this binary configuration.[31] Moreover, such a strong deviation in the Cl—Pd—Pd—Cl angle has so far never been observed. Only one other complex was found by Gelman and coworkers to show a similar $[Pd_2(\mu\text{-}Cl)_2\text{-}Cl_2L]$ (L = diphosphine) framework.[24a] Reporting about a diphosphine ligand with a triptycene-

based backbone, this group reported a unique non-planar Pd_2Cl_4 core. In their structure the terminal chlorides were *syn* to each other.

The Pd_2Cl_4 core in complex (**56**) can be considered to possess axial chirality. This unit consists of a stereogenic axis *via* a Cl—Pd–Pd—Cl bonding system. If this apparently unique $Pd_2(\mu\text{-}Cl)_2\text{-}Cl_2$ core can be considered as chiral, then according to CIP rules this axis can be labeled as a (*R*) enantiomer.

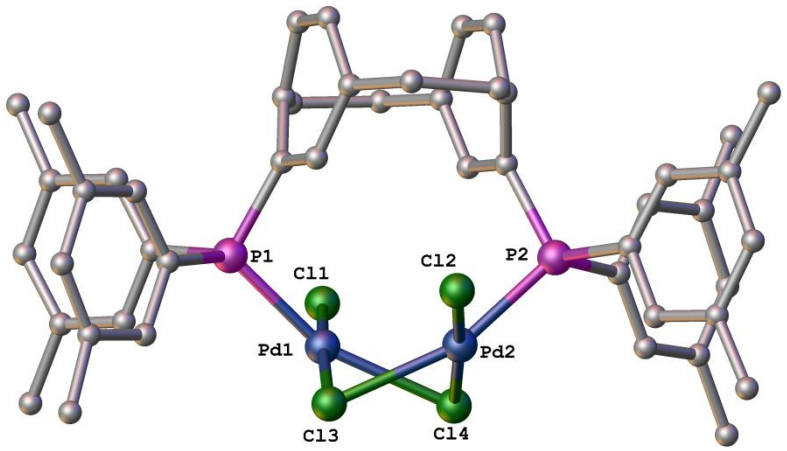


Figure 24 Molecular structure of the di-Pd(II)-(*S*)-Xyl-phanephos (**56**) (protons removed for clarity).

Table 14 Selected bond lengths (Å) and angles (°) for the crystal structure (**56**).

Pd(1)—P(2) 2.229(5)	Pd(1)—Cl(2) 2.258(4)	Pd(1)—Cl(3) 2.341(4)
Pd(1)—Cl(1) 2.456(4)	Pd(2)—Cl(1) 2.337(4)	Pd(2)—Cl(3) 2.443(4)
Pd(2)—Cl(4) 2.270(4)	Pd(2)—P(1) 2.227(4)	Pd(1)—Pd(2) 2.9133(19)
Cl(2)-Pd(1)-Cl(3) 173.79(17)	Cl(1)-Pd(2)-Cl(4) 175.84(16)	P(2)-Pd(1)-Cl(2) 86.85(16)
P(1)-Pd(2)-Cl(4) 86.48(16)	P(2)-Pd(1)-Cl(3) 99.01(16)	P(1)-Pd(2)-Cl(1) 97.61(16)
P(2)-Pd(1)-Cl(1) 159.83(16)	P(1)-Pd(2)-Cl(3) 161.65(16)	Cl(2)-Pd(1)-Cl(1) 90.24(16)
Cl(4)-Pd(2)-Cl(3) 90.53(15)	Cl(3)-Pd (1)-Cl(1) 84.95(15)	Cl(1)-Pd(2)-Cl(3) 85.34(14)
Pd(2)-Cl(1)-Pd(1) 74.82(12)	Pd(1)-Cl(3)-Pd(2) 74.99(12)	

The crystal structure of complex (**57**) is shown in Figure 25. This crystal structure also confirms the presence of two palladium atoms and the Pd_2Cl_4 core. However, in contrast to (**56**), (**57**) was found to possess a Pd_2Cl_4 core in which the terminal chlorides are nearly *syn* to each other. The Pd—Pd distance within the four membered ring is 3.109(2) Å, which is similar to the Pd—Pd distance reported by Gelman and coworkers (3.036

Å).[24a] In contrast to (**56**), this $Pd_2(\mu\text{-}Cl)_2$ structure was found to consist of a strongly distorted deltoid geometry.

Furthermore, minor deviations were found between the Pd—P bond lengths of crystal structures (**56**) and (**57**). As a result of the cyclohexyl groups, complex (**56**) is more sterically hindered than the xylyl analogue and due to the incorporation of this four membered network into a very rigid diphosphine backbone, this has been found to slightly increase all bond lengths participating in this $[Pd_2(\mu\text{-}Cl)_2\text{-}Cl_2(P—P)_1]$ core.

The P—P distances in (**56**) and (**57**) are 5.561(1) Å and 5.582(6) Å, respectively, which is strongly bent compared to the P—P distance of 3.616 Å in the monomeric $PdCl_2$(Xyl-phanephos) (**48**). The distances observed by Gelman and co-workers for the P—P distances in the Pd monomer and dimer are 4.549 and 5.907 Å, respectively. Due to the backbone arrangement in the triptycene structure a generally larger bite angle, hence larger P—P distance, is already existent (triptycene free ligand P—P distance is 4.53 Å). Therefore, there is not such a great need to bend the phosphines, as it is the case for the *para*cyclophane backbone. Other, large *bite angles* have been observed to form di-rhodium complexes. Van Leeuwen and co-workers reported diphophine ligands based on benzofurobenzofuran, P—P distances were observed to differ from 4.36 Å for mono-rhodium complexes up to 6.64 Å for halogen bridged Rh_2Cl_2L compounds.[32]

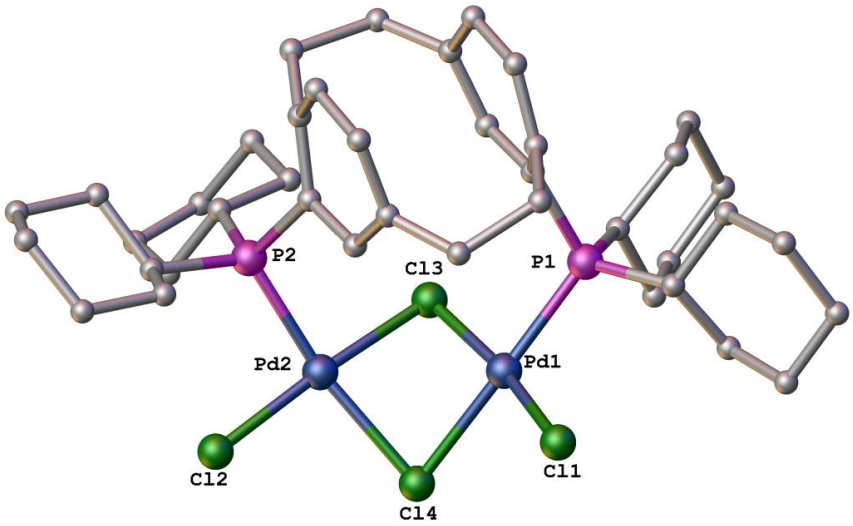


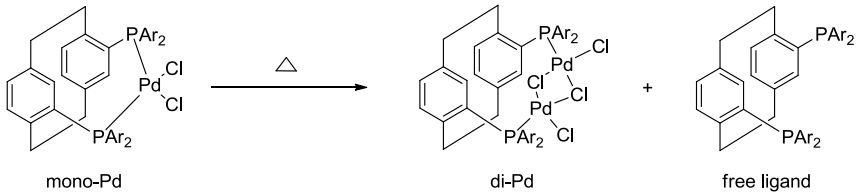
Figure 25 Crystal structure of the di-Pd(II)-(*R*)-cyclohexyl-phanephos (**57**).

Table 15 Selected bond lengths (Å) and angles (deg) for crystal structure (**57**).

Pd (1)—P (1) 2.2581(7)	Pd (1)—Cl (2) 2.3201(7)	Pd (1)—Cl (3) 2.4508(7)
Pd (1)—Cl (1) 2.2909(7)	Pd (2)—Cl (2) 2.3401(8)	Pd (2)—Cl (3) 2.4341(1)
Pd (2)—Cl(4) 2.2685(8)	Pd (2)—P (4) 2.2467(1)	Pd (1)—Pd (2) 3.1092(10)
P(1)-Pd(1)-Cl(1) 94.634(16)	P(4)-Pd(2)-Cl(4) 91.951(16)	P (1)-Pd(1)-Cl(2) 90.250(16)
P(4)-Pd(2)-Cl(2) 92.562(17)	P(1)-Pd(1)-Cl(3) 171.048(20)	P(4)-Pd(2)-Cl(3) 167.145(17)
Cl(1)-Pd(1)-Cl(2) 170.556(17)	Cl(4)-Pd(2)-Cl(2) 173.450(22)	Cl(1)-Pd(1)-Cl(3) 92.937(15)
Cl(4)-Pd(2)-Cl(3) 93.654(17)	Cl(2)-Pd(1)-Cl(3) 82.948(14)	Cl(2)-Pd(2)-Cl(3) 82.903(15)
Pd(1)-Cl(2)-Pd(2) 83.699(16)	Pd(2)-Cl(3)-Pd(1) 79.060(14)	

These dipalladium complexes are not considered as chelating ligands anymore but coordinate in a monodentate manner to each palladium metal, which are themselves connected to one another *via* bridging chloride anions.

Preliminary computational calculations were carried out to gain some insight into the dipalladium complexes (carried out by Prof. Dr. Michael Bühl). These calculations suggested (**56**) to be a thermodynamically more stable species than (**48**). If the dipalladium is truly the more stable species, then we should be able to prepare the dipalladium complex from the monopalladium species by simply heating the monopalladium complex (without any added Palladium salts), unless the reaction is kinetically disfavoured.



Scheme 25 Attempts for preparing the dipalladium complex from the monomeric species. The monopalladium catalyst (**48**) was treated with heating, although formation of the dipalladium complex (**56**) was not observed.

After refluxing for 4 hours in CH_2Cl_2 or MeOH no change in the ^{31}P $\{^1H\}$ NMR spectrum occurred. Samples of (**48**) were even heated in the microwave for 30 min at 100 °C in CH_2Cl_2, resulting again in the monopalladium species as the only product in the ^{31}P $\{^1H\}$ NMR spectra.

Another experiment was undertaken to investigate the stability of the dipalladium species. The dipalladium complex was dissolved in an NMR tube in degassed $CDCl_3$ under argon atmosphere and free ligand was added. The monopalladium species could be regained, according to the colour changes, within seconds. This experiment was carried out on 3 different dipalladium complexes, (**56**), (**57**) and (**58**). Both monomers and dimers are therefore both accessible depending upon the relative amounts of ligand and Pd.

2.2.4 Catalysis Studies: Hydroxycarbonylation

After studying the coordination chemistry of these novel dipalladium complexes, the catalytic activity of the mono- and di-palladium Phanephos derived complexes were investigated.

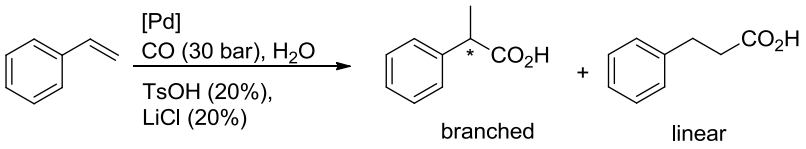
Chaudhari and coworkers found when using monophosphine palladium(II) catalysts that LiCl and *p*-TsOH promoters give high chemo- and regioselectivity in styrene hydroxycarbonylations, using monophosphine palladium(II) catalysts. The same promoters (LiCl and *p*-TsOH) were observed to give promising results in the hydroxycarbonylation of styrene using achiral diphosphine catalysts.[33] All hydroxycarbonylation reactions were carried out at 30 bar CO, in 2-butanone, 2.5 equiv of H_2O, with preformed catalysts, a substrate/catalyst ratio of 100/1 and promoter concentrations were 20 mol% LiCl and *p*-TsOH*H_2O, unless otherwise stated.

Methoxycarbonylations, is discussed in detail in 2.1.4.1.2, were carried out at 30 bar CO, in MeOH, 20 mol% LiCl and *p*-TsOH*H_2O, with preformed catalysts and a Pd/S ratio of 1/100, unless otherwise stated.

A series of experiments was performed to compare the catalytic performance of mono- and di-Pd(II) diphosphine systems. Primarily 3 different substrates were tested in hydroxycarbonylation reactions, including styrene derivatives (styrene, 4-*tert*butylstyrene, *cis*-β-methylstyrene and 2-methoxy-6-vinylnaphtalene), norbornene and 1-(4-toluenesulfonyl)-pyrrolidine. All complexes were found to exhibit good catalytic activity. Hydroxycarbonylation of styrene was found to be highly chemoselective towards the acid with no noticeable by-product formation. Of great value are the di-Pd(II) complexes, which were found to combine valuable B/L ratios with excellent enantioselectivity and conversions. The relative amount of branched acid to linear acid will be articulated in B/L ratios.

2.2.4.1 Hydroxycarbonylation of styrene

In Table 16 and Table 17 temperature effects on the performance of catalyst (**47**)/ (**55**) and (**48**)/ (**56**) in the hydroxycarbonylation of styrene are listed, comparing their catalytic behaviour at temperatures between 45-100 °C.



Scheme 26 Asymmetric hydroxycarbonylation of styrene results branched and linear carboxylic acids.

At a higher temperature of 100 °C, high conversions were observed, although regioselectivity towards the branched carboxylic acid was low and almost no enantioselectivity was induced. When decreasing temperatures to 50 °C, regio- and enantio-selectivities were observed to improve up to 5 times, in some cases even higher. It is a well known fact that decreasing the temperature in many catalytic systems enhances stereoselectivity but also leads to lower activity.

A very useful feature is that both mono- and di-Pd(II) complexes did give better results without adding an excess of free ligand, which leads to higher (unwanted) linear product. Entry 2, 4 and 6 display the catalyst behavior when adding an excess of ligand to the reaction (Table 16).

Table 16 Hydroxycarbonylation of styrene with catalysts (**47**)/ (**55**) and (**48**)/ (**56**) at 100°C.

Entry[a]	Catalyst	Time (h)	Yield[b] (%)	B/L[c] (B:L)	e.e.[d] (%)
1	(**47**)	4	60	0.5 (32:68)	7
2[e]	(**47**)	4	57	0.3 (21:79)	rac
3	(**55**)	4	56	0.4 (30:70)	10
4[e]	(**55**)	4	55	0.2 (19:81)	5
5	(**55**)	18	66	0.5 (31:69)	7
6[e]	(**55**)	16	77	0.2 (17:83)	4
7	(**48**)	17	60	0.3 (21:79)	16
8	(**56**)	17	67	0.3 (21:79)	18
9	**PPh_3 + Pd(dba)$_2$**	19	67	18	rac

[a] Reactions were carried out in 2-butanone and 2.5 equiv. of water, using 1mol% catalyst, 1mmol styrene and 30 bar CO pressure. [b] Yields of pure acid isolated after acid-base extraction of the crude reaction mixture. [c] The branched to linear (B/L) ratio was determined by ^{1}H-NMR spectroscopy. [d] Enantiomeric excess (e.e.) was determined by HPLC analysis, the (*R*) catalyst gives the (*R*) enantiomer and vice versa. [e] 3mol% ligand added.

Investigations of the commercially available monophospine system PPh_3/Pd(dba)$_2$ at 100 °C, resulted in a high B/L ratio of 18 and the same activity as was observed for the diphosphine catalysts (**47**)/ (**55**) and (**48**)/ (**56**).

The high regioselectivity of the PPh_3/Pd(dba)$_2$ system can be attributed to the monophosphines. As already discussed in *chapter I* diphosphine systems have been observed to behave differently from monophosphines in most carbonylation reactions. Conversions and regioselectivity for hydroxy- and alkoxy-carbonylations are generally reported to be higher with monophosphines than with diphosphines. However, diphosphine ligands are known to offer better control over chiral induction due to their formation of more stable complexes.

Remarkably, when decreasing the temperature from 100 °C to 70 °C and lower, dipalladium complexes were generally found to provide better yields, stereo- and regio-selectivity than the analogous monomers. Of special interest is complex (**56**), as it gives 80 % e.e and a B/L ratio of 1.1, with 71 % yield. (Table 17; Entry 10)

Table 17 Hydroxycarbonylation of styrene with palladium complexes of Ph-phanephos (**47**)/ (**55**) and Xyl-phanephos (**48**)/ (**56**) at temperatures of 45-70 °C.

Entry[a]	Catalyst	Temp (° C)	Time (h)	Yield[b] (%)	B/L[c] (B:L)	e.e.[d] (%)
1	(**47**)	70	17	10	0.6 (38:62)	38
2	(**55**)	70	17	73	1.1 (52:48)	52
3	(**56**)	70	17	77	0.8 (44:56)	63
4	(**47**)	60	17	4	1.2 (55:45)	55
5	(**55**)	60	17	29	1.2 (55:45)	59
6[e]	(**55**)	60	16	32	1.1 (52:48)	63
7	(**48**)	60	17	14	0.7 (41:59)	66
8	(**56**)	60	16	58	1 (50:50)	76
9	(**55**)	50	72	35	1.1 (52:48)	69
10	(**56**)	50	72	71	1.1 (52:48)	80
11	(**48**)	50	72	8	0.4 (30:70)	50
12	(**55**)	45	17	18	1.3 (57:43)	57
13[e]	(**55**)	45	17	13	1.2 (55:45)	59
14	(**56**)	45	17	15	1.2 (55:45)	81
15[e]	(**56**)	45	17	7	1.2 (55:45)	80

[a] Reactions were carried out using 1mol% catalyst, 1mmol styrene, 2.5mmol H_2O, in 1.5ml butanone at 30 bar CO. [b] Yields of pure acid isolated after acid-base extraction. [c] The branched to linear (B/L) ratio was determined by ^{1}H-NMR spectroscopy. [d] Enantiomeric excess (e.e.) was determined by HPLC analysis, the (*R*) catalyst gives the (*R*) enantiomer and vice versa. [e] Experiment was conducted a second time to confirm reproducibility.

The enantiomeric excess of 80 % is exceptionally high for this reaction, and to the best of our knowledge the highest obtained up to date. Alper and coworkers reported in 1990 about an e.e. of over 90 % and total selectivity towards the branched product but this reaction has not yet been reproduced and the enantiomeric excess was determined by optical rotation.[34] A number of researcher have contacted our group reporting lower selectivity with this system, and in any case high catalyst loadings were used. A more relevant comparison is the e.e. of 43 % reported for a diphosphine system which was accomplished by Claver and co-workers, using a chiral sulfonated diphosphine, (*S*,*S*)-2,4-bis(diphenylphosphino)pentane ((*S*,*S*)-BDPPTS) (**62**).

All catalytic systems showed low enantioselectivity when hydroxycarbonylation was performed at temperatures higher than 70 °C. Therefore, it was necessary to decrease temperatures and lengthen reaction times to achieve higher yields and good stereoselectivity.

Temperature is a very important parameter in catalysis; therefore, it was necessary to perform catalytic runs at different temperatures, as shown in Table 16 and Table 17. Especially stereo- and regioselectivity appeared to get negatively affected by higher temperatures. For temperatures ranging from 70 °C to 100 °C the yields were not affected tremendously. As mentioned above the high enantioselectivity (81 % e.e.) obtained with the chiral di-Pd(II) complex (**56**) between 45 °C- 50 °C and 30 bar is remarkable. Most of the prepared catalysts were found to give better results at lower temperatures (around 60-70 °C) and 30 bar CO.

A short experiment was carried out by dissolving the dipalladium complex (**56**) in $CDCl_3$, pressurising it to 30 bar and then releasing the CO to check for changes in the $^{31}P\{^1H\}$ NMR spectrum. The recorded spectrum showed two palladium species, (**48**) and (**56**). This suggests that during the catalytic cycle the dipalladium catalyst releases the palladium, possibly to act as a monopalladium species, with a free palladium to act as a co-catalyst. Co-catalysts have been reported before in literature to improve catalysis, using co-catalysts such as Cu or Sn.

It is certainly too early to say that the active species does or does not keep a bridging diphosphine ligand, but the results suggest that there is something unique about the dimeric pre-catalysts that allows it to give higher activity and selectivity than the monomer.

Several experiments were performed to compare the catalytic performance of these novel complexes under different promotor conditions. These experiments were carried out at 100 °C, before we realised that low temperature carbonylations were possible. As mentioned earlier, previous studies by Chaudhari and coworkers have shown that the promotors LiCl and *p*-TsOH display highest activity and selectivity with monophosphine ligands. Additional studies with diphosphine ligands in this group again indicated this promoter combination to be very useful, resulting in good yields and high B/L ratios. Also, a previous PhD student in this group further investigated different types of promoters, which can be found in *chapter I*. Furthermore a current PhD student in this group will carry out further investigations using different promoters, solvents and substrates. Therefore, in this project the role of the promoter concentration was only briefly investigated, by observing changes in the activity and selectivity with changes in the promoter concentrations (Table 18).

Table 18 Hydroxycarbonylation reactions of styrene at different promotor concentrations at 100 °C.

Entry[a]	Cat	Time (h)	Promotor (%)	Yield[b] (%)	B/L[c] (%)	e.e. [d] (%)
1	(**47**)	18	5	51	0.3 (22:78)	8
2	(**47**)	18	20	51	0.3 (21:79)	8
3	(**55**)	16	5	59	0.4 (29:71)	5
4[e]	(**55**)	18	5	44	0.5 (32:68)	9
5	(**55**)	18	20	66	0.5 (31:69)	7
6	(**55**)	16	No LiCl, 20% acid	38	0.3 (20:80)	5
7[e]	(**55**)	18	No LiCl, 20% acid	57	0.2 (19:81)	2
8	(**55**)	16	40	53	0.7 (42:58)	2
9[e]	(**55**)	18	40	75	0.7 (40:60)	4

[a] Reactions were carried out using 1mol% catalyst and 1mmol styrene at 100°C and 30bar CO pressure, in butanone and 2.5 equiv. of water. [b] Yields of pure acid isolated after acid-base extraction of the crude reaction mixture. [c] The branched to linear (B/L) ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess (e.e.) was determined by HPLC analysis, the (*R*) catalyst gives the (*R*) enantiomere and vice versa. [e] Experiment was conducted a second time to assure reproducability.

The results show that the catalyst activity is not significantly affected by the varying concentrations. It appears that increasing the amount of acid results in slightly higher B/L ratios. (Entry 8 and 9) Omitting LiCl seems to have a significant effect on the B/L ratio for the catalytic system studied.

Chelating diphosphine ligands are particularly important for a wide range of valuable transformations, particularly due to their control over stereoselectivity. A number of factors have been found to affect the catalytic performance. Ligand electronic and steric properties have a great influence on various reaction parameters, such as activity, chemo- and stereo-selectivity. At the beginning of *chapter II* the electronic χ and for steric properties the cone angle was introduced. The natural *bite angle* β_n for bidentate ligands was introduced by Casey and Whiteker as an additional concept.[35] This angle is strongly dependent upon the backbone between this 2 donor atoms and over the years many reports have discussed this ligand characteristic.[36]

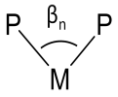


Figure 26 Natural *bite angle*.

The *bite angle* of diphosphines was observed to be also an important parameter influencing the catalytic selectivity and activity. The *bite angle* effect on the activity and selectivity has been studied and reviewed many times for numerous catalytic reactions.[36b, 37] Also the *bite angle* effect in hydroxycarbonylations of styrene with different diphosphines ligands was investigated. The control of regioselectivity with diphosphine ligands is still a key issue in hydroxy- and alkoxy-carbonylations of styrene and derivatives. A detailed study, carried out by Claver and co-workers, examined the impact of steric interaction between different diphosphine *bite angles*.[38] Therefore diphosphine with calculated bite angles between 80-110° were investigated in hydroxycarbonylations of styrene and showed significant differences in their activity, chemo- and stereo-selectivity (Figure 27). The highest activity in hydroxycarbonylation reaction of styrene was obtained with larger bite angles around >103°.

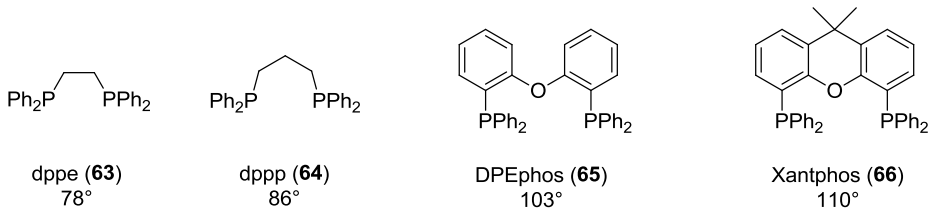


Figure 27 Various diphosphine ligands were tested in styrene hydroxycarbonylation with special attention for trends between catalyst acitivity and their *bite angles*, which are listed (calculated).

Diphosphines with bite angles smaller than 90°, such as 1,2-bis(diphenylphosphino)ethane (dppe, (**63**)) and 1,2-bis(diphenylphophino)propane (dppp, (**64**)), provided only low conversions of 5 % and 28 % (150°C, 75 bar, 24 hours), respectively. However, dppe was observed to give the best B/L ratio of 0.9 whereas DPEphos (**65**) and Xantphos (**66**), with larger bite angles around 102°-110°, provided total chemoselectivity with conversions up to 99 %, although very low regioselectivity (B/L = 0.2).

The preference towards linear acids is explained by the width of the bite angle. This possibly increases the steric hindrance of the ligand and enhances steric interactions between the styrene and substrate and therefore circumvents the formation of the branched product. Another study carried out by Claver and co-worker examined possible electronic effects of phosphine ligands on the methoxycarbonylation of styrene.[39]

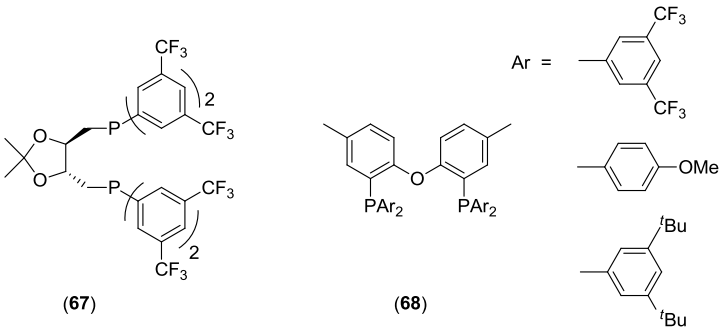


Figure 28 Different electronic and steric parameters of DIOP (**67**) and Xanthphos type (**68**) diphosphine ligands were investigated.

Electronic withdrawing (-CF_3) and donating (–OMe, ^{t}Bu) groups on diphosphine ligands have been screened in methoxycarbonylation reactions (Figure 28). The electronic and steric properties of DIOP (**67**) and Xantphos type (**68**) ligands, either bearing electronic withdrawing (in *meta* position -CF_3) or electron donating (*para* position -OMe) groups were prepared and examined in asymmetric methoxycarbonylation reactions. The branched ester was observed to be the preferred product when electronically withdrawing groups -CF_3 in the *meta* positions of the phenyl DIOP phosphine were conducted (B/L ratio of 11.5 and e.e. of 3%; with lower promoter concentration B/L ratio 2.03 and e.e. 14%).

Motivated by these encouraging results reported in literature and the excellent enantioselectivity achieved with the dipalladium complexes, different diphosphine ligands with varying electronic and steric properties were synthesised and studied in asymmetric hydroxy- and methoxy-carbonylation reactions. Since the slightly bulkier xylyl phanephos (**56**) ligand gave higher activity and selectivity than its simplier phenyl groups analogue (**55**), further investigations were carried out with *meta* functionalised phenyl groups.

Of particular interest was the functionalised phanephos derived ligand with electronic withdrawing -CF_3 groups in *meta* position, due to the very promising results reported.[1]

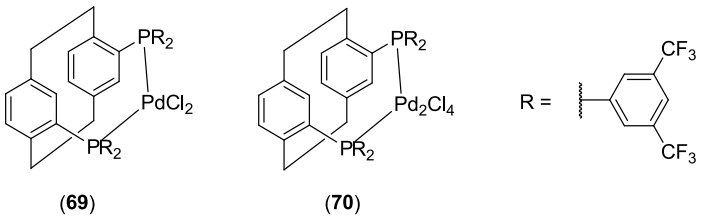


Figure 29 Electron withdrawing ligand with –CF_3 groups in meta position. Also the mono- and dipalladium complexes were formed and examined in hydroxy- and alkoxy-carbonylation reactions.

1 This ligand was prepared in collaboration with another PhD student in the group (Jamie Durrani). Catalysis results carried out by Mr Durrani are highlighted in purple (4 entries in total: in Table 19, Table 26 and Table 31). Characteristic details of the monopalladium catalyst are described in the *experimental II 2.3*. The ligand and catalysts were prepared following the same reaction route as summarised in Scheme 20 and Scheme 23. Further characterisation details and catalysis experiments, were carried out by Mr. Durrani.

Table 19 Asymmetric hydroxycarbonylation of styrene of electronic and steric different phanephos derived catalysts.

Entry[a]	Catalyst	T (°C)	Time (h)	%Acid[b]	B/L[c]	Ee[c] (%)
1	(**47**)	50	42	35	0.8	62
2	(**55**)	50	42	4	1.1	69
3	(**48**)	50	42	71	0.4	50
4	(**56**)	50	42	8	1.1	80
5	(**50**)	50	20	10	1.7	25
6[d]	(**58**)	50	20	7	3.0	48
7	(**51**)	50	20	98	6.0	50
8	(**59**)	50	20	>99	15.7	55
9	(**52**)	50	20	38	2.9	69
10	(**60**)	50	20	>99	4.2	53
11	(**54**)	50	72	70	174	8
12[1]	(**70**)	50	19	90	100	77

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in 1.5ml of degassed butanone as solvent ; 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoter unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H-NMR spectroscopy. Yield refers to yield of pure acid isolated after acid/base extraction. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] Mono-Pd complex added and 1 equiv. $[PdCl_2(PhCN)_2]$ added to result in the formation of di-Pd complex.

All catalysts were screened at 50 °C to compare their activity and stereoselectivity (Table 19). Furthermore, all catalysts were tested at lower and/or higher temperatures, to improve their catalytic performance. Interestingly, when comparing the electronic withdrawing catalyst (**51**)/(**59**) with the electronic donating catalyst (**52**)/(**60**), no significant difference could be spotted, except for lower B/L ratios. Catalyst (**70**) was found to give an outstanding B/L ratio of almost pure branched acid combined with good e.e. of up to 77 %. Attempts were undertaken to improve enantioselectivity but when decreasing temperatures, the highest e.e. accomplished was 70 %. Although catalyst (**54**) and (**49**)/ (**57**) gave the branched acid as the only product, they were not able to induce chirality.

Comparison of the two crystal structures of complexes (**56**) and (**57**) showed a shorter P-P distance for the Pd_2Cl_4 system in catalyst (**56**) than for complex (**57**). This places the assumption that catalyst (**57**) might open up and not retain its structure and therefore act as a monodentate ligand during catalysis, whereas catalyst (**56**) might remain in some dimeric form (or at least bidentate coordination) even in solution. It has

been suggested that in diphosphine catalytic systems, the ligands can adopt unidentate coordination modes, and therefore give high regioselectivity towards branched acids.[40] If the catalyst retains its structural integrity, also the asymmetric core of catalyst (**56**) might be relevant. It is, however, far too early to say this with confidence.

Catalyst performances at higher and lower temperatures are summarised in Table 20, *highlighting* the best performance combining regio- and stereo-selectivity. For temperatures of 50 °C the dipalladium catalysts were observed to perform slightly better than the monopalladium catalysts. Conversions were found to be either equal or improved with the dipalladium complexes and B/L ratios were generally twice as high as with the monomeric counterparts.

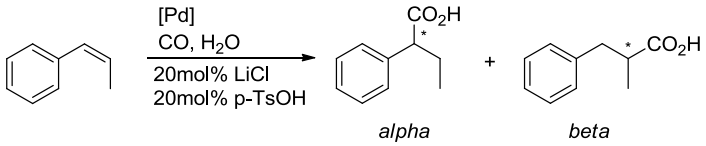
Table 20 Comparing the different electronic and steric effects of phanephos derived ligands at temperatures from 30 - 100 °C.

Entry[a]	Catalyst	T (°C)	Time (h)	%Acid[b] {yield}	B/L[c]	Ee[c] %
1	(**48**)	60	18	42{17}	0.3	65
2	(**56**)	60	18	>99{49}	0.6	76
3	(**49**)	60	20	39	b	rac
4[d]	(**57**)	60	20	40	b	rac
5	(**49**)	40	20	3	b	9
6	(**57**)	40	20	1	b	9
7	(**50**)	35	20	3	16.0	69
8[d]	(**58**)	35	20	6	11.0	82
9	(**51**)	60	20	>99	16.0	36
10	(**59**)	35	20	34{29}	19	57
11	(**52**)	60	20	>99{72}	5.2	33
12	(**60**)	60	20	>99{63}	5.0	35
13	(**53**)	60	22	>99{95}	0.7	33
14	(**61**)	60	22	>99{90}	3.6	20
15	(**53**)	30	18	55{52}	1.3	64
16	(**53**)	30	18	67{60}	1.6	66
17	(**54**)	100	19	65	50	6

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in 1.5ml of degassed butanone as solvent ; 20 mol% LiCl and 20 mol% *p*-toluene sulfonic acid hydrate co-catalyst unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H-NMR spectroscopy. Yield refers to yield of pure acid isolated after acid/base extraction. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] Mono-Pd complex added and 1 equiv. $[PdCl_2(PhCN)_2]$ added to result in the formation of di-Pd complex. [e] Experiment was conducted a second time to assure reproducibility.

Exceptionally good stereoselectivity of 82 % combined with impressive B/L ratios of 11 were accomplished using catalyst (**58**) at 35 °C. Probably due to steric hindrance, the catalyst overall reaction is much lower in comparison to other substrates. Also minor changes in temperature, such as increasing it up to 50 °C, results in a great loss of stereoselectivity (B/L = 3.0, e.e. 48 %). Quite the opposite was observed using catalyst (**59**), which gave good e.e.s of 57 % with B/L ratios of 19 and good activity at temperatures of 50 or 35 °C.

Another styrene derivative, *cis-β*-styrene was tested in hydroxycarbonylations, although was found to almost give racemic acids exclusively (Scheme 27). Also the α/β ratio was found to be similar to B/L ratios observed in the hydroxycarbonylation of styrene.



Scheme 27 Asymmetric hydroxycarbonylation of *cis-β*-styrene using the same conditions applied for styrene. The reaction results 2 regioisomers, the *α* and the *β* isomer. Different to the normal styrene substrate, is it possible to induce chirality in both isomers.

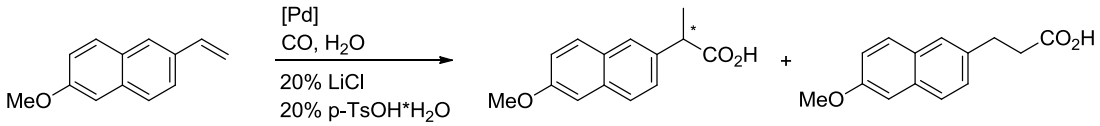
As shown in Table 21 activity was found to be slightly lower, most likely due to the more sterically hindered vinyl group. Interestingly, unreacted starting material was not observed as the *cis-β*-styrene anymore but the *trans* isomer. Early mechanistic studies on the mechanism of styrene hydroxycarbonylation reactions revealed that insertion into the Pd-H bond can lead to 2 alkyl isomers, the branched and linear, which were found to interconvert through β-elimination.[41] This suggests that the *cis-β*-styrene inserts into the Pd-H bond and *via* β-elimination, forms the thermodynamically more favoured *trans-β*-styrene. Since the parent catalysts, (**38**) and (**39**) gave low enantioselectivity, no further studies using the regioselectivite catalysts were carried out.

Table 21 Asymmetric hydroxycarbonylation of *cis*-*β*-styrene.

Entry[a]	Cat	Temp (°C)	Time (h)	H_2O (equiv)	Acid[b] {yield}(%)	α/β[c]	e.e.[d] (α:β) (%)
1	(**47**)	60	72	2.5	95{52}	0.6	6 : 15
2	(**55**)	60	72	2.5	60{48}	0.4	10 : 20
3	(**48**)	60	72	2.5	90{79}	1.5	7 : 13
4	(**56**)	60	72	2.5	91{27}	1.5	12 : 10
5	(**56**)	80	22	2.5	52{27}	1.6	-

[a] Reactions were carried out using 1mol% catalyst and 1mmol *cis*-*β*-styrene at 30bar CO pressure, in 2-butanone. [b] Conversions determined by ^{1}H-NMR integration using tetramethylsilane as internal standard; {Yields} of pure acid isolated after acid-base extraction of the crude reaction mixture. [c] The branched to linear (B/L) ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess (e.e.) was determined by HPLC analysis, (*R*) catalyst resulted the (*R*) enantiomere and vice versa.

When changing the substrate to 6-methoxy-2-vinylnaphthalene, the hydroxycarbonylation was found to be more challenging (Scheme 28). Only catalyst (**47**), (**48**)**,** (**49**), (**55**), (**56**) and (**57**) were screened for this substrate.



Scheme 28 Asymmetric hydroxycarbonylation of 6-methoxy-2-vinylnaphthalene conducting the same conditions (60 °C, 20 hours, 30 bar CO, 1 mol% catalyst, 20 mol% promoters, 1 mmol substrate) as with styrene carbonylations.

Catalysts (**47**), (**48**), (**55**) and (**56**) were found to be less enantioselective than with styrene as the substrate. Using catalysts (**47**) and (**57**) resulted in the branched isomer only and again no chiral induction was observed. Surprisingly, catalysts (**51**) and (**59**) were found to give low activity and enantioselectivity of up to 24 %, but high regioselectivity with the branched isomer as the only product. The *N*-functionalised catalyst (**53**) was found to be similar to other catalyst with a loss in activity but retaining stereoselectivity, with enantioselectivities of up to 69 % (Table 22).

Table 22 Hydroxycarbonylation of 6-methoxy-2-vinylnaphthalene.

Entry[a]	Cat	Temp (°C)	Time (h)	H_2O (equiv)	Acid[b] (%)	B/L[c] (%)	e.e.[d] (%)
1	(**47**)	60	19	2.5	99	0.6	27
2	(**55**)	60	19	2.5	98	0.7	33
3	(**48**)	60	19	2.5	80	0.4	26
4	(**56**)	60	19	2.5	99	0.6	41
5	(**49**)	60	20	5	24	>100:1	5
6	(**57**)	60	20	5	24	>100:1	5
7	(**51**)	60	20	5	2	>100:1	20
8	(**59**)	60	20	5	3	>100:1	24
9	(**53**)	60	20	5	5	1.3	69

[a] Reactions were carried out using 1mol% catalyst and 1mmol 6-methoxy-2-vinylnaphthalene at 30 bar CO pressure, in 2-butanone. [b] Conversions to acid were determined by ^{1}H NMR integration using tetramethylsilane as internal standard. [c] The branched to linear (B/L) ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess (e.e.) was determined by HPLC analysis, (*R*) catalyst gives the (*R*) enantiomere and vice versa.

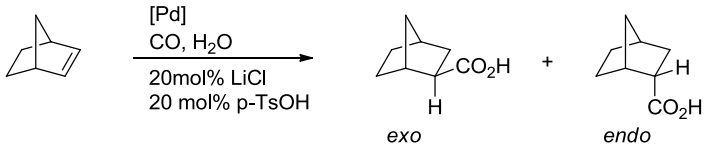
Very promising results could be achieved with all phanephos derived mono- and di-palladium catalysts. Although big improvements were made concerning enantio- and regio-selectivity, the catalytic activity, selectivity and substrate scope still need to be further improved for making these catalysts more interesting for industrial applications.

Even though no good enantioselectivity could be obtained with the catalytic systems (**49**), (**54**) and (**57**), these catalysts still showed great activity and regioselectivity towards the branched isomer. Catalyst (**54**) gives even better regioselectivity under much milder conditions, such as 50 °C and 30 bar CO, than the catalyst systems previously reported in this group. The lack of enantioselectivity observed with catalysts (**49**) and (**57**) could be due to an impure catalyst, although when the catalyst was prepared *in-situ*, by addition of 1 equiv. of palladium precursor to the pure ligand, the same results were obtained; very similar results for *in-situ* and isolated catalyst were recorded with (**39**).

2.2.4.2 Hydroxycarbonylation of norbornene

In order to investigate the stereoselectivity of novel dipalladium catalysts with other prochiral alkenes, norbornene was also tested. Norbornene seemed to be a great candidate since it is a very different alkene substrate, and the product has attracted industrial interest in its own right and as an intermediate to the chiral amine.[42]

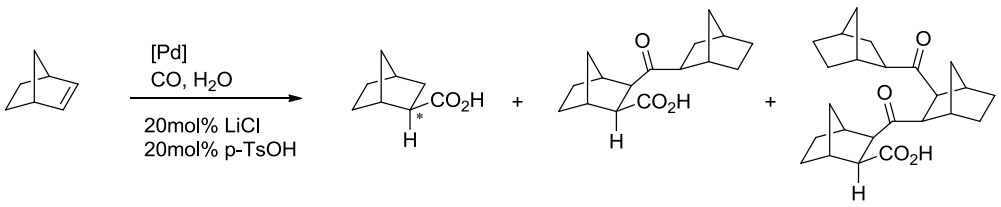
Hydroxycarbonylation of norbornene has been less studied than the styrene model substrate, most likely due to difficulties controlling the chemoselectivity, additionally the *exo* and *endo* selectivity needs to be controlled. The reaction is closely related to the aforementioned hydroxycarbonylation of styrene using an acidic palladium/phosphine system with CO and water and norbornene as the alkene, leading directly to 2 possible carboxylic acids, the *exo* and/or *endo* isomers (Scheme 29).



Scheme 29 Asymmetric hydroxycarbonylation of norbornene commonly results in two isomers the *exo* and *endo* carboxylic acid.

Prior to this work asymmetric hydroxycarbonylation of norbornene had not been accomplished. In 2009 the asymmetric methoxycarbonylation of norbornene was found by Claver and coworker to give enantioselectivities of up to 40 %, with high chemoselectivity and the *exo* isomer as the only ester, using a monodentate chiral monophosphine a chiral (*S,S*)-1,2,3 triphenyl 2-phospha[3]ferrocenophane.[43]

The phanephos derived catalysts were furthermore investigated in norbornene hydroxycarbonylations. First attempts of asymmetric hydroxycarbonylation of norbornene were carried out with the monopalladium complex (**47**). Chemoselectivity of this substrate was generally found to be challenging, and the formation of oligomers through CO insertion was observed (Scheme 30). Electrospray MS suggested these products to be the copolymerized acid terminating dimer and the corresponding trimer. Such products are not unreasonable given the precedent for co-polymerisaton of norbornene and carbon monoxide.[44]

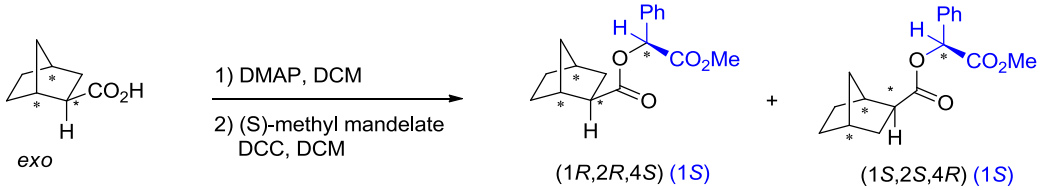


Scheme 30 Asymmetric hydroxycarbonylation of norbornene was carried out and observed to result in by-product formation. These by-products were examined by MS and found to be dimers and trimer oligomers.

After studying different reaction temperatures, water concentrations and solution concentrations, the best chemoselectivity towards the acid product accomplished was 79

%. In all norbornene hydroxycarbonylations, including using monophosphine catalyst [$PdCl_2(PPh_3)_2$], the presence of oligomers as by-products was observed.

Reaction conditions used were 1 mol% palladium diphosphine complex, 20 mol% LiCl and *p*-TsOH*H_2O to styrene in 2-butanone and different equivalent of water. In order to determine the enantiomeric excess, the formation of the mandelate ester from the carboxylic acid and calculation of diastereomeric excess by ^1H NMR integration was necessary (Scheme 31).[45]



Scheme 31 For determinining the enantiomeric excess of the chiral norbornene carboxylic acid by formation of the mandelate ester.

Figure 30 and Figure 31 represent examples for determining the enantiomeric excess. In order to obtain the compounds clean enough to calculate the diastereomeric excess, all samples needed to be columned first. For (1*R*,2*R*,4*S*)-bicyclo[2.2.1]heptane-2-carboxylic acid, with the mandelic ester of (*1R,*2*R*,4*R*)-2-methoxy-2-oxo-1-phenylethyl bicycle[2.2.1]heptanes-2-carboxylate has ^1H NMR (300 MHz, C_6D_6) resonances at 2.55 ppm (s, norbornene ring CH (*S*) diastereomer, 1H) and 6.09 ppm (s, benzylic CH, 1H).

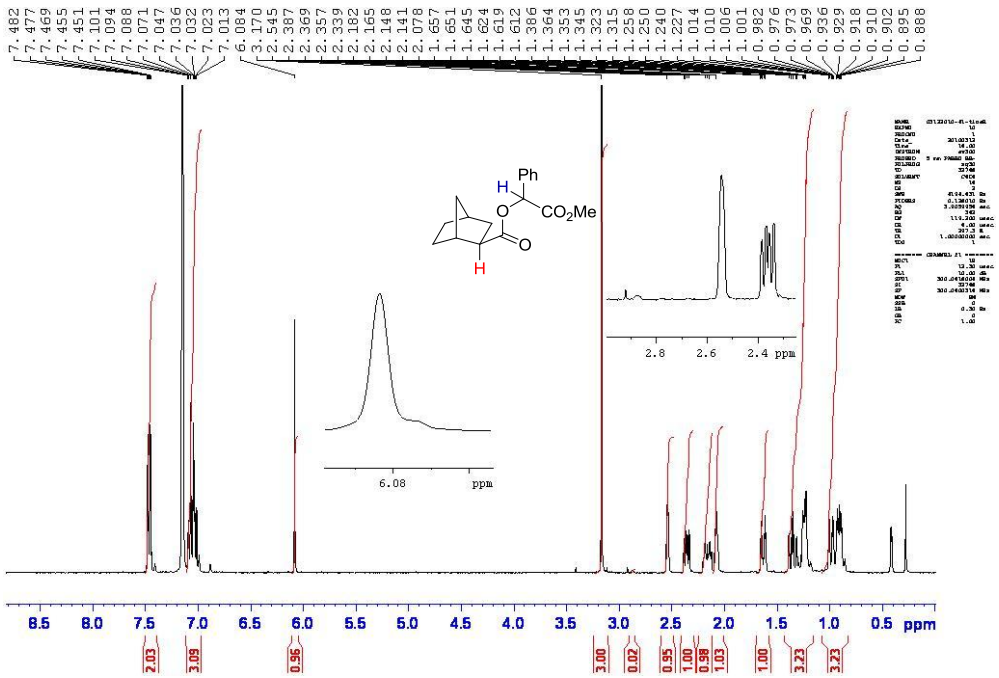


Figure 30 ^1H NMR of the Mandelic ester derived from enantiomerically enriched (1*R*, 2*R*, 4*S*) norbornene-2 carboxylic acid.

The other diasteriomer of (1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptane-2-carboxylic acid has ^{1}H NMR (300 MHz, C_6D_6) resonances at 2.88 ppm (s, norbornene ring CH (*R*) diastereomer, 1H) and at 6.08 ppm (s, benzylic CH, 1H).

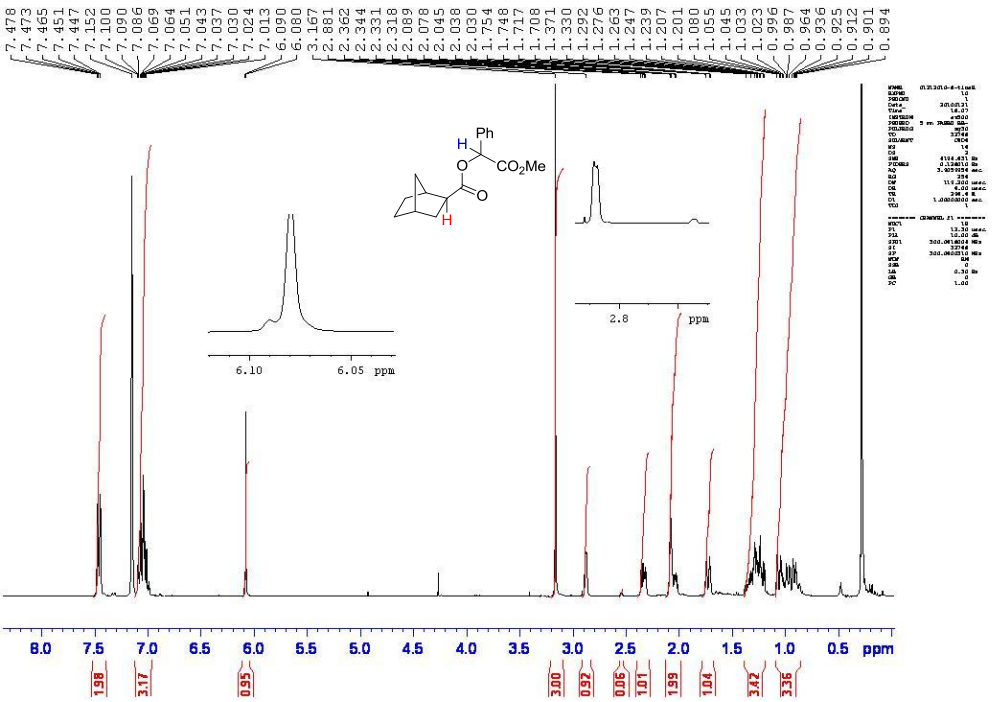


Figure 31 ^{1}H NMR of the Mandelic ester derived from enantiomerically enriched (1*S*, 2*S*, 4*R*) norbornene-2 carboxylic acid.

For the hydroxycarbonylation of norbornene only catalysts (**47**)/ (**55**) and (**48**)/ (**56**) were examined. All catalytical studies of hydroxycarbonylation reactions can be found in the experimental part and are displayed in more detail in tables, including all the necessary experimental information. The different effects of Ph-phanephos and Xyl-phanephos catalysts are presented below, with the Ph-phanephos (**38**) and Xyl-phanephos (**39**) resulting in almost equal chemo-and regio-selectivity. In order to optimise the selectivity, the effect of different equiv. of water (5, 7.5, 10, 12.5) and temperatures (45, 65 and 90 °C) were investigated using catalyst (**47**) and (**56**). The results are summarised in Table 32-35, presenting the conversions to the acid, the yield (after work up), *exo*/*endo* ratio and e.e. under various conditions.

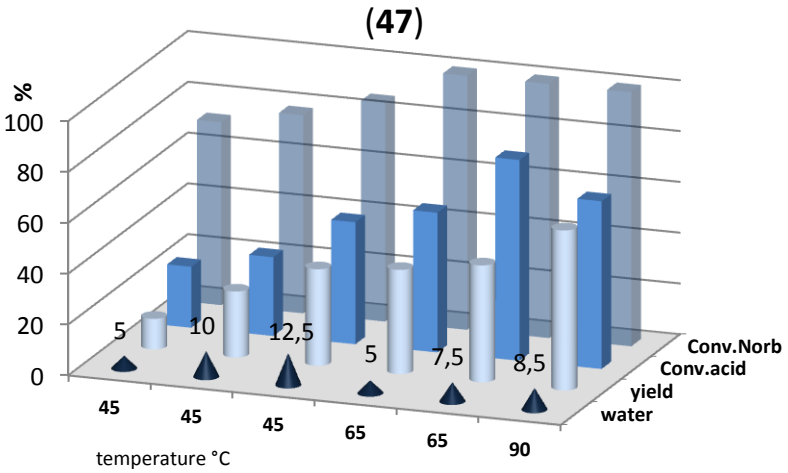


Figure 32 Asymmetric hydroxycarbonylation of norbornene investigating the importance of different equivalents of water used and temperature effects.

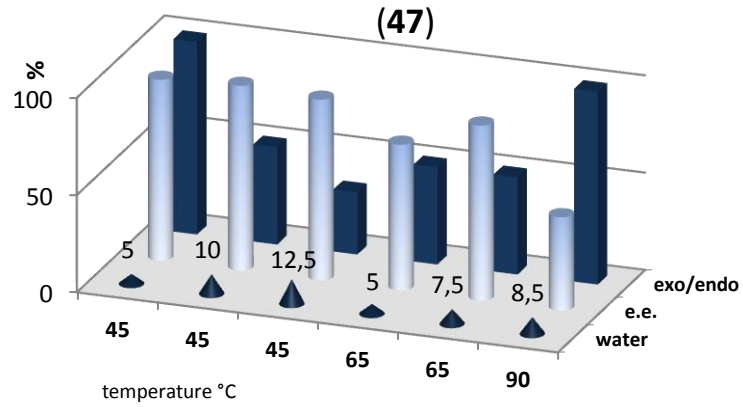


Figure 33 The impact on enantioselectivity by adding different equivalents of water and temperature.

When increasing the water concentration with a constant temperature of 45 °C the reaction was found to be more chemoselective, which seems reasonable since the addition of more water would prevent the formation of oligomers, favouring the acid formation. When increasing the temperature to 65 °C, a similar trend in chemoselectivity

with increasing the water concentrations was noted, leading to enhanced conversions. High chemoselectivity of up to 79 % was achieved with 7.5 equiv. water and temperatures of 65 °C. Increasing the temperature further up to 90 °C, a high overall activity was observed, but chemoselectivity dropped slightly to 66 % acid.

The impact of various temperatures and equivalents of water on regio- and enantio-selectivity are displayed in Figure 33. It is important to note that at low temperatures an enantiomeric excess of up to 95 % was obtained. Although no significant change in the enantioselectivity was found when different water concentrations were applied, severe changes in the enantiomeric excess were observed at higher temperatures. The *exo*/*endo* selectivity was greatly affected by low temperatures around 45 °C.

Similar results were obtained for the hydroxycarbonylation of norbornene with the dipalladium catalyst (**55**). Similar to the (**47**) catalytic runs, observed conversions were high, although the chemoselectivity was restricted. A study at a fixed temperature of 45 °C with varying water concentration showed that increasing the amount of water improves chemoselectivity. Changing promoter concentrations from 20 mol% to 5 mol% was observed to slightly enhance chemoselectivity for 10 equiv. of H_2O. At higher water concentrations of 15 equiv. and promoter concentration of 5 mol%, no significant change was detected. At temperatures around 65 °C, the chemoselectivity was lower than observed for the monopalladium complex (**47**). When higher reaction temperatures, such as 90 °C were applied similar conversions of acid were observed for (**55**), as was found for (**47**).

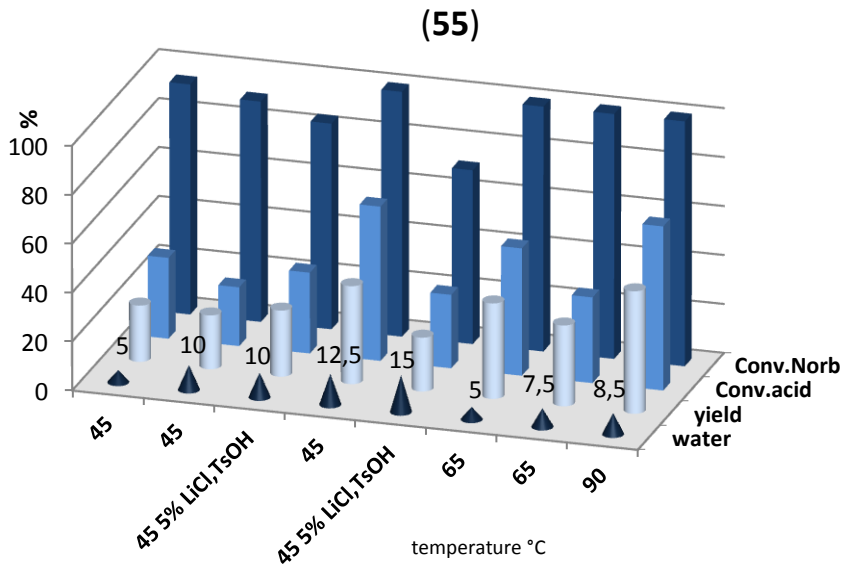


Figure 34 Asymmetric hydroxycarbonylation of norbornene investigating the effect of different equivalent of water, varying the equivalents of promoters and temperatures.

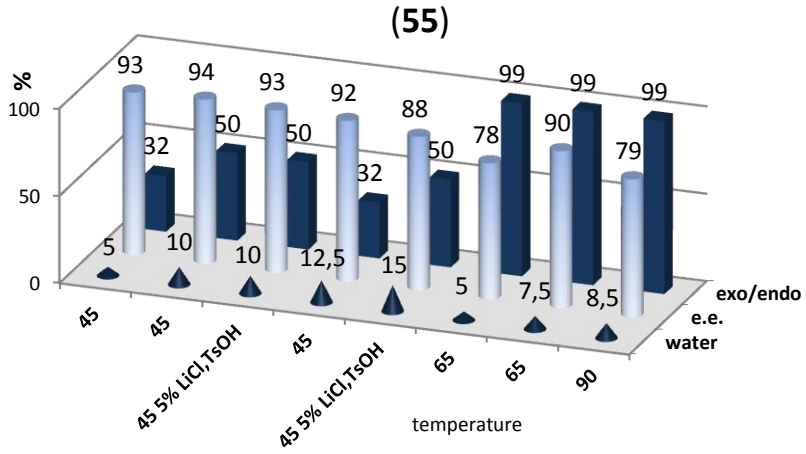


Figure 35 Effect of different equivalents of water, various equivalents of promoters and temperature on regio- and enantioselectivity for catalyst (**55**) onto the hydroxycarbonylation of norbornene.

The enantio- and regio-selectivity for (**55**) are summarised in Figure 35. In this study catalyst (**55**) displayed high enantioselectivities of 93 % with a variety of water concentrations at 45 °C. The *exo*/*endo* selectivity was observed in the same ratio as with catalyst (**47**). When changing to higher temperatures, the *exo* isomer was observed to be the favoured isomer. This is not surprising since the *exo* isomer is the more thermodynamically stable product, whereas the *endo* species is kinetically favoured.

Fortunately, good enantioselectivity could still be accomplished at higher temperatures of 65 °C with 90 % e.e. and high 99:1 *exo*:*endo* selectivity. Enantioselectivity of 79 % was accomplished at surprisingly high temperatures of 90 °C. When the monomeric counterpart was used enantioselectivity was found to drop to 48 %. When catalyst (**48**) and (**56**) were examined in hydroxycarbonylations of norbornene a similar trend was observed.

(**48**) and (**56**)

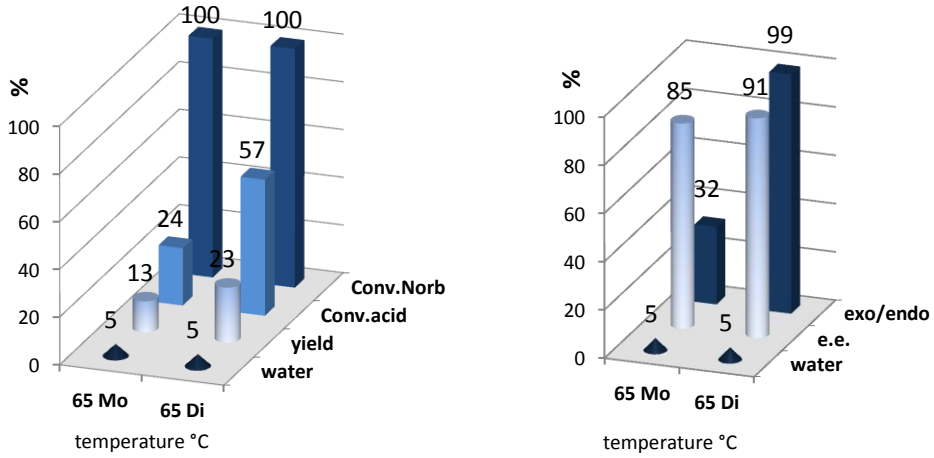


Figure 36 Hydroxycarbonylation of norbornene using (**48**) and (**56**)at 65 °C and 5 equiv H_2O.

Reactions at 65 °C and 5 equiv. of H_2O was found to give reasonable chemoselectivity of 57 % acid, great *exo*/*endo* ratio of 99 and high e.e. of 91 %. A clear trend between the mono- and di-palladium complexes can be observed; mainly chemo- and regio-selectivity seem to diverge. Different molar concentrations of the catalyst solutions were briefly investigated and are displayed in Table 23. It appears that less concentrated solutions lead to lower chemoselectivity, which is plausible due to lack of availability of water, as the nucleophile, it is likely that oligomerisation occurs. No positive consequence is observed at water concentrations higher than 3.4 M.

Table 23 Investigating chemoselectivity of norbornene hydroxycarbonylation with different solvent concentrations with (**47**) at 65 °C and 20 hours.

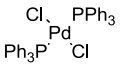
Entry[a]	Solvent (ml)	C_M (H_2O)	H_2O (equiv)	Conv.[b] (%)	Acid[b] (%)
1	3	2.5	7.5	>99	58
2	2.2	3.4	7.5	>99	80
3	1.5	5.0	7.5	>99	79
4	0.7	10.7	7.5	>99	79

[a] Reactions were carried out using 1mol% catalyst and 1mmol norbornene at 30bar CO pressure, in 2-butanone. [b] Conversions determined by ^1H NMR integration using 1-methylnaphtalene as internal standard.

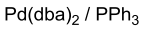
In Table 25 the results of catalyst (**53**), which was briefly investigated, are summarised. With this catalyst only mediocre chemoselectivity was accomplished, but with a high *exo*/*endo* ratio of 97:3 and good enantioselectivity of 80%. Claver and co-

workers investigated different acids in methoxycarbonylation of norbornene and found that when using TFA outstanding chemoselectivity can be achieved. Therefore, TFA was investigated as the only promoter instead of *p*-TsOH*H_2O (Table 24). No significant difference between these two different conditions could be observed, with conversions and selectivities comparable to that of the previously used promoter system.

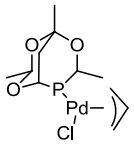
Additionally, several achiral monophosphine catalysts were also investigated in norbornene hydroxycarbonylation and the results are summarised in Table 24. The commercially available monophosphine catalysts [$PdCl_2(PPh_3)_2$] (**71**) and $Pd(dba)_2/PPh_3$ (**72**) gave low chemoselectivities but comparable *exo*/*endo* ratios. When applying the very active and selective allyl-cage monophosphine ligand (**73**) (illustrated in Figure 37), high chemoselectivity of up to 78 % and good regioselectivity could be achieved.



(**71**)



(**72**)



(**73**)

Figure 37 Monophosphine palladium catalyst systems examined in norbornene hydroxycarbonylation.

Table 24 Comparing hydroxycarbonylation of norbornene with different acids and results of applying monophosphine ligands.

Entry[a]	Catalyst	T (°C)	Time (h)	Acid (mol%)	Conv. (%)	% product[b] {yield}	*exo* / *endo*[b]	e.e.[c] (%)
1	(**47**)	45	19	20% PTSA	>99	67	97:3	91
2	(**55**)	45	19	20% PTSA	>99	44	98:2	95
3	(**48**)	45	22	20% PTSA	>99	47	97:3	90
4	(**56**)	45	22	20% PTSA	>99	40	93:7	91
5	(**48**)	45	22	20% TFA[d]	>99	47	95:5	95
6	(**56**)	45	22	20% TFA[d]	>99	39	90:10	80
7	(**71**)	60	23	20% PTSA	>99	{21}	96:4	rac
8	(**71**)	60	67	20% PTSA	>99	{21}	88:12	rac
9	(**72**)	60	23	20% PTSA	>99	{24}	n.d.	rac
10	(**73**)	60	18	20% PTSA	>99	78{48}	98:2	rac

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol norbornene, 5 mmol water in 1.5 mL of degassed butanone as solvent, 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoter. [b] Conversion refers to norbornene consumed. % Product determined against 1-methyl napthalene internal standard as determined using ^{1}H NMR spectroscopy and checked using GC-MS. Yield is >99% pure material after chromatography. Exo/endo determined by ^{1}H NMR spectroscopy. [c] e.e determined by conversion to the Ester of methyl mandelate and determined using ^{1}H NMR spectroscopy. [d] Trifluoroacetic acid (TFA) used without LiCl promoter.

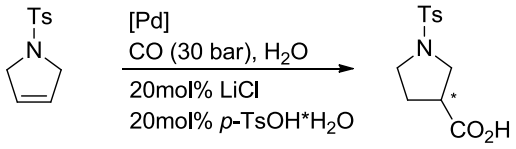
Table 25 Hydroxycarbonylation of norbornene and the effect of water concentration.

Entry [a]	Cat	T (°C)	Time (h)	[H_2O] (mmol)	Conv. (%)	% product[b] {yield}	*exo* : *endo*	e.e.[c] (%)
1	(**47**)	45	18	5	72	24	>99:1	93
2	(**47**)	45	18	12.5	85	48	97:3	93
2rep	(**47**)	45	18	12.5	83	50	97:3	n.d.
3	(**55**)	45	18	5	92	33 {23}	97:3	93
4	(**55**)	45	18	12.5	>99	63	93:7	92
4rep	(**55**)	45	18	12.5	>99	63	93:7	n.d.
5	(**53**)	45	21	5	>99	55{54}	90:10	n.d.
6	(**53**)	45	21	7.5	>99	47{46}	93:7	80

[a]Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol norbornene, with varying amounts of water in 1.5 mL of degassed butanone as solvent, 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoters. [b] The conversion refers to norbornene consumed. % Product determined against 1-methyl napthalene internal standard as determined using ^{1}H NMR spectroscopy. Yield is >99% pure material after chromatography. *Exo*/*endo* determined by ^{1}H NMR spectroscopy. [c] e.e determined by conversion to the ester of methyl mandelate and determined using ^{1}H NMR spectroscopy.

2.2.4.3 Hydroxycarbonylation of *N*-(*p*-toluenesulfonyl)-3-pyrroline

Several enantioselective synthetic methods for heterocyclic *β*-proline derivatives are described in literature. Several approaches using biocatalysts for inducing chirality, were successful applied, however, multistep reactions were necessary. An easier approach towards chiral heterocyclic carboxylic acids could be by starting from the alkene of 4-(tosyl)-pyrrolidine. The carboxylic acid can then be obtained by asymmetric hydroxycarbonylation reactions with chiral phanephos derived palladium catalyst (Scheme 32).



Scheme 32 Asymmetric hydroxycarbonylation of the heterocyclic alkene, *N*-(*p*-toluenesulfonyl)-3-pyrroline to the chiral acid, *N*-(*p*-toluenesulfonyl)-pyrrolidine-3-carboxylic acid.

Although the reaction time was long (72 hours) and temperatures up to 90 °C were necessary, good e.e.s and chemoselectivity could be accomplished. A clear difference between the styrene (a relatively electronic poor alkene) and Ts-pyrrolidine (a relatively electronically rich alkene) could be observed, when using electronically distinct ligands. When using more electron donating ligands, the resulting complexes (**56**) and (**60**) were more active than with electronic withdrawing ligands (Entry 7 of Table 26).[2]

Table 26 Asymmetric hydroxycarbonylation of *N*-(*p*-toluenesulfonyl)-3-pyrroline.

Entry[a]	Cat	T (°C)	Time (h)	Conv[b] (%)	% Acid[b] {yield}	E.e.[c] (%)
1	(**56**)	70	72	52	45	84
2	(**56**)	70	72	93	52{41}	87
3[1]	(**56**)	90	72	>99	95 {90}	81
4	(**50**)	70	72	8	8	70
5	(**60**)	70	72	73	56{55}	79
6[d]	(**60**)	90	72	>99	85{69}	68
7[1]	(**70**)	90	72	13	13 {10}	59
8	(**49**)	70	72	-	-	n.d.

[a] Reactions were carried out using 0.25 mol% catalyst at 30 bar CO in 1.5 ml of degassed butanone. 5 mol% LiCl and 5 mol% *p*-toluene sulfonic acid hydrate (PTSA) co-catalyst unless stated otherwise. [b] Conversion refers to *N*-(*p*-toluenesulfonyl)-3-pyrroline consumed. % Product determined against 1-methylnaphtalene internal standard using ^{1}H NMR spectroscopy. Yield refers to yield of pure acid isolated after acid/base extraction. [c] Enantiomeric excess determined by HPLC. [d] 0.5 mol% catalyst using 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O.

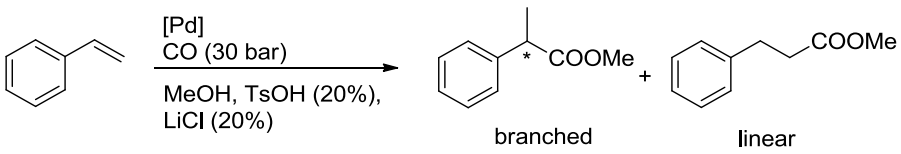
2 Preliminary results were obtained by Jamie Durani. Encouraged by this result further catalysts and conditions were examined.

Catalyst (**50**) was again found to be sterically too bulky for high catalytic activity. In addition the e.e. was found to be merely 70 %, whereas when using (**56**) enantioselectivity of up to 87 % could be achieved.

2.2.5 Catalytic studies: Alkoxycarbonylation of styrene

2.2.5.1 Methoxycarbonylation of styrene

Methoxycarbonylation of styrene uses the same reaction conditions as hydroxycarbonylations with regard to the nucleophile (Scheme 33). All reactions were carried out using 1 mol% catalyst in 1.5 ml MeOH, with 20 mol% LiCl and *p*-TsOH*H_2O, with 30 bar CO, unless otherwise stated.



Scheme 33 Asymmetric ethoxycarbonylation of styrene commonly results in 2 isomers, branched and linear propionic ester. Reaction conditions are very similar to hydroxycarbonylation, however, MeOH was not only used as the reagent but also solvent.

In Table 27 catalyst (**47**)/(**55**) and (**48**)/(**56**) were screened in methoxycarbonylations performed at different temperatures. Asymmetric methoxycarbonylation was found to be an easier task than the previously discussed hydroxycarbonylation in term of activity and selectivity. The catalysts were found to be active at much lower temperatures around 65 °C, yielding full conversions after 17 hours, which was not the case for the hydroxycarbonylation. Furthermore, both mono- and di-palladium catalytic systems were observed to give similar conversions, regio- and enantio-selectivities. High e.e.s of 79 % could be obtained already around temperatures of 60 °C; again both (**48**) and (**56**) performed well.

Entries 7-10 in Table 27 were carried out at 50 °C for only 3 hours. Reaction times were shortened in order to evaluate possible differences between the mono- and dipalladium complexes. The **mono** and **di** catalysts retained a similar activity and selectivity.

When decreasing the temperature to 35 °C enantioselectivity of up to 89 % with a B/L ratio of 1.0 combined with high conversions could be accomplished and in this case the monomeric catalyst was at least as active as the dimer. In entry 12-14 of Table 27 the

same catalyst (**56**) was applied, however the the catalytic system was prepared differently. Entry 12 was a preformed catalytic system; entry 13 was the monopalladium compound (**48**) and 1 equiv. $[PdCl_2(PhCN)_2]$ *in-situ*, showing slightly better conversions than the preformed catalyst (**56**); and entry 14 reports the results of the dipalladium compound obtained by adding ligand (**39**) and 2 equiv. $[PdCl_2(PhCN)_2]$ *in-situ*, achieving lower conversions, B/L ratios and enantioselectivity. This result could indicate that the catalyst formation might need some time to assemble, before the catalyst is properly able to induce enantioselectivity.

Entries 13 and 14 suggest the monopalladium complex as the more active system with the second Pd acting as a type of co-catalyst. However, it is too early to make any clear statements.

Table 27 Asymmetric methoxycarbonylation of styrene with catalyst system Ph-phanephos (**47**)/(**55**) and Xyl-phanephos (**48**)/(**56**) at different temperatures from 65-35 °C.

Entry[a]	Catalyst	T (°C)	Time (h)	%Ester[b] {yield}	B/L[c]	Ee[c] (%)
1	(**47**)	65	17	>99{66}	0.5	63
2	(**55**)	65	17	>99{71}	0.5	61
3	(**48**)	65	17	>99{59}	0.5	70
4	(**56**)	65	17	>99{68}	0.6	71
5	(**48**)	60	20	>99	0.7	79
6	(**56**)	60	20	>99	0.7	79
7	(**47**)	50	3	3	0.7	69
8	(**55**)	50	3	12	0.6	54
9	(**48**)	50	3	24	0.7	80
10	(**56**)	50	3	16	0.9	79
11	(**56**)	35	22	>99	1.0	89
12	(**56**)	35	22	43	0.9	81
13[d]	(**48**)**+Pd**	35	17	81{66}	0.9	81
14[e]	(**39**)**+2Pd**	35	17	60{54}	0.8	60

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol styrene, in 1.5 ml of degassed and dry MeOH; 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^1H NMR spectroscopy. Yield refers to pure ester after column work up. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] 1 mol% (**48**) complex and 1 mol% $[PdCl_2(PhCN)_2]$ added to result in the formation of di-Pd complex. [e] (**56**) complex formed *in-situ*, 0.5 mol% (**39**) plus 1 mol% $[PdCl_2(PhCN)_2]$ added.

Further studies were carried out using (**48**) and (**56**) to investigate possible differences in conversion, B/L ratio and e.e., when the catalyst was formed *in-situ* rather than using preformed catalysts (Table 28). All reactions were carried out at 60 °C and ran for 20 hours. When adding the preformed monopalladium catalyst (**48**) good e.e., and B/L ratio and good yields for this type of catalyst could be obtained after 6 hours. When compared to entry 2 in Table 28 where the same catalyst was formed *in-situ* and displayed the same stereoselectivity but improved activity. When the dipalladium complex is generated *in-situ* by simply adding 1 equiv. of ligand (**39**) to 2 equiv. of the Pd precursor, the catalytic activity and selectivity remained the same. In comparison to the result obtained earlier, displayed in Table 27 with entries 11-13, these don't quite agree. Suggestions for that could be that temperature plays a vital role in catalyst formation.

Table 28 Comparison study of the *in-situ* preparation of the Pd complex with the preformed complex at 60 °C for 6 hours, to investigate any differences in activity or selectivity.

Entry[a]	Catalyst	T (°C)	Time (h)	%Ester[b] {yield}	B/L[c]	Ee[c] (%)
1	(**48**)	60	6	59	0.8	81
2[d]	(**48**) = (**39**)+[Pd]	60	6	80{53}	0.9	77
3	(**56**)	60	6	73{42}	0.7	76
4[e]	(**56**) = (**48**)+[Pd]	60	6	65	1.0	80
5[f]	(**56**) = (**39**)+2 [Pd]	60	6	86{55}	0.6	74

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol styrene, in 1.5 ml of degassed and dry MeOH; 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoter unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H-NMR spectroscopy, as is B/L ratio. Yield refers to pure ester after column work up. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] Mono-Pd complex formed in situ, ligand plus 1 equiv. [$PdCl_2(PhCN)_2$] added. [e] Mono-Pd complex added and 1 equiv. [$PdCl_2(PhCN)_2$] added to result in the formation of di-Pd complex. [f] Di-Pd complex formed *in situ*, ligand plus 2 equiv. [$PdCl_2(PhCN)_2$] added.

The new chiral palladium catalysts (**49**)-(**54**); (**57**)-(**61**) were also investigated in methoxycarbonylation reactions under the same conditions of 60 °C for 20 hours. The best overall result at this reaction temperature is *highlighted* in Entry 10 of Table 29. The fluorinated catalyst (**70**) was found to give 63 % e.e. and high activity, although a low B/L ratio of 1.3. Other catalysts resulted in lower enantioselectivities and B/L ratios, although most catalyst resulted in higher activity.

Table 29 Methoxycarbonylation of styrene, comparing the different electronic and steric catalyst properties at 60 °C for 20 hours.

Entry[a]	Catalyst	T (°C)	Time (h)	Conv.[b] (%)	%Ester[b] {yield}	B/L[c]	Ee[c] (%)
1	(**48**)	60	20	>99	>99	0.7	79
2	(**56**)	60	20	>99	>99	0.7	79
3	(**49**)	60	20	26	26	b	Rac
4	(**57**)	60	20	25	25	b	Rac
5[e]	(**50**)	60	20	60	60	1.3	35
6[f]	(**58**)	60	20	57	57	1.5	27
7	(**51**)	60	20	>99	>99	2.2	48
8	(**59**)	60	20	99	99	2.1	47
9	(**52**)	60	20	>99	>99{51}	1.9	54
10	(**60**)	60	20	>99	>99{60}	1.3	63
12	(**53**)	60	24	>99	>99	1.3	42
13	(**61**)	60	24	>99	>99	1.2	40

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol styrene, in 1.5 ml of degassed and dry MeOH; 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoter unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^1H NMR spectroscopy; Yield refers to pure ester after column work up. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] Mono-Pd complex added and 1 equiv. [$PdCl_2(PhCN)_2$] added to result in the formation of di-Pd complex. [e] Mono-Pd complex formed *in-situ*, ligand plus 1 equiv. [$PdCl_2(PhCN)_2$] added. [f] Di-Pd complex formed *in-situ*, ligand plus 2 equiv. [$PdCl_2(PhCN)_2$] added.

When temperature is decreased, all catalysts gave improved regio- and enantio-selectivity, with the exception of catalyst (**49**)/(**57**). Similar to the hydroxycarbonylation reactions, this catalyst was found to deliver the branched ester as the only isomer, although with no induction of chirality. On the other hand, catalyst (**50**) and (**58**) gave exceptionally high enantioselectivity (Table 30; Entry 5), even better than (**56**) and improved B/L ratio of up to 4.0, although with the disadvantage of low activity. When comparing the differences between catalyst (**51**)/(**59**) (electronic withdrawing group) and (**52**)/(**60**) (electronic donating groups), no exceptional differences between these very electronically distinct catalysts could be observed.

Table 30 Methoxycarbonylation of styrene, comparing electronically and sterically different catalysts at various temperatures.

Entry[a]	Catalyst	T (°C)	Time (h)	Conv.[b] (%)	%Ester[b] {yield}	B/L[c]	Ee[c] (%)
1	(**49**)	40	20	2	2	b	rac
2[d]	(**57**)	40	20	3	3	b	rac
3	(**50**)	50	20	39	39	1.5	85
4	(**58**)	50	20	22	22	2.0	91
5	(**50**)	35	71	72	72	4.0	93
6	(**58**)	35	71	42	42	3.5	93
7	(**51**)	50	20	95	95[10]	1.8	57
8	(**59**)	50	20	87	87{77}	1.7	51
9	(**59**)	35	19	31	31	1.8	63
10	(**52**)	40	24	70	70{67}	2.1	61
11	(**60**)	40	24	81	81{76}	1.9	76
12	(**53**)	35	17	40	40	1.4	42

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol styrene, in 1.5 ml of degassed and dry MeOH; 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoter unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H NMR spectroscopy; Yield refers to pure ester after column work up. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] Mono-Pd complex added and 1 equiv. [$PdCl_2(PhCN)_2$] added to result in the formation of di-Pd complex. [e] Mono-Pd complex formed *in-situ*, ligand plus 1 equiv. [$PdCl_2(PhCN)_2$] added. [f] Di-Pd complex formed in situ, ligand plus 2 equiv. [$PdCl_2(PhCN)_2$] added.

Another study was undertaken, using different solvent mixtures for methoxycarbonylations of styrene. Claver and coworkers reported when running methoxycarbonylation reactions with diphosphines, that a THF/MeOH = 1 mixture gave the best overall results, when using the fluorinated catalyst DIOP with CF_3 groups in meta position on the phenyl groups (Figure 28). Table 31 summarises reactions carried out using MeOH as a reagent rather than a solvent and *highlights* the reactions carried out in 2-butanone as a solvent and MeOH as a reagent. Generally for non-fluorinated ligands an improvement in the B/L ratios can be observed, although combined with a decrease in the e.e.s. Also the activity seems to decrease, except for catalyst (**52**). Interestingly, with the fluorinated catalysts (**51**)/ (**59**) and (**70**) an outstanding enhancement in the B/L ratio and enantioselectivity can be achieved by simply using MeOH only as a reagent. Entries 10 and 14 display the highest increase of B/L ratio and enantioselectivity.

Table 31 Asymmetric methoxycarbonylation of styrene investigating the effect of MeOH as the reagent and solvent *versus* MeOH as reagent and 2-butanone as the solvent. MeOH as solvent and reagent is listed black and when 1.5ml 2-butanone/5mmol MeOH are used, the catalytic runs are *highlighted*.

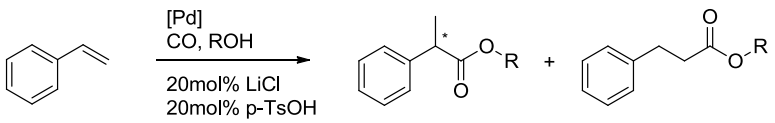
Entry[a]	Catalyst	Temp. (°C)	Time (h)	%Ester[b] {yield}	B/L[d]	e.e.[c] (%)
1	(**48**)	50	3	18	0.7	69
2[d], 2	(**56**)	50	17	>1	n.d.	n.d.
3 2	(**56**)	50	17	93	0.7	78
4[d], 2	(**56**)	50	17	18	1.0	77
5	(**50**)	60	20	60	1.3	35
6[d]	(**50**)	60	20	49	32	15
7	(**50**)	35	71	72	4.0	93
8[]	(**50**)	35	72	34	19	38
9	(**59**)	50	20	87	1.7	51
10[d]	(**59**)	50	20	>99	14	61
11	(**60**)	60	20	>99	1.3	63
12[d]	(**60**)	60	20	>99	5.4	33
13	(**70**)	60	20	88	7.6	40
14[f]	(**70**)	60	22	>99	100	79

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol styrene, in 1.5 ml of degassed and dry MeOH; 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoter unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H-NMR spectroscopy. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] Reactions were carried out using 3 mmol MeOH in 1.5 ml 2-butanone. [e] Reaction carried out by Dr. Jóse Fuéntes in collaboration for a shared publication. [f] Reaction carried out by another Ph.D. student, using 2.5 mmol MeOH in 1.5 mol 2-butanone. Enantiomeric excess determined by HPLC chromatography and B/L ratio by ^{1}H NMR spectroscopy.

Further studies regarding investigations of the effects of different solvents on the catalytic activity will be carried out by another student in this group.

2.2.5.2 Alkoxycarbonylation of styrene

Alkoxycarbonylation of styrene with different alcohols other than methanol were investigated briefly using catalysts (**47**)/(**55**) and (**48**)/(**56**). Both catalysts were found to result in similar activity and stereoselectivity as was achieved in methoxycarbonylation reactions.



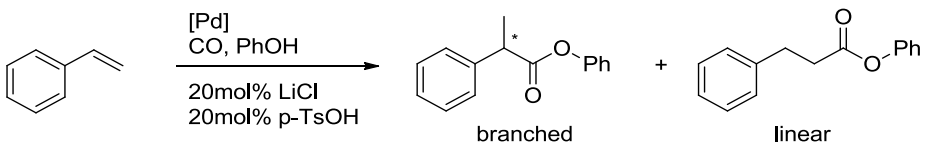
Scheme 34 Asymmetric alkoxycarbonylation of styrene with *n*-propanol and *i*-propanol. (R = *iso*-PrOH; *n*-PrOH).

Table 32 shortly summarises alkoxycarbonylation runs with styrene and *n*-propanol (*n*-PrOH) or *iso*-propanol (*i*-PrOH) as the nucleophile. Similar to methoxycarbonylation reactions, good activity could be achieved when using *i*-PrOH as the alcohol, although slightly lower reaction rates were noted when *n*-PrOH was used. Comparable enantioselectivities of up to 81% and a B/L ratio of 0.9 could be obtained for *iso*-propoxycarbonylation reactions. For *n*-propoxycarbonylation the enantioselectivity of 75 % and B/L ratio 0.7 was found to be slightly decreased in comparison to the selectivity obtained in the methoxycarbonylation of styrene.

Table 32 Asymmetric alkoxycarbonylation of styrene.

Entry[a]	ROH	Catalyst	Temp. (°C)	Time (h)	%Ester[b] {yield}	B/L[d]	e.e.[c] (%=
1	***i*-PrOH**	(**55**)	75	24	61{59}	0.6	45
2	***i*-PrOH**	(**56**)	75	24	100{97}	0.5	58
3	***i*-PrOH**	(**56**)	50	24	24{19}	0.9	81
4 [d]	***n*-PrOH**	(**48**)	50	42	48{39}	0.4	80
5 [d]	***n*-PrOH**	(**56**)	50	42	94{78}	0.7	75

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in using 1 mmol styrene, in 1.5 ml of degassed and dry alcohol; 20 mol% LiCl and 20 mol% *p*-TsOH*H_2O promoter unless stated otherwise. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^1H NMR spectroscopy, as is B/L ratio. Yield refers to pure ester after column work up. [c] Enantiomeric excess was determined by chiral HPLC. [d] These catalysis runs were carried out by Dr. Jóse Fuéntes in collaboration for a shared publication.



Scheme 35 Asymmetric phenoxycarbonylation of styrene, resulting branched and linear regioisomers of the ester product.

The catalyst activity for phenoxycarbonylation of styrene was briefly examined (Scheme 35). Although the phenoxyester could be obtained, any traces of water in the

reaction mixture possibly promoted a competing hydroxycarbonylation reaction, resulting in the carboxylic acid rather than the desired ester. Due to the *p*-TsOH*H_2O species used for carbonylation reaction, mainly the acid was obtained. When changing to oxalylic acid, which was recrystallised prior to use, the main product was still in the carboxylic acid with the phenoxyester as the by-product. It is also possible that the higly activated phenoxy ester can be hydrolysed. In any case this potentially interesting application was not developed further due to other priorities.

2.3 Conclusion

This work presents the preparation of new bimetallic complexes, based on a [Pd_2Cl_4L] (L = diphosphine ligand) unit and their great potential for the production of enantio-enriched chiral carboxylic acids and esters from prochiral alkenes. Catalytic activity has been obtained for the monopalladium complexes too; however the overall catalyst productivity and selectivity much lower than for the dipalladium catalyst analogues, in particular for hydroxycarbonylation reactions.

Furthermore, other prochiral heterocyclic alkene substrates and norbornene has been found to give enantioselectivity in hydroxycarbonylation reactions. These complexes not only show outstanding results for asymmetric hydroxy- and methoxy-carbonylations of styrene but gave first promising results for the alkoxycarbonylation reactions with *i*-PrOH, *n*-PrOH and PhOH.

Depending on the ligand design, different [Pd_2Cl_4L] arrangements were observed for the dipalladium catalysts by crystal structures ((**56**) and (**57**)). This raised questions about the active catalyst nature, since with catalyst (**57**), which consists of a more open Pd-Pd core, only racemic mixtures of the branched acids and esters could be obtained. For the catalyst (**56**), which consists of a much shorter Pd-Pd distance, enantioselectivities of up to 92 % were obtained.

A number of interesting conclusions were drawn from this work, which most certainly can assist in the future design of more active and selective catalysts, based on the original ligand and catalyst design.

Generally phanephos ligands with phenyl groups on the phosphine moieties were observed to result better control of enantioselectivity, relative to cycloalkanes such as cyclohexyl groups and phospholane substituents.

Furthermore, substituents in the *meta* position on the phenyl groups of the phosphine moiety provide better control of enantioselectivity with aryl alkenes. Almost

all diphosphine ligands have been reported to be problematic in terms of regioselectivity, favouring the linear isomer over the branched. Problems concerning regioselectivity could be resolved by changing the steric and electronic properties of the ligand. Both more sterically bulky and electronic deficient phosphorus atoms result in enhanced branched regioselectivity. The impact of the electronic and steric nature has also been investigated for -Me, -OMe, -F, -CF_3, -*t*Bu in *meta* position respectively. The rational modifications of ligand design was directed by experimental observations, leading to high enantioselectivity and great control over regioselectivity, which has always been a problematic area for diphosphine ligands in hydroxy- and alkoxy-carbonylation of aryl alkenes.

In comparison to the results found in literature, the combination of good activity, high regio- and enantio-selectivity shown in this chapter has not been reported before, which makes the results presented in this thesis the most promising to date. Most complexes exhibit high catalytic activity, enabling reactions to be run at much lower temperatures than previously thought possible.

Whether the 2 Pd atoms during catalysis stay bridged and cooperate with each other is unclear and most certainly requires further mechanistic investigations. One plausible explanation could be that the second palladium is acting as a co-catalyst, which has been reported before to enhance catalytic activity for alkoxycarbonylation with $CuCl_2$.[47]

Although catalyst optimisation via diphosphine ligand modifications has led to even better catalysts, further optimisations are required to make these catalysts a more economically viable process with lower catalyst loadings in particular.

Most certainly very valuable catalyst systems, very efficient for the preparation of enantio-enriched chiral aryl acids and esters, of which many are important precursors in medicinal and organic synthesis, have been designed and prepared. Future work is anticipated and will aim to elucidate the true nature of the dipalladium active species.

We have found that phanephos type catalysts are not only very efficient catalysts for hydrogenation and amination reactions but also hydroxy- and alkoxy-carbonylations.

2.4 Experimental

2.4.1 Instrumentation and Chemicals

Unless otherwise stated all reactions were carried out under inert atmosphere using standard Schlenk techniques.

NMR All ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded either on a Bruker Avance 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz, ^{31}P at 121 MHz) or Bruker Avance II 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{31}P at 161 MHz) spectrometer. Chemical shift values are given in parts per million and were referenced to external standards (^{1}H and ^{13}C were referenced to tetramethylsilane and ^{31}P spectra to phosphoric acid). All deuterated solvents were purchased from Deuterio GmbH. Proton signals multiplicities are gieven as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), dq (double quartet), quint (quintet), m (multiplet), br s (broad singlet) or a combination of them. **EA and MS** Elemental analyses were carried out by the Elemental Analysis Service at the London Metropolitan University by Mr. Stephen Boyer. Mass spectroscopy was carried out by the EPSRC National Mass Spectroscopy Service Centre, Swansea or the University of St Andrews MS service. **X-ray data** X-ray crystallography data were performed on a Rigaku MM007/Mercury diffractometer (confocal optics Mo K_{α} radiation) at 93 K. Structures were solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL), by Prof. Dr. Alexandra Slawin. **Solvents** Dichloromethane (CH_2Cl_2), hexane, toluene and ether (Et_2O) were dried and purified via an Innovative Technologies Puresolve 400 solvent purification system, and degassed by purging with nitrogen. Methanol (MeOH) was dried over $CaCl_2$ and tetrahydrofuran (THF) was dried over Na wires (benzophenone as indicator). Other solvents were bought and used as received without further purification other than degassing by purging with nitrogen.

OR Optical rotations were measured on an Optical Activity Ltd AA-1000 digital polarimeter using a 5ml cell with a 1 m path length at room temperature using the sodium D-line, and a suitable solvent that is reported along with the concentration (c = g/100ml). **HPLC** Analysis was determined on a Varion Prostar operated by Galaxie workstation PC software. **Infrared spectra** were recorded on a Perkin Elmer Paragon 1000 Spectrum GX FTIR system. Compounds were analysed using KBr disks. Absorptions maxima are reported in wavenumbers (cm-1) and the characteristic absorption are reported as strong (s), medium (m) or weak (w). **Materials** (*R*)- and (*S*)-4,12-dibromo[2.2]-*para*cyclophane was kindly donated by Dr. Reddy's (formerly Chirotech) and used as received. 4,12-Bis(diphenylphosphino)-[2.2]-*para*cyclophane (**38**) ((*R*)-(–)- and (*S*)-(+)-PHANEPHOS) and 4,12-Bis[di(3,5-xylyl)phosphino]-[2.2]-*para*cyclophane (**39**) ((*R*)-(–)- and (*S*)-(+)- Xylyl-PHANEPHOS) were purchased from Aldrich chemical company and used as received without further purification, after checking optical rotation data with the literature.[113] $[PdCl_2(PhCN)_2]$, LiCl, *p*-toluenesulfonic acid monohydrate (*p*-TsOH*H_2O), styrene, 2-methoxy-6-vinylnaphtalene and norbornene

were obtained from Aldrich and used as received. *N*-(*p*-toluenesulfonyl)-3-pyrroline was obtained from Strem. Carbon monoxide was obtained from BOC. Flash column chromatography (eluents given in brackets) was performed using Davasil silica gel Fluorochem 60 Å particle size 40-63µm and normal grade solvents. Thin-layer chromatography (TLC) was performed on pre-coated Aldrich TLC plates, POLYGRAM SIL G/UV_{254}.

2.4.2 Catalysis Experiments

2.4.2.1 General procedure for hydroxycarbonylation of styrene

Lithium chloride (8.4 mg, 0.20 mmol), *para*-toluenesulfonic acid monohydrate (34.4 mg, 0.20 mmol) and [LPd_xCl_y] (L = diphosphine) (0.01mmol) were weighed into a Biotage 5 ml microwave vial. A stirring bar was added and the vial was sealed with a crimp cap and put under inert atmosphere. Styrene (114 µl, 1 mmol), degassed water (45 µl, 2.5 mmol), degassed 2-butanone (1.5 ml) and in some instances an internal standard (approximately 10µl of either tetraethylsilane) were added using a syringe. The solution was mixed before 20 µl of the solution was diluted in $CDCl_3$ and analysed using NMR (to give a t_0 spectra that calibrates the internal standard against starting material). The caps were pierced with two needles and quickly placed in an autoclave that had previously been placed under an argon atmosphere before being opened under a flow of argon. The autoclave was sealed, purged three times with CO and then pressurised to 30bar and heated in a preheated oil bath or heating jacket with constant magnetic stirring. After the desired time, the autoclave was cooled to room temperature and the pressure released slowly. The mixture was then analysed by taking a sample, diluting with $CDCl_3$ and obtaining a ^1H NMR spectrum. The solvent was carefully removed from the reaction mixture and the residue was dissolved in toluene and extracted 3 times with saturated $NaHCO_3$ solution and the combined extracts were acidified with conc. HCl. The solution was then extracted 3 times with dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and the solvent removed to give chemically pure regioisomers 2-phenylpropanoic and 3-phenylpropanoic acid.

The enantiomeric excess was determined by HPLC, using a Chiracel OD-H column, 250 x 4.6 mm, 5 µm with guard cartridge, 0.5 mL min^{-1}, 97:3:0.1 hexane : *i*-PrOH: trifluoroacetic acid, t_R[(+)-*S*] = 19 min, t_R[(–)-*R*] = 17 min, t_R[linear] = 21 min.

2-phenylpropanoic acid[49]

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (d, J^3 = 7.2 Hz, 3H, CH_3), 3.69 (q, J^3= 7.2 Hz, 1H, CH), 7.18-7.29 (m, 5H $C_{Ar}H$), 10.2 (br s, OH). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 18.3, 45.5, 127.5, 127.7, 128.8, 139.8, 181.2.

3-phenylpropanoic acid[50]

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (t, J^3 = 7.7 Hz, 2H, CO-CH_2), 2.98 (t, J^3 = 7.7 Hz, 2H, CH_2), 7.18-7.29 (m, 5H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 30.6, 35.7, 126.4, 128.3, 128.6, 140.2, 179.6.

MS ES- : m/z 149.0 (M^- requires 150.2) Data are in agreement with literature.

2.4.2.2 General procedure for hydroxycarbonylation of norbornene

Lithium chloride (8.4 mg, 0.20 mmol), *para*-toluenesulfonic acid monohydrate (34.4 mg, 0.20 mmol), [LPd_xCl_y] (L = diphosphine) (0.01mmol) and norbornene (94.2 mg, 1 mmol) were weighed into a Biotage 5 ml microwave vial. A stirring bar was added and the vial was sealed with a crimp cap and put under inert atmosphere. Degassed water (between 2.5 equiv. and 15 equiv.), degassed 2-butanone (1.5 ml) and internal standard (approximately 10μl of either 1-methylnaphtalene) were added using a syringe. The solution was mixed before 20 μl of the solution was diluted in $CDCl_3$ and analysed using NMR (to give a t_0 spectra that calibrates the internal standard against starting material). The caps were pierced with two needles and quickly placed in an autoclave that had previously been placed under an argon atmosphere before being opened under a flow of argon. The autoclave was sealed, purged three times with CO and then pressurised to 30 bar and heated in a preheated oil bath or heating jacket with constant magnetic stirring. After the desired time, the autoclave was cooled to room temperature and the pressure released slowly. The mixture was then analysed by taking a sample, diluting with $CDCl_3$ and obtaining an ^{1}H NMR spectrum. The solvent was carefully removed from the reaction mixture and the residue was purified by column chromatography (SiO_2, using hexane: ethylacetate 8:1 as eluent) to give colourless crystals of bicyclo[2.2.1]heptane-2-carboxylic acid. This purification method is not ideal in that only on some occasions was complete separation of the side product achieved (these are those isolated yield given in the tables). The side product appears in GCMS analysis of this reaction mixtures (in addition to the desired product) as a less volatile component that gives EI MS for $[M\text{-}OH]^+$ suggesting a fragmentation. It also shows up as distinct, but similar collections of peaks to the product in the ^{1}H NMR spectrum. This side product can be made in greater concentration if the carbonylation is carried in the absence of water, and in this case

gives two related products. Electrospray MS suggest these to be a copolymerised-acid-terminated-dimer (Norbornane)-C(=O)-Norbornane-2-carboxylic acid (263.1644 (MH+), 280.1910 (M+ NH4+), 307.1283 (M+Na+), and the corresponding trimer, (Norbornane)-C(=O)-(Norbornane)-C(=O)-Norbornane-2-carboxylic acid 385.2376 (MH+), 402.2640 ($M+NH_4+$). The component observed as the main side product in the reactions that is less volatile than the acid product is proposed to be the dimer. The enantiomeric excess was determined by forming the mandelate ester of the carboxylic acid (see below) and calculating the diastereomeric excess by ^{1}H-NMR integration.

(1R, 2R 4S)bicyclo[2.2.1]heptane-2-carboxylic acid (exo)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31-1.12 (m, 3H), 1.65-1.40 (m, 4H), 1.9-1.78 (m, 1H), 2.42-2.50 (m, 2H), 2.55 (br s, 1H), 11.02-12.21 (br s, OH). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 29.0, 29.9, 34.5, 36.9, 41.3, 46.8, 182.8. $[\alpha]_D$ = -16.6 (c = 2.32, EtOH, using 75 % e.e. sample) (Literature for pure (1*R*, 2*R* 4*S*)-bicyclo[2.2.1]heptane-2-carboxylic acid was reported $[\alpha]_D$ = -25.5 (c = 3.5, $CHCl_3$)[45, 51] MS ES- : m/z 139.01 ($[M-H]^+$ requires 139.07) Data are in agreement with literature.

2.4.2.3 Determination of enantiomeric excess via formation of the mandelate ester of the carboxylic acid[45]

Bicyclo[2.2.1]heptane-2-carboxylic acid (53 mg, 0.378 mmol) and DMAP (2 mg, 0.016 mmol) were dissolved in CH_2Cl_2 (2ml) and cooled to –5 °C. (*S*)-methyl mandelate (85 mg, 0.512 mmol) and DCC (115 mg, 0.558 mmol) were dissolved in CH_2Cl_2 (2ml) and then added to the acid solution. The mixture was stirred for 4 hours and then filtered through a silica pad and the mandelate ester was subsequently purified by column chromatography using hexane/ethylacetate (97/3). The mandelate ester was isolated in 91% (100mg, 0.347 mmol) yield.

Key data for determination of e.e.; Literature and our racemic sample[45]

(1*S*,2*S*,4*R*)- *Bicyclo[2.2.1]heptane-2-carboxylic acid*, *(1S)-2-methoxy-2-oxo-1 phenylethyl ester* : ^{1}H NMR (300 MHz, C_6D_6) δ 2.88 (s, 1H, ring CH from the 2 (*S*) diastereomer) 6.09 (s, 1H, benzylic hydrogen).

(1R,2R,4S)- Bicyclo[2.2.1]heptane-2-carboxylic acid, (1S)-2-methoxy-2-oxo-1 phenylethyl ester : ^{1}H NMR (300 MHz, C_6D_6) δ 2.55 (s, 1H, ring CH from the 2 (*R*) diastereomer) 6.08 (s, 1H, benzylic hydrogen).

NMR data for the predominantly *(1R,2R,4S)-Bicyclo[2.2.1]heptane-2-carboxylic acid, (1S)-2-methoxy-2-oxo-1 phenylethyl ester*

^{1}H NMR (300 MHz, C_6D_6) δ 1.03-0.84 (m, 3H, CH_3), 1.41-1.17 (m, 3H, CH_2), 1.67-1.59 (m, 1H, CH_2), 2.08 (br s, 1H, CH_2), 2.22-2.12 (m, 1H, CH), 2.40-2.31 (m, 1H, CH), 2.54 (br s, 0.95 H, CH), 2.88 (br s, 0.03H, CH), 3.17 (s, 3H, CH_2), 6.08 (s, 1H, CH), 7.12-6.98 (m, 3H, $C_{Ar}H$), 7.51-7.39 (m, 2H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 28.8, 29.4, 34.4, 36.4, 36.8, 41.0, 46.4, 51.9, 74.9, 127.7, 128.0, 128.1, 128.4, 128.9, 129.3, 134.9, 169.5, 175.1. MS ES$^+$: m/z 310.88 (requires [M+Na] 311.3). Data are in agreement with literature.

2.4.2.4 General procedure for hydroxycarbonylation of 2-methoxy-6-vinylnaphtalene

All reactions were performed under a carbon monoxide atmosphere. Lithium chloride (8.4 mg, 0.20 mmol), *para*-toluenesulfonic acid monohydrate (34.4 mg, 0.20 mmol) and [LPd_xCl_y] (L = diphosphine) (0.01 mmol) were weighed into a Biotage 5 ml microwave vial. A stirring bar was added and the vial was sealed with a crimp cap and put under inert atmosphere. 2-methoxy 6-vinylnaphtalene (184.23 mg, 1 mmol), degassed water (45 µl, 2.5 mmol), degassed 2-butanone (1.5 ml) and internal standard (approximately 10µl of tetraethylsilane) were added using a syringe. The solution was mixed before taking a crude NMR sample (for t_0 NMR approximately 20 µl of solution were taken). The caps were pierced with two needles and placed in the autoclave that was put under inert atmosphere and opened under argon flow before quickly sealed. The autoclave was purged three times with CO and then pressurised to 30 bar and heated in a preheated oil bath or heating jacket. After the desired time, the autoclave was cooled to room temperature and the pressure released slowly. The mixture was stirred before taking another NMR sample (for t_1 NMR approximately 20 µl of solution were taken for calculating % product). The solvent was carefully removed from the reaction mixture and the residue was dissolved in toluene and filtered to remove precipitate. The toluene filtrate was extracted 3 times with saturated $NaHCO_3$ solution and the combined extracts were acidified with conc. HCl. The solution was then extracted 3 times with dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and the solvent removed to give a colourless viscous solution of product mixture of 2-propanoic acid and 3-propanoic acid. The enantiomeric excess was determined by HPLC, using a Chiracel AD column, 0.5 ml/min, 95:5:0.1 hexane: *i*-PrOH: trifluoroacetic acid. t_R[(+)-S] = 38.78 min, t_R[(+)-R] = 42.69 min.

2-(6-methoxynaphthalen-2-yl)propionic acid[52]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (d, ^3J = 7.16 Hz, 3H, $ArCHCH_3$), 3.88 (q, ^3J = 7.16 Hz, 1H, ArCH), 3.91 (s, 3H, $-OCH_3$), 7.11-7.13 (m, 2H, $C_{Ar}H$), 7.30 (dd, ^3J = 8.40 Hz, 1H, $C_{Ar}H$), 7.67-7.70 (m, 3H, $C_{Ar}H$).

3-(6-methoxynaphthalen-2-yl)propionic acid[53]

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.01 (t, ^3J = 7.4 Hz, 2H, CH_2), 3.84 (s, 3H, $-OCH_3$), 7.03-7.08 (m, 3H, $C_{Ar}H$), 7.59-7.65 (m, 3H, $C_{Ar}H$).

MS (ES−): 229 (M−H). Data are in agreement with literature.

2.4.2.5 General procedure for hydroxycarbonylation of *cis*-β-styrene

All reactions were performed under a carbon monoxide atmosphere. Lithium chloride (8.4 mg, 0.20 mmol), *para*-toluenesulfonic acid monohydrate (34.4 mg, 0.20 mmol) and [LPd_xCl_y] (L = diphosphine) (0.01 mmol) were weighed into a Biotage 5 ml microwave vial. A stirring bar was added and the vial was sealed with a crimp cap and put under inert atmosphere. *Cis*-β-styrene (129µl, 1 mmol), degassed water (45 µl, 2.5 mmol), degassed 2-butanone (1.5 ml) and internal standard (approximately 10µl of tetraethylsilane) were added using a syringe. The solution was mixed before taking a crude NMR sample (for t_0 NMR approximately 20 µl of solution were taken). The caps were pierced with two needles and placed in the autoclave that was put under inert atmosphere and opened under argon flow before quickly sealed. The autoclave was purged three times with CO and then pressurised to 30 bar and heated in a preheated oil bath or heating jacket. After the desired time, the autoclave was cooled to room temperature and the pressure released slowly. The mixture was stirred before taking another NMR sample (for t_1 NMR approximately 20 µl of solution were taken for calculating % product). The solvent was carefully removed from the reaction mixture and the residue was dissolved in toluene and filtered to remove precipitate. The toluene filtrate was extracted 3 times with saturated $NaHCO_3$ solution and the combined extracts were acidified with conc. HCl. The solution was then extracted 3 times with dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and the solvent removed to give a colourless viscous solution of product mixture of 2-benzylpropanoic acid and 2-methyl-3-phenylpropanoic acid. The enantiomeric excess was determined by HPLC, using a Chiracel AS-H and AD-H column, 0.5 ml/min, 95:5:0.1 hexane : IPA: trifluoroacetic acid. t_R[linear R/S] = 25.88 min, t_R[linear R/S] = 27.29 min; t_R[branched R/S] = 28.46 min, t_R[branched R/S] = 31.58 min.

α-ethylphenylacetic acid[54]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.94 (t, ^3J = 6.0 Hz, 3H, CH_3), 1.67-1.82 (m, 1H, CH_2), 1.97-2.11 (m, 1H, CH_2), 3.49 (t, ^3J = 6.3 Hz, 1H, CH), 7.19-7.26 (m, 5H, $C_{Ar}H$).

2-methyl-3-phenylpropanoic acid[55]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.10 (d, ^3J = 6.0 Hz, 3H, CH_3), 2.51-2.63 (m, 2H), 3.00 (dq, ^3J = 6.2, 13.0 Hz, 1H), 7.10-7.27 (m, 5H, $C_{Ar}H$).

trans-β-styrene[56]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.83 (d, ^3J = 7.2 Hz, 3H, CH_3), 6.21 (dq, J = 6.3, 12.9 Hz, 1H, CH), 6.30 (dq, J = 1.5, 14.1 Hz, 1H, CH), 7.12-7.28 (m, 5H, $C_{Ar}H$).

Data are in agreement with literature.

2.4.2.6 General procedure for hydroxycarbonylation of 1-(4-Toluenesulfonyl)-pyrrolidine

Lithium chloride (4.2 mg, 0.10 mmol), *para*-toluenesulfonic acid monohydrate (17.2 mg, 0.10 mmol), [LPd_xCl_y] (L = diphosphine) (0.005 mmol) and 1-(4-toluenesulfonyl)pyrrolidine (112 mg, 0.5 mmol) were weighed into a Biotage 5 ml microwave vial. A stirring bar was added and the vial was sealed with a crimp cap and put under inert atmosphere. Degassed water (45 µl, 2.5 mmol), degassed 2-butanone (1.5 ml) and internal standard (approximately 10 µl of 1-methylnaphtalene) were added using a syringe. The solution was mixed before taking a crude NMR sample (for t_0 NMR approximately 20 µl of solution were taken). The caps were pierced with two needles and placed in the autoclave that was put under inert atmosphere and opened under argon flow before quickly sealed. The autoclave was purged three times with CO and then pressurised to 30 bar and heated in a preheated oil bath or heating jacket. After the desired time, the autoclave was cooled to room temperature and the pressure released slowly. The mixture was stirred before taking another NMR sample (for t_1 NMR approximately 20 µl of solution were taken for calculating % product). The solvent was carefully removed from the reaction mixture and the residue was dissolved in toluene and filtered to remove precipitate. The toluene filtrate was extracted 3 times with saturated $NaHCO_3$ solution and the combined extracts were acidified with conc. HCl. The solution was then extracted 3 times with dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and the solvent removed to give a white solid of 1-(4-toluenesulfonyl)-pyrrolindine-3-carboxylic acid, in 90% yield. The enantiomeric excess was determined by HPLC, using Chirapak OD-H and Chiracel AD-H columns in

series, 0.5 ml/min, 90:10:0.1 hexane : *i*-PrOH: trifluoroacetic acid. t_R[(+)-S] = 64.05 min, t_R[(+)-R] = 68.71 min.

1-(4-methylphenylsulfonyl)-pyrrolidine-3-carboxylic acid:

^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.97-2.05 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.87-2.97 (quint, ^3J = 7.4 Hz, 1H, CH), 3.19-3.31 (m, 2H, CH_2), 3.36 (dd, J^2 = 10.5 Hz, ^3J = 6.6 Hz 1H), 3.49 (dd, ^2J = 10.5 Hz, ^3J = 8.1 Hz 1H), 7.26 (d, ^3J = 9.0 Hz, 2H, $C_{Ar}H$), 7.65 (d, ^3J = 9.0 Hz, 2H, $C_{Ar}H$). MS (CI): 268.[57] Data are in agreement with literature.

2.4.2.7 General procedure for methoxycarbonylation of styrene

Lithium chloride (8.4 mg, 0.20 mmol), *p*-toluenesulfonic acid monohydrate (34.4 mg, 0.20 mmol) and [LPd_xCl_y] (L = diphosphine) (0.01mmol) were weighed into a Biotage 5 ml microwave vial. A stirring bar was added and the vial was sealed with a crimp cap and put under inert atmosphere. Styrene (1 mmol), dry and degassed methanol (1.5 ml) and an internal standard (approximately 10 µl of either tetraethylsilane) were added using a syringe. The solution was mixed before 20 µl of the solution was diluted in $CDCl_3$ and analysed using NMR (to give a t_0 spectra that calibrates the internal standard against starting material). The caps were pierced with two needles and quickly placed in an autoclave that had previously been placed under an argon atmosphere before being opened under a flow of argon. The autoclave was sealed, purged three times with CO and then pressurised to 30 bar and heated in a preheated oil bath or heating jacket with constant magnetic stirring. After the desired time, the autoclave was cooled to room temperature and the pressure released slowly. The mixture was then analysed by taking a sample, diluting with $CDCl_3$ and obtaining a ^{1}H NMR spectrum. The solvent was carefully removed from the reaction mixture and the crude product was filtered through a small column packed with SiO_2 eluting with hexane: ethylacetate 8:1. The solvent was removed to give colourless chemically pure mixture of linear methyl-3-phenylpropanoate and branched methyl-2-phenylpropanoate.

The enantiomeric excess was determined by chiral GC, using a MEGA-DEX DMP Beta (stationary phase), 0.25 µl film thickness, 0.25 mm internal diameter, 25 m length, maximum temperature of 230 °C. Method used: Oven temperature: 80 °C isotherm for 5 minutes; then heat 5 °C/min up to 180 °C. Flow of 20 ml/min; carrier gas: He; injection of 1 µl; split 1:100; with solvent of CH_2Cl_2. Branched methyl-2-phenylpropanoate t_R[(+)-*S*] = 17.24 min, t_R[(+)-*R*] = 17.38 min, t_R[linear] = 19.9 min. The enantiomeric excess was determined by HPLC, using a Chirapak AD-H, 250 x 4.6 mm, 5 µm with guard cartridge, *n*-

hexane 100%, 0.5 mL min^{-1}, 210 nm, t_R[(+)-*S*] = 17.9 min, t_R[(–)-*R*] = 20.0 min, t_R[linear] = 25.1 min. The absolute configuration of the ester was determined by comparison of the sign of the optical rotation with the literature values.[58]

Methyl-2-phenylpropanoate[59]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.42 (d, ^3J = 9.0 Hz, 3H, CH_3), 3.57 (s, 3H, -OCH_3), 3.65 (q, ^3J = 9.0 Hz, 1H, CH), 7.07-7.28 (m, 5H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 18.6, 45.5, 52.1, 127.2, 127.5, 128.7, 140.5, 175.1.

Methyl-3-phenylpropanoate[60]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.55 (t, ^3J = 7.5 Hz, 2H, CH_2), 2.87 (t, ^3J = 7.5 Hz, 2H, CH_2), 3.58 (s, 3H, -OCH_3), 7.07-7.28 (m, 5H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 31.0, 35.7, 51.7, 126.3, 128.3, 128.5, 173.4. GC-MS shows the expected ester. MS (EI^+) 164(M+). Data are in agreement with literature

2.4.2.8 General procedure *iso*-propoxycarbonylation of styrene

LiCl (8.4 mg, 0.20 mmol, 20%), *p*-TsOH (34.4 mg, 0.20 mmol, 20%) and [Pd_2(Xyl-Phanephos)Cl_4] (10.3 mg, 0.01 mmol, 1%) were weighed into a 5 ml sealable vial. A stirring bar was placed inside and vial sealed with a crimp cap and put under inert atmosphere using a needle connected to vacuum line. Styrene (114 µl, 1 mmol, 100%) and anhydrous *i*-PrOH (1.5 ml) were added. The caps were pierced with two needles and placed in the autoclave which was quickly sealed. The autoclave was purged three times with CO and then pressurized to 30 bar and heated in a preheated oil bath to 75 °C for 24 hours. After this time, the autoclave was cooled to room temperature and the pressure released slowly. NMR analysis shows full converstion to the ester product. The solvent of the reaction mixture was remove and the solids dissolved in toluene (1ml) and suspension was filtered through a plug of silica and the solvent removed to give the product mixture of *iso*-propyl 2-phenylpropanoate ('branched') and *iso*-propyl 3-phenylpropanoate ('linear') (97 %; Branched/Linear = 0.52 (determined by ^{1}H NMR). The enantiomeric excess (58 % e.e.) was determined by HPLC analysis (CHIRALPACK AD and CHIRALPACK AD-H; hexane, 0.5ml/min).

iso-Propyl-2-phenylpropanoate[61]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.13 (d, ^3J = 6.3 Hz, 3H, CH_3), 1.22 (d, ^3J = 6.3 Hz, 3H, CH_3), 1.48 (d, ^3J = 7.2 Hz, 3H, CH), 3.67 (q, ^3J = 7.2 Hz, 1H, CH), 5.05-4.93 (m, 1H, -OCH), 7.35-7.21 (m, 5H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 19.00, 22.19, 46.15, 68.35, 127.86, 128.94, 141.03, 174.51.

iso-Propyl-3-phenylpropanoate[62]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.17 (d, ^3J = 6.3 Hz, 6H, CH_3), 2.55 (t, ^3J = 6.1 Hz, 2H, CH_2), 2.91 (t, ^3J = 6.1 Hz, 2H, CH_2), 5.05-4.93 (m, 1H, -OCH), 7.35-7.19 (m, 5H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 22.23, 31.49, 36.68, 68.14, 126.62, 128.75, 128.87, 141.03, 172.92. MS (EI^+): m/z 192.0 (M^+ requires 192.2) Data are in agreement with literature.

2.4.2.9 General procedure phenoxycarbonylation of styrene

LiCl (8.4 mg, 0.20 mmol, 20%), p-TsOH (34.4 mg, 0.20 mmol, 20%) and [Pd_2(Xyl-Phanephos)Cl_4] (10.3 mg, 0.01 mmol, 1%) were weighed into a 5 ml sealable vial. A stirring bar was placed inside and vial sealed with a crimp cap and put under inert atmosphere using a needle connected to vacuum line. Styrene (114 µl, 1 mmol, 100%), PhOH (94.1 mg, 1 mmol, 100%) and 2-butanone (1.5 ml) were added. The caps were pierced with two needles and placed in the autoclave which was quickly sealed. The autoclave was purged three times with CO and then pressurized to 30 bar and heated in a preheated oil bath to 75 °C for 24 hours. After this time, the autoclave was cooled to room temperature and the pressure released slowly. NMR analysis shows a high conversion to the ester product, phenyl 2-phenylpropanoate ('branched') and phenyl 3-phenylpropanoate ('linear') (17%; Branched/Linear = 1.6 (determined by ^{1}H NMR).

phenyl 2-phenylpropanoate[63]

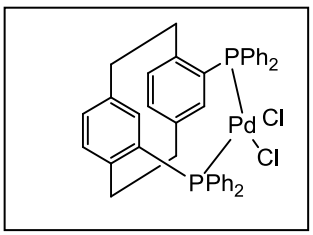
^{1}H NMR: 1.59 (d, ^3J = 9.1 Hz, 3H, CH_3), 3.94 (q, ^3J = 9.1 Hz, 1H, CH), 7.18-7.40 (m, 10H, $C_{Ar}H$).

phenyl 3-phenylpropanoate[64]

^{1}H NMR : 2.86 (t, ^3J = 7.5 Hz, 2H), 3.05 (t, ^3J = 7.5 Hz, 2H), 6.94-7.00 (m, 2H, $C_{Ar}H$), 7.18-7.40 (m, 8H, $C_{Ar}H$). GC- MS (EI^+) : m/z 226.0 (M^+ requires 226.2). Data are in agreement with literature.

2.4.3 Synthesis

2.4.3.1 {[(*R*)-(–)-4,12-Bis(diphenylphosphino)-[2.2]-*para*cyclophane] palladium(II)dichloride}, (**47**)

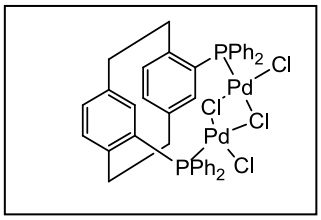


(*R*)-(–)-4,12-Bis(diphenylphosphino)-[2.2]-*para*-cyclophane (**38** (500 mg, 0.867 mmol) and [$PdCl_2(PhCN)_2$] (333 mg, 0.867 mmol) were used as described above, resulting

the title compound as bright yellow crystals in 90 % yield (600 mg, 0.797 mmol). This compound is already known but was prepared as described above.[23]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.13-2.19 (m, 2H, CH_2), 2.36-2.38 (m, 1H, CH_2), 2.39-2.40 (m, 1H, CH_2), 2.44-2.57 (m, 4H, CH_2), 6.31 (d, *J* = 5.0 Hz, 1H, $C_{Ar}H$), 6.34 (d, *J* = 5.0 Hz, 1H, $C_{Ar}H$), 6.40-6.43 (m, 2H, $C_{Ar}H$), 7.08-7.14 (m, 3H, $C_{Ar}H$), 7.26-7.35 (m, 6H, $C_{Ar}H$), 7.39-7.44 (m, 5H, $C_{Ar}H$), 7.47-7.52 (m, 3H, $C_{Ar}H$), 7.59-7.61 (d, *J* = 6.8 Hz, 1H, $C_{Ar}H$), 7.98-8.04 (m, 4H, $C_{Ar}H$). ^{31}P {^{1}H} NMR (121 MHz, $CDCl_3$) δ_P 43.7 (s). MP: 220 °C. The compound was further characterised by X-ray crystallography. Data are in agreement with literature.

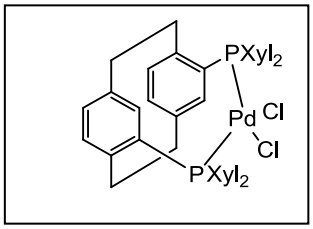
2.4.3.2 {[(*R*)-(–)-4,12-Bis(diphenylphosphino)-[2.2]-*para*cyclophane] dipalladium(II)tetrachloride}, (**55**)



(*R*)-(–)-4,12-Bis(diphenylphosphino)-[2.2]-*para*cyclophane (**38**) (100 mg, 0.173 mmol) and two equiv. of $[PdCl_2(PhCN)_2]$ (150 mg, 0.391 mmol) were used as described above, resulting the title compound as red crystalline powder that is sparingly soluble in any solvent, in 88 % yield (141 mg, 0.151 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.77-2.99 (m, 6H, CH_2), 3.36 (t, *J* = 11.2 Hz, 2H, CH_2), 7.00-7.06 (m, 13H, $C_{Ar}H$), 7.15-7.20 (m, 11H, $C_{Ar}H$), 7.99 (d, *J* = 16.4 Hz, 2H, $C_{Ar}H$). ^{31}P {^{1}H} NMR (161 MHz, $CDCl_3$) δ_P 35.6. ^{13}C NMR the complex was too insoluble for ^{13}C measurments even after 12 hours acquisition time. MS CI$^-$: m/z 931.8 (M^- requires 931.9). Anal. calcd. $C_{40}H_{34}Cl_4P_2Pd_2$: C, 51.59; H, 3.68; Found: C, 51.61; H, 3.62. No optical rotation possible due to little solubility. MP : >240 °C (decomposition).

2.4.3.3 {[(*S*)-(+)-3,5-Bis(dixylylphosphino)-[2.2]-*para*cyclophane] palladium(II)dichloride}, (**48**)

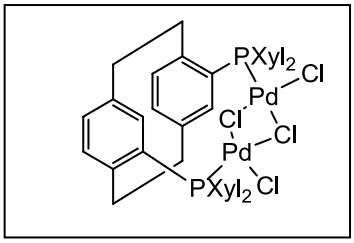


(*S*)-(+)-3,5-Bis(dixyly)phosphino)-[2.2]-*para*cyclophane (**39**) (30 mg, 0.043 mmol) and $[PdCl_2(PhCN)_2]$ (16.7 mg, 0.043 mmol) were used as described above, resulting the title

compound as yellow crystalline powder in 87 % yield (33 mg, 0.038 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.97-2.04 (m, 2H, CH_2), 2.20 (s, 12H, CH_3), 2.276 (s, 12H, CH_3), 2.35-2.56 (m, 6H, CH_2), 6.30 (d, *J* = 3.5 Hz, 1H, $C_{Ar}H$), 6.27 (d, *J* = 3.5 Hz, 1H, $C_{Ar}H$), 6.36-6.38 (m, 2H, $C_{Ar}H$), 6.94 (s, 2H, $C_{Ar}H$), 7.10 (s, 2H, $C_{Ar}H$), 7.21-7.27 (m, 2H, $C_{Ar}H$), 7.39-7.43 (m, 2H, $C_{Ar}H$), 7.52-7.55 (m, 5H, $C_{Ar}H$), 7.58-7.60 (m, 1H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 21.50 (d, *J* = 6.1 Hz, CH_3), 31.24 (s, CH_2), 34.67 (s, CH_2), 128.09 (s, $C_{Ar}H$), 131.16 (s, $C_{Ar}H$), 131.42 (s, $C_{Ar}H$), 131.77 (s, $C_{Ar}H$), 132.67 (s, $C_{Ar}H$), 133.34 (s, $C_{Ar}H$), 133.75 (s, $C_{Ar}H$), 133.82 (t, *J* = 5.7 Hz, $C_{Ar}H$), 135.76 (t, J = 5.7 Hz, $C_{Ar}H$), 136.02 (t, *J* = 6.1 Hz, C_{qu}), 136.81 (s, $C_{Ar}H$), 136.87 (d, *J* = 5.6 Hz, C_{qu}), 136.96 (s, $C_{Ar}H$), 137.12 (s, $C_{Ar}H$), 138.53 (t, *J* = 7.3 Hz, C_{qu}), 142.34 (s, C_{qu}). ^{31}P {^{1}H} NMR (161 MHz, $CDCl_3$) δ_P 43.6. $[\alpha]_D$= -0.513 (c = 0.405, $CHCl_3$). MS EI+: m/z 865.8 (M^+ requires 866.2), 828.8 ($M\text{-}Cl^+$ requires 829.2) (Good agreement was found between measured and calculated isotope patterns). Anal. calcd. $C_{48}H_{50}Cl_2P_2Pd$: C, 66.56; H, 5.82; Found: C, 66.61; H, 5.76. MP: 215 °C (decomposition). $[\alpha]_D$= +125.22 (c = 0.23, $CHCl_3$). The compound was further characterised by X-ray crystallography.

2.4.3.4 {[(*S*)-(+)-3,5-Bis(dixylylphosphino)-[2.2]-*para*cyclophane]dipalladium(II)tetrachloride}, (**56**)

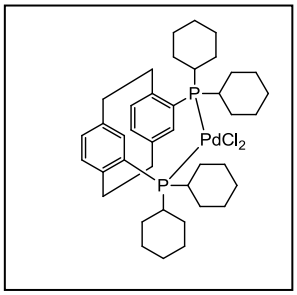


(*S*)-(+)-3,5-Bis(dixylylphosphino)-[2.2]-*para*cyclophane (**39**) (50 mg, 0.073 mmol) and two equiv. $[PdCl_2(PhCN)_2]$ (55.7 mg, 0.145 mmol) were used as described above, resulting the title compound as a red crystalline powder in 78 % yield (59 mg, 0.057 mmol). Single crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a CH_2Cl_2 solution of the product.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.01 (s, 12H, CH_3), 2.17 (s, 12H, CH_3), 2.76-2.89 (m, 4H, CH_2), 3.05-3,10 (m, 2H, CH_2), 3.38-3.44 (m, 2H, CH_2), 6.54-6.58 (m, 3H, $C_{Ar}H$), 6.70 (s, 2H, $C_{Ar}H$), 6.84-6.86 (m, 3H, $C_{Ar}H$), 6.98-6.99 (m, 6H, $C_{Ar}H$), 7.97 (d, *J* = 16.7 Hz, 2H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 21.35 (s, CH_3), 34.98 (s, CH_2), 36.37 (s, CH_2), 125.74 (s, $C_{Ar}H$), 126.59 (s, $C_{Ar}H$), 129.56 (s, $C_{Ar}H$), 130.04 (d, *J* = 10.7 Hz, C_{qu}), 132.57 (s, $C_{Ar}H$), 132.84 (s, $C_{Ar}H$), 133.23 (s, C_{qu}), 133.44 (s, C_{qu}), 134.01 (s, $C_{Ar}H$), 134.95 (d, *J* = 11.1 Hz, $C_{Ar}H$), 137.11

(d, *J* = 12.9 Hz, C_{qu}), 137.86 (t, *J* =13.6 Hz, C_{qu}) 138.98 (s, $C_{Ar}H$), 139.72 (d, *J* = 15.4 Hz, $C_{Ar}H$). ^{31}P $\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ_P 37.0 (s). MS CI^-: m/z 1043.9 (M^- requires 1044.0). Anal. calcd. For $C_{48}H_{50}Cl_4P_2Pd_2$: C, 55.25; H, 4.83; Found: C, 55.37; H, 4.78. MP: >240 (decomposition). $[\alpha]_D$= -1003.00 (c = 0.1, $CHCl_3$). The compound was further characterised by X-ray crystallography.

2.4.3.5 {[(*S*)-(+)-4,12-Bis(dicyclohexylphosphino)-[2.2]-*para*cyclophane]palladium(II)chloride}, (**49**)



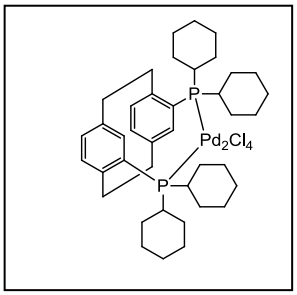
The ligand was prepared by lithiation with *n*-BuLi (0.90 ml, 1.40 mmol, 1.6M in pentane) of (*S*)-(+)-4,12-dibromo[2.2]-*para*cyclophane (250 mg, 0.680 mmol) and stirring for 3 hours at room temperature. Then dicyclohexylphosphinochloride (0.30 ml, 1.40 mmol) was added and stirred over night. After taking a small sample for ^{31}P $\{^1H\}$ NMR to assure the completion of the reaction, MeOH was added to quench any unreacted *n*-BuLi. The solvent was removed under reduced pressure and hexane added. The solution was filtered off via cannula filtration. The resulting white precipitate was further utilized in the complex formation. The ligand is mentioned in literature.[65] Ligand ^{31}P $\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ_P 5.81 (s).

Due to difficulties to obtain a clean ^{31}P $\{^1H\}$ NMR spectrum for this complex, 1 equiv. of ligand (*S*)-(+)-3,5-bis(dicyclohexylphosphino)-[2.2]-*para*cyclophane (**40**) (100 mg, 0.166 mmol) and 1 equiv. $[PdCl_2(PhCN)_2]$ (64 mg, 0.166 mmol) were dissolved in CH_2Cl_2 and stirred for ~3 hours. The solution was removed until few ml left and the precipitate washed with hexane. The yellow solid was dried under vacuum, and a sample was submitted to elemental analysis and mass spectrometry. The ^{31}P $\{^1H\}$ NMR was observed with the main compound at 48.2 ppm, which is around the area where all other monopalladium complexes typically have been observed. Crystallisation or other purifications of this compound were not successful.

^{31}P $\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ_P 48.2 (s). ^{31}P $\{^1H\}$ NMR impurity peaks at 6.9 (s), 25.6 (s), 50.6 (s), 60.0 (s), 61.2 (s). Anal. calcd. For $C_{40}H_{50}P_2PdCl_2$: C, 61.74; H, 7.51; Found : C, 61.83; H, 7.47. MS (CI^+): m/z calcd. for $C_{40}H_{58}P_2PdCl$ $[M-Cl]^+$: 743.27; found 743.27. By-

products identified by MS: 2x (**40**)+$PdCl_2$ [$C_{80}H_{116}Cl_2P_4Pd$] : 1379.00; found 1379.65; 2x **L3**+Pd_2Cl [$C_{80}H_{116}ClP_4Pd_2$] : 1449.97; found 1449.59.

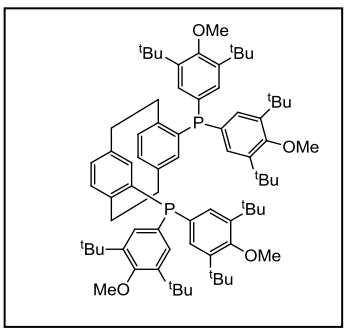
2.4.3.6 [(*S*)-(+)-4,12-Bis(dicyclohexylphosphino)-[2.2]-*para*cyclophane]dipalladium(II) tetrachloride}, (**57**)



(*S*)-(+)-3,5-Bis(dicyclohexylphosphino)-[2.2]-*para*cyclophane (**40**) (210 mg, 0.352 mmol) and 2 equiv. of [$PdCl_2(PhCN)_2$] (270 mg, 0.704 mmol) were dissolved in CH_2Cl_2 and stirred. Similar to the monopalladium formation, also this compound was found troubled to obtain a clean ^{31}P {^1H} NMR. The NMR spectra shows 3 main peaks in the ^{31}P {^1H} NMR around 55 ppm were 2 peaks and 1 peak at 39.7. Although no pure sample was obtained this peak is in good agreement for usual appearance from all other dipalladium complexes. Crystals suitable for X-ray crystallography were obtained by slow diffusion of hexane into a CH_2Cl_2 solution of the product under inert conditions. After work up, by removing the solution, washing with hexane and drying under vacuum, the product was obtained as an orange solid.

^{31}P {^1H} NMR (161 MHz, $CDCl_3$) δ_P 39.7 (s). ^{31}P {^1H} NMR impurity peaks at 54.1 (s), 55.9 (s). MS (CI): m/z calcd. for $C_{40}H_{58}P_2Pd_2$ $[M\text{-}4Cl]^+$: 919.1; found 920.4. X-ray single crystal structure was obtained for further characterisation.

2.4.3.7 (*S*)-(+)-4,12-bis(bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino)-[2.2]-*para*cyclophane, (**41**)

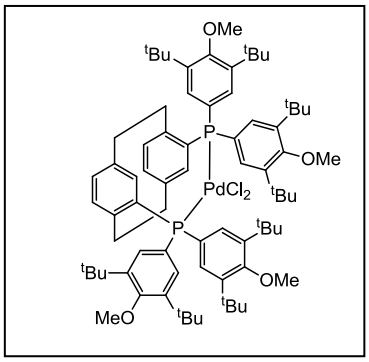


(*S*)-(+)-4,12-Dibromo-*para*cyclophane (181.2 mg, 0.495 mmol) was placed in a dry Schlenk flask under inert atmosphere, Et_2O (15 ml) added and *n*-BuLi (0.40 ml, 0.990 mmol, 2.5 M in hexane) was slowly added. The resulting solution was stirred for 3 hours and then bis(3,5-di-*tert*-butyl-4-methoxyphenyl)chlorophosphine (500 mg, 0.990 mmol) was added in one portion and stirred overnight. A small sample (0.5ml) was taken and analysed by ^{31}P {^1H} NMR spectroscopy confirming the reaction has gone to completion. MeOH (1 ml) was added and the solvent was

removed under vacuum. The product was then dissolved in hexane, the precipitate filtered off and solvent removed leaving the title compound in 81% yield (456 mg, 0.3980 mmol).

^{1}H NMR (300 MHz, CD_2Cl_2) δ_H 1.30 (br s, 72H, C(CH_3)), 2.5-3.00 (m, 8H, CH_2), 3.58 (br s, 12H, -OCH_3), 6.34-6.46 (m, 5H, $C_{Ar}H$), 6.64 (d, *J* = 2.37 Hz, 1H, $C_{Ar}H$), 7.18-7.26 (m, 2H, $C_{Ar}H$), 7.39-7.56 (m, 6H, $C_{Ar}H$). ^{31}P {^{1}H} NMR (161 MHz, $CDCl_3$) δ_P 0.21 (s). MS (CI): m/z calcd. for $C_{76}H_{106}O_4P_2$: 1144.76; found 1145.76. Anal.calcd. for $C_{76}H_{106}O_4P_2$: C 79.68, H 9.33 Found : C 79.56, H 9.26.

2.4.3.8 {{(*S*)-(+)-4,12-bis[bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-[2.2]-*para*cyclophane} palladium(II)chloride}, (**50**)

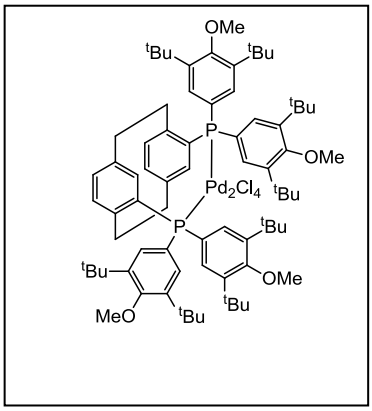


(*S*)-(+)-4,12-Bis[bis (3,5 di-*tert*-butyl-4-methoxyphenyl) phosphino]-[2.2]-*para*cyclophane (142 mg, 0.124 mmol) was put under inert atmosphere and dissolved in CH_2Cl_2. One equiv. of [$PdCl_2(PhCN)_2$] (48 mg, 0.124 mmol) was added. The solution was stirred overnight. A small sample was taken for ^{31}P {^{1}H} NMR confirming the reaction has gone to completion. The solvent was removed and the complex washed with hexane (3 x 20 ml). The solid obtained was dried under vacuum, yielding the desired compound as a bright yellow solid in 88% yield (144 mg, 0.109 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.23 (br s, 54H, C(CH_3)), 1.38 (bs, 18H, C(CH_3)), 2.26-2.33 (m, 2H, CH_2), 2.37-2.51 (m, 4H, CH_2), 3.01 (s, 2H, CH_2), 3.56 (s, 6H, -OCH_3), 3.64 (s, 6H, -OCH_3), 6.26-6.37 (m, 4H, $C_{Ar}H$), 6.41 (s, 2H, $C_{Ar}H$), 6.91-7.01 (m, 2H, $C_{Ar}H$), 7.23 (d, *J* = 6.0 Hz, 1H, $C_{Ar}H$), 7.87-7.91 (m, 3H, $C_{Ar}H$), 8.53-8.58 (m, 2H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ_C 31.64 (s, CH_2), 31.88 (s, CH_3), 32.06 (s, CH_3), 32.40 (s, CH_3), 36.40 (s, CH_2), 64.66 (s, CH_2), 66.28 (s, CH_2), 124.28 (s, C_{qu}), 124.82 (s, C_{qu}), 127.06 (s, C_{qu}), 127.52 (s, C_{qu}), 130.45 (s, $C_{Ar}H$), 134.76 (s, $C_{Ar}H$), 136.42 (m, $C_{Ar}H$), 136.70 (m, $C_{Ar}H$), 137.49 (t, *J* = 8.1 Hz, $C_{Ar}H$), 139.97 (t, *J* = 4.4 Hz, C_{qu}), 143.16 (t, *J* = 4.0 Hz, C_{qu}), 144.60 (s, C_{qu}),163.14 (s, C_{qu}), 163.22 (s, C_{qu}). ^{31}P {^{1}H} NMR (161 MHz, $CDCl_3$) δ_P 45.67 ppm (s). MS (CI): m/z calcd. for $C_{76}H_{106}O_4P_2PdCH_3COO$ [M-2Cl+CH_3CO_2]$^{+}$: 1309.67; found 1309.67. Anal.calcd. for

$C_{76}H_{106}Cl_2O_4P_2Pd$: C 69.0, H 8.08 Found : C 69.14, H 8.17. $[\alpha]_D$= -132.3 (c = 0.065, $CHCl_3$). 168 °C (decomposition).

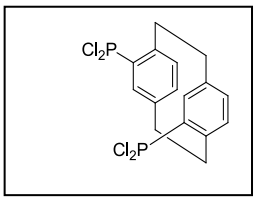
2.4.3.9 {{(*S*)-(+)-4,12-bis[bis(3,5-di-*tert*-butyl-4-methoxy-phenyl)phosphino]-[2.2]-*para*cyclophane}dipalladium(II)tetrachloride}, (58)



(*S*)-(+)-4,12-bis [bis (3,5 di-*tert*-butyl-4-methoxyphenyl) phosphino]-[2.2]-*para*cyclophane (45 mg, 0.040 mmol) was weighed into a dry schlenk flask and dissolved in CH_2Cl_2 (10 ml). Two equiv. of $[PdCl_2(PhCN)_2]$ (30.4 mg, 0.079 mmol) added to the solution and stirred overnight. A dark brown/orange solid was formed over night. A small sample (0.5 ml) was taken for ^{31}P $\{^1H\}$ NMR spectroscopy but no signal could be found. Due to the insolubility of the compound no ^{1} H NMR or ^{13}C $\{^1H\}$ NMR was obtained. Mass spectrometry was taken to assure that this solid was the suggested compound. The compound was purified by removing solvent and washing with hexane (2 x 20 ml). The solution was filtered off and the precipitate dried under vacuum, giving a dark red/brown solid in 95% yield (57 mg, 0.038 mmol).

MS (CI): m/z calcd. for $C_{76}H_{106}Cl_4O_4P_2Pd_2$ $[M^-+NH_3]^+$: 1500.4; found 1500.6.

2.4.3.10 (*R*)-(-)-4,12-bis(dichlorophosphino)-[2.2]-*para*cyclophane (46)

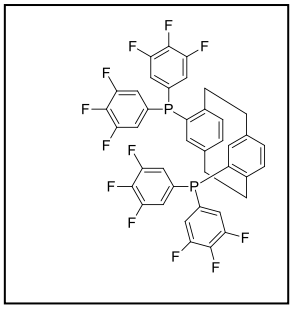


(*R*)-(-)-4,12-dibromo-[2.2]-*para*cyclophane (3.02 g, 8.249 mmol) was placed in a dry Schlenk flask under argon atmosphere and partly dissolved in dry Et_2O (40 ml). *n*-BuLi (14 ml, 35.00 mmol, 2.5 M in hexane) was added slowly under room temperature and stirred for 3 hours. Bis(di-*iso*-propylamino)chlorophosphine (5 g, 0.019 mol) was added in one portion and the solution stirred overnight. Anhydrous MeOH (30 ml) was added and some solvent was removed under vacuum, until half the solvent was removed, then more MeOH (100 ml) was added. The solution was filtered off by cannula filtration and the white precipitate dried under vacuum, resulting then (*R*)-(-)-4,12-bis[bis(di-*iso*-

propylamino)phosphino]-[2.2]-*para*cyclophane in 87 % yield (4.80 g, 7.172 mmol). ($^{31}P\{^{1}H\}$ NMR in $CDCl_3$ 72.3 ppm).

A solution of $HCl*Et_2O$ (2 M, 100 ml, 0.200 mol) was added to the solid (*R*)-(-)-4,12-bis[bis(di-*iso*-propylamino)phosphino]-[2.2]-*para*cyclophane and stirred overnight at room temperature. The solvent was removed and hexane (100 ml) was added. The solution was filtered through a cannula and the solvent removed. More hexane (100 ml) was added and the solution again filtered off and the solvent removed. Hexane (100 ml) was added and the cloudy solution was filtered again. The solvent was evaporated resulting in the product (*R*)-(-)-4,12-bis(dichlorophosphino)-[2.2]-*para*cyclophane as a white powder in 31% yield (908 mg, 2.214 mmol). ($^{31}P\{^{1}H\}$ NMR in $CDCl_3$ 166.0 ppm (s)) Data in agreement with literature.[3]

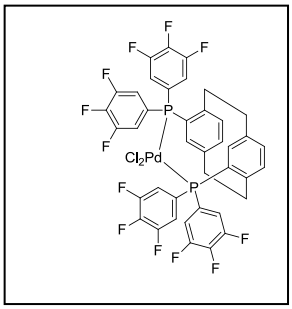
2.4.3.11 (*R*)-(-)-4,12-bis[bis(3,4,5-trifluorophenyl)phosphino]-[2.2]-*para*cyclophane, (42)



(*R*)-(-)-4, 12-bis(dichlorophosphino)-[2.2]-*para*cyclophane (385.0 mg, 0.939 mmol) was dissolved in THF (5 ml) and 3,4,5 trifluorophenylmagnesiumbromide (16 ml, 4.695 mmol, 0.3 M in THF) was added slowly. After stirring for 2 hours at room temperature the solution was heated to 50 °C for one hour and cooled to room temperature. After checking the completion of the reaction using $^{31}P\{^{1}H\}$ NMR MeOH (1 ml) was added and stirred, the solvent removed and hexane added and the solution was filtered off. After removing the solvent under reduced pressure, the crude product was obtained as brownish solid. The solid was dissolved in hexane (30 ml) and charcoal (spatula point) was added. The solution was filtered under argon over celite. After removing the solvent under reduced pressure the product was obtained in 33% yield (348 mg, 0.3103 mmol) as a white solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ_H 2.61-3.28 (m, 8H, CH_2), 6.29-6.80 (m, 6H, $C_{Ar}H$), 6.87-7.01 (m, 4H, $C_{Ar}H$), 7.05-7.23 (m, 4H, $C_{Ar}H$). $^{31}P\{^{1}H\}$ NMR (121 MHz, $CDCl_3$) δ_P 2.09 (s). Anal. calcd. For $C_{40}H_{22}F_{12}P_2$: C, 60.62; H, 2.80; Found : C, 60.53; H 2.93. MS (CI): m/z calcd. for $C_{40}H_{22}F_{12}P_2$ $[M-F]^+$: 774.54; found 774.0. $[\alpha]_D$= -27.1 (c = 0.16, $CHCl_3$).

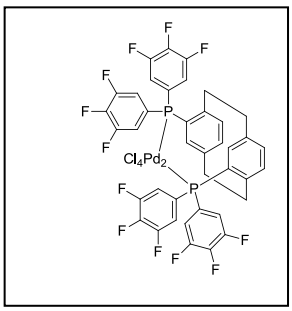
2.4.3.12 {{(*R*)-(-)-4,12-bis[bis-(3,4,5-trifluorophenyl)phosphino]-[2.2]-*para*cyclophane}palladium(II) dichloride}, (**51**)



(*R*)-(-)-4,12-Bis[bis(3,4,5-trifluorophenyl)phosphino]-[2.2]-*para*cyclophane (103 mg, 0.1300 mmol) was dissolved in CH_2Cl_2 (10 ml) before adding one equiv. [$PdCl_2(PhCN)_2$] (50 mg, 0.130 mmol). The solution was stirred overnight. Taking a small sample (0.5 ml) for ^{31}P {^1H} NMR spectroscopy confirmed the reaction had gone to completion. The solvent was removed under vacuum, until a few ml were left and then hexane (20 ml) was added. The yellowish precipitate was washed 3 times with hexane before dried under vacuum, yielding the palladium complex as a bright yellow powder in 70 % yield (88 mg, 0.091 mmol).

^1H NMR (400 MHz, CD_2Cl_2) δ_H 2.59-2.82 (m, 6H, CH_2), 2. 87-3.33 (m, 2H, CH_2), 6.51-6.54 (m, 2H, $C_{Ar}H$), 6.60-6.69 (m, 2H, $C_{Ar}H$), 6.76-6.80 (m, 2H, $C_{Ar}H$), 6.99-7.12 (m, 1H, $C_{Ar}H$), 7.16-7.26 (m, 1H, $C_{Ar}H$), 7.41 (t, *J* = 7.6 Hz, 1H, $C_{Ar}H$), 7.52-7.62 (m, 5H, $C_{Ar}H$). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ_C 32.77 (s, CH_2), 36.32 (s, CH_2), 117.00 (s, C_{qu}), 121.77-122.12 (m, $C_{Ar}H$), 127.59 (s, C_{qu}), 128.20 (s, C_{qu}), 137.01 (s, $C_{Ar}H$), 137.15 (s, $C_{Ar}H$), 137.28 (d, CH, *J* = 4.42 Hz, $C_{Ar}H$), 137.37 (s, $C_{Ar}H$), 137.49 (t, *J* = 4.5 Hz, $C_{Ar}H$), 140.77-140.91 (m, C_{qu}), 144.72 (s, C_{qu}), 149.49-149.77 (m, C_{qu}), 150.15-150.62 (m, C_{qu}), 152.08-152.49 (m, C_{qu}), 152.70-153.06 (m, C_{qu}). ^{31}P {^1H} NMR (161 MHz, $CDCl_3$) δ_P 40.8 (s). Anal. calcd. for $C_{40}H_{22}Cl_2F_{12}P_2Pd$: C, 49.54; H, 2.29; Found : C, 49.62; H 2.39,. MS (CI $(NH3)^-$): m/z calcd. for $C_{40}H_{22}Cl_2F_{12}P_2Pd$ (NH_3) : 969.9; found 969.8. $[\alpha]_D$= +12.0 (c = 0.075, $CHCl_3$). MP: 180 °C (decomposition).

2.4.3.13 {{(*R*)-(-)-4,12-bis[bis(3,4,5-trifluorophenyl)phosphino]-[2.2]-*para*cyclophane}dipalladium(II) tetrachloride}, (**59**)

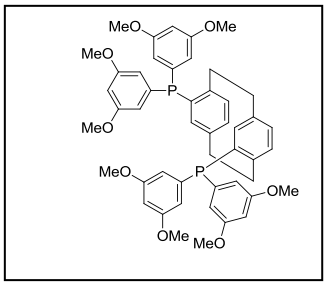


(*R*)-(-)-4,12-Bis[bis (3,4,5-trifluorophenyl) phosphino]-[2.2]- *para*cyclophane (193 mg, 0.244 mmol) was weighed into an dry schlenk flask and put under argon. The compound was dissolved in CH_2Cl_2 (30 ml) before adding 2 equiv. of [$PdCl_2(PhCN)_2$] (187 mg, 0.488 mmol). The resulting solution

was then stirred overnight. A small sample (0.5 ml) was taken for ^{31}P {^{1}H} NMR spectroscopy confirming the reaction has gone to completion. Then the solvent was removed until a few ml were left and the reddish precipitate obtained washed 5 times with hexane. After cannula filtration the precipitate was dried under vacuum, yielding the title compound as an orange solid in 43% yield (126 mg, 0.110 mmol).

^{1}H NMR (300 MHz, CD_2Cl_2) δ_H 2.87-3.33 (m, 8H, CH_2), 6.55 (br s, 4H, $C_{Ar}H$), 7.04-7.13 (m, 4H, $C_{Ar}H$), 7.38-7.44 (m, 3H, $C_{Ar}H$), 7.52-7.61 (m, 3H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, CD_2Cl_2) δ_C 33.68 (s, CH_2), 35.25 (s, CH_2), 115.69 (s, $C_{Ar}H$), 116.11 (s, $C_{Ar}H$), 128.29 (s, $C_{Ar}H$), 131.40 (s, $C_{Ar}H$), 131.97 (s, $C_{Ar}H$), 135.06 (d, J= 2.7 Hz, $C_{Ar}H$), 139.51 (s, $C_{Ar}H$), 148.18 (s, C_{qu}), 151.32 (s, C_{qu}), 151.63 (s, C_{qu}). ^{31}P {^{1}H} NMR (121 MHz, $CDCl_3$) δ_P 36.06 (s). Anal. calcd. For $C_{40}H_{22}Cl_4F_{12}P_2Pd_2$: C, 41.88; H, 1.93; Found : C, 41.95; H, 1.86. MS (CI): m/z calcd. for $C_{40}H_{22}Cl_4F_{12}P_2Pd_2$: 1147.8; found 1147.7. $[\alpha]_D$= +691.7 (c = 0.06, $CHCl_3$). MP: 172 °C (decomposition).

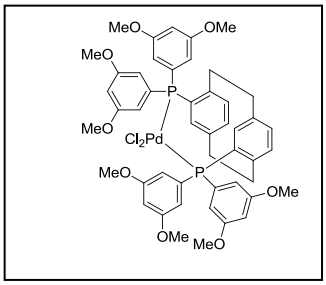
2.4.3.14 (*R*)-(-)-4,12-bis[bis(3,5-dimethoxyphenyl)phosphino]-[2.2]-*para*cyclophane, (**43**)



(*R*)-(-)-4,12-bis(dichlorophosphino)-[2.2]-*para*cyclophane (600 mg, 1.463 mmol) was dissolved in THF (10 ml) and 3,5 dimethoxyphenylmagnesiumbromide (7.5 ml, 7.316 mmol, 1M in THF) slowly added. The solution was heated to 68 °C for 3 hours, then cooled to room temperature and stirred overnight. The completion of the reaction was checked using ^{31}P {^{1}H} NMR spectroscopy. MeOH (5 ml) was added to quench the rest of the unreacted Grignard. The solvent was removed, hexane added and the solution filtered via cannula filtration. After removing the solvent under reduced pressure, the product was obtained in 79% yield (943 mg, 1.154 mmol) as a white sticky solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67-3.76 (m, 32H, -OCH_3, CH_2), 6.38-6.45 (m, 14H, $C_{Ar}H$), 7.11 (t, J = 8.2 Hz, 4H, $C_{Ar}H$). ^{31}P {^{1}H} NMR (161 MHz, $CDCl_3$) δ_P 3.87 (s). MS (CI): m/z calcd. for $[C_{48}H_{50}O_8P_2+H]^+$: 817.30 found 817.30. Anal. calcd. for $C_{48}H_{50}O_8P_2$: C, 70.58; H, 6.17; Found : C, 70.39; H 6.05. $[\alpha]_D$= -32.1 (c = 0.28, $CHCl_3$).

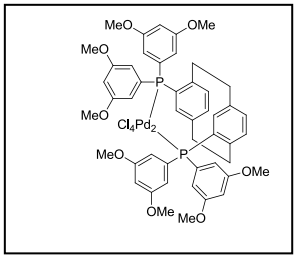
2.4.3.15 {{(*R*)-(-)-4,12-bis[bis(3,5-dimethoxyphenyl)phosphino]-[2.2]-*para*cyclophane}palladium(II) dichloride}, (52)



(*R*)-(-)-4,12-Bis[bis(3,5-dimethoxyphenyl)phosphino]-[2.2]-*para*cyclophane (262 mg, 0.3208 mmol) was dissolved in CH_2Cl_2 (10 ml) and $[PdCl_2(PhCN)_2]$ (123 mg, 0.3208 mmol) added in one portion and stirred overnight. A small sample (0.5 ml) was taken for $^{31}P\{^1H\}$ NMR spectroscopy confirming the reaction has gone to completion. The solution was removed leaving a yellowish oily residue, which was then washed with hexane resulting in a yellow precipitate. Filtering off the solution and drying the yellow precipitate under vacuum resulted in a yellow sticky solid. In order to have the compound washed thoroughly this solid was dissolved again in CH_2Cl_2 (6 ml) and then precipitated with hexane (20 ml). About one third of the solution was removed prior to cannula filtration. The residue was dried under vacuum again leaving a yellow sticky solid in 73 % yield (233.3 mg, 0.235 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ_H 3.54-3.84 (m, 32H, $-OCH_3$, CH_2), 6.36-6.44 (m, 6H, $C_{Ar}H$), 6.63 (d, J = 2.2 Hz, 4H, $C_{Ar}H$), 7.09 (t, J = 8.1 Hz, 2H, $C_{Ar}H$), 7.47-7.51 (m, 2H, $C_{Ar}H$), 7.66-7.73 (m, 4H, $C_{Ar}H$). $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2) δ_C 30.92 (s, CH_2), 35.10 (s, CH_2), 54.24 (s, $-OCH_3$), 54.42 (s, $-OCH_3$), 54.57 (s, $-OCH_3$), 98.46 (s, $C_{Ar}H$), 99.50 (s, $C_{Ar}H$), 102.59 (s, $C_{Ar}H$), 103.24 (s, $C_{Ar}H$), 104.51 (s, $C_{Ar}H$), 105.40 (s, $C_{Ar}H$), 114.52 (t, J = 5.25 Hz, $C_{Ar}H$), 128.86 (s, $C_{Ar}H$), 130.78 (d, J = 11.25 Hz, C_{qu}), 131.50 (d, J = 8.25 Hz, C_{qu}), 133.22 (d, J = 7.5 Hz, C_{qu}), 133.93 (s, CH), 134.75 (d, J = 7.5 Hz, C_{qu}), 135.58 (t, J = 5.25 Hz, CH), 136.28 (t, J = 11.25 Hz, CH), 138.66 (t, J = 7.5 Hz, C_{qu}), 142.43 (s, C_{qu}), 143.10 (s, C_{qu}), 158.82 (t, J = 7.5 Hz, C_{qu}), 159.55 (t, J = 8.25 Hz, C_{qu}), 159.96 (s, C_{qu}). $^{31}P\{^1H\}$ NMR (161 MHz, CD_2Cl_2) δ_P 45.65 (s). MS (EI): m/z calcd. for $[C_{48}H_{50}Cl_2O_8P_2Pd]$: 994.1; found 994.2. Anal. calcd. for $C_{48}H_{50}Cl_2O_8P_2Pd$: C, 57.99; H, 5.07; Found : C, 58.18; H, 4.99. $[\alpha]_D$= +134.3 (c = 2.69, $CHCl_3$).

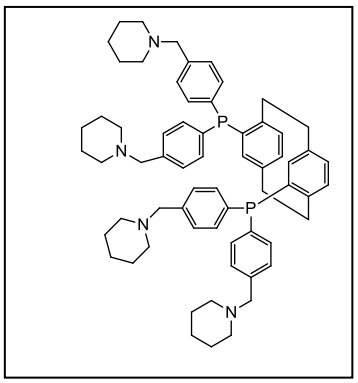
2.4.3.16 {{(*R*)-(-)-4,12-bis[bis(3,5-dimethoxyphenyl)phosphino]-[2.2]-*para*cyclophane} dipalladium(II)tetrachloride}, (60)



{{(*R*)-(-)-4,12-bis[bis(3,5-dimethoxyphenyl)phosphino]-[2.2]-*para*cyclophane}palladium(II)chloride} (233 mg, 0.235 mmol) was dissolved in CH_2Cl_2 (15 ml) and $[PdCl_2(PhCN)_2]$ (90 mg, 0.235 mmol) added and stirred overnight. A small sample (0.5 ml) was taken ^{31}P $\{^1H\}$ NMR spectroscopy confirming the reaction has gone to completion. Solvent was removed until a few ml of CH_2Cl_2 left and hexane (2 x 20 ml) added to precipitate and wash the complex. After cannula filtration the solution was dried under vacuum, leaving a red crystalline powder in 55% yield (150.2 mg, 0.129 mmol).

^1H NMR (400 MHz, $CDCl_3$) δ_H 3.54-3.75 (m, 32H, $-OCH_3$), 6.10-6.14 (m, 3H, $C_{Ar}H$), 6.23-6.24 (m, 2H, $C_{Ar}H$), 6.32-6.46 (m, 4H, $C_{Ar}H$), 6.63 (d, *J*= 2.32 Hz, 2H, $C_{Ar}H$), 6.88-7.03 (m, 6H, $C_{Ar}H$), 7.92-7.97 (m, 1H, $C_{Ar}H$). ^{13}C $\{^1H\}$ NMR (75 MHz, CD_2Cl_2) δ_C 34.78 (s, CH_2), 36.64 (s, CH_2), 55.96 (s, OMe, CH_3), 55.78 (s, OMe, CH_3), 102.49 (s, $C_{Ar}H$), 103.42 (s, $C_{Ar}H$), 110.74 (d, *J* = 12.75 Hz, $C_{Ar}H$), 125.05 (s, C_{qu}), 125.84 (s, C_{qu}), 131.89 (s, C_{qu}), 132.75 (s, C_{qu}), 135.20 (d, *J* = 9.0 Hz, $C_{Ar}H$), 136.83 (d, *J* = 12.8 Hz, $C_{Ar}H$), 139.58 (s, $C_{Ar}H$), 139.85 (s, C_{qu}), 147.26 (s, C_{qu}), 160.23 (d, *J* = 12.0 Hz, C_{qu}), 160.47 (d, *J* = 12.0 Hz, C_{qu}). ^{31}P $\{^1H\}$ NMR (161 MHz, CD_2Cl_2) δ_P 38.69 (s). MS (CI) (NH_3): m/z calcd. for $[C_{48}H_{50}Cl_4O_8P_2Pd2]$ $[M\text{-}2Cl]^+$: 1100.04; found 1100.1; $[M\text{-}3Cl]^+$ 1066.08; found 1066.07. Anal. calcd. for $C_{48}H_{50}Cl_4O_8P_2Pd_2$: C, 49.21; H, 4.30; Found : C, 49.29; H, 4.24. $[\alpha]_D$= +708.4 (c = 0.22, $CHCl_3$, 20 °C).

2.4.3.17 (*R*)-(-)-Bis(4-piperidinylmethylphenylphosphino)-[2.2]-*para*cyclophane, (**44**)

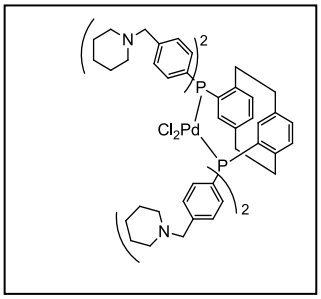


(*R*)-(-)-bis(dichlorophosphino)-[2.2]-*para*cyclophane (143 mg, 0.350 mmol) was dissolved in in THF (15 ml) and 4-piperidinyl-methylphenylmagnesiumbromid (0.25 M in THF, 7ml, 1.75 mmol) was added slowly. After stirring for 2 hours at room temperature the solution was heated to 50 °C for one hour and cooled to room temperature. A ^{31}P $\{^1H\}$ NMR was taken of the solution to assure that the reaction went to completion, the rest of the Grignard was quenched with MeOH (1 ml) and the solvent removed until ~2ml of solvent left and hexane added.

The solution was filtered off via cannula filtration. After removing the solvent under reduced pressure, the product was obtained in 68% yield (229 mg, 0.237 mmol) as a white sticky solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.36-1.53 (m, 24H, CH_2), 2.29-2.31 (m, 20H, CH_2), 2.81-3.00 (m, 2H, CH_2), 3.29-3.43 (m, 10H, CH_2), 6.40-6.51 (m, 2H, $C_{Ar}H$), 7.04-7.07 (m, 1H, CH_{arom}), 7.14-7.37 (m, 16H, $C_{Ar}H$), 7.44-7.50 (m, 3H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 23.31-23.36 (m, CH_2), 24.89-24.97 (m, CH_2), 32.13, 34.77 (d, *J* = 8.25 Hz, CH_2), 53.45-53.69 (d, *J* = 3.55 Hz, CH_2), 53.45-53.69 (m, CH_2), 62.57-62.86 (m, CH_2), 125.70 (s, $C_{Ar}H$), 125.79 (s, $C_{Ar}H$), 127.05 (s, $C_{Ar}H$), 127.91-128.20 (m, $C_{Ar}H$), 128.57 (s, $C_{Ar}H$), 131.50 (s, $C_{Ar}H$), 131.71 (s, $C_{Ar}H$), 131.99 (s, $C_{Ar}H$), 132.28 (t, *J* = 3.75 Hz, $C_{Ar}H$), 133.19 (d, *J* = 3.75 Hz, $C_{Ar}H$), 134.35 (s, $C_{Ar}H$), 134.46 (s, $C_{Ar}H$), 134.76 (s, $C_{Ar}H$), 136.90 (d, *J* = 11 Hz, $C_{Ar}H$), 138.02 (s, C_{qu}), 138.91 (s, C_{qu}), 142.03 (s, C_{qu}), 142.24 (s, C_{qu}). ^{31}P {^{1}H} NMR (121 MHz, $CDCl_3$) δ_P -2.93. MS (CI): m/z calcd. for $C_{64}H_{78}N_4P_2$ 965.3; found 965.6. Anal. calcd. For $C_{64}H_{78}N_4P_2$: C, 79.63; H, 8.14; N 5.80 Found : C, 79.53; H, 8.09; N 5.72. $[\alpha]_D$= -29.99 (c = 0.157, $CHCl_3$).

2.4.3.18 {[(*R*)-(-)-Bis(4-piperidinylmethylphenylphosphino)-[2.2]-*para*cyclophane]palladium(II) chloride}, (**53**)

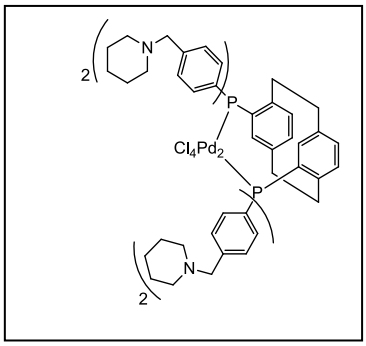


(*R*)-(-)-bis(4-piperidinylmethylphenylphosphino)-[2.2]-*para*cyclophane (114.5 mg, 0.119 mmol) was dissolved in CH_2Cl_2 and $[PdCl_2(PhCN)_2]$ (45.5 mg, 0.119 mmol) was added and stirred over night. ^{31}P {^{1}H} NMR was taken to make assure the completion of the reaction. Then the solvent was removed and hexane was added, stirred for 10 minutes and yellow precipitate collected via filtration. The yellow solid was dried under vacuum, leaving the product in 73% yield (98.8 mg, 0.087 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.36-1.57 (m, 24H, CH_2), 2.33-2.50 (m, 24H, CH_2), 3.39-3.54 (m, 8H, CH_2), 6.28-6.49 (m, 4H, $C_{Ar}H$), 7.07-7.60 (m, 16H, $C_{Ar}H$), 7.87-7.74 (m, 2H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 23.13-23.23 (m, CH_2), 24.66-24.89 (m, CH_2), 31.03 (s, CH_2), 34.80 (s, CH_2), 53.28-53.54 (m, CH_2), 62.03-62.65 (m, CH_2), 125.79 (s, $C_{Ar}H$), 127.15 (s, $C_{Ar}H$), 127.45 (t, *J* = 5.46 Hz, $C_{Ar}H$), 128.15-128.20 (m, $C_{Ar}H$), 128.43 (s, $C_{Ar}H$), 128.82 (s, $C_{Ar}H$), 133.65 (s, $C_{Ar}H$), 135.50 (t, *J* = 3.41 Hz, $C_{Ar}H$), 135.50 (t, *J* = 5.06 Hz, $C_{Ar}H$), 136.03 (t,

J = 11.09 Hz, $C_{Ar}H$), 138.69 (t, *J* = 7.04 Hz, C_{qu}), 142.00 (s, C_{qu}), 142.67 (s, C_{qu}). ^{31}P {^{1}H} NMR (121 MHz, $CDCl_3$) δ_P 42.50 (s). MS (CI): m/z calcd. for $C_{64}H_{78}N_4P_2PdCl$ [M-Cl]$^+$: 1107.4 ; found 1107.5. Anal. calcd. for $C_{64}H_{78}Cl_2N_4P_2Pd$: C, 67.27; H, 6.88; N 4.90 Found : C, 67.28; H, 6.91; N 4.84. $[\alpha]_D$= +82.54 (c = 0.106, $CHCl_3$, 20 °C). MP : 175-177 °C (decomposition).

2.4.3.19 {[(*R*)-(-)-Bis(4-piperidinylmethylphenylphosphino)-[2.2]-*para*cyclophane]dipalladium(II) tetrachloride, (**61**)

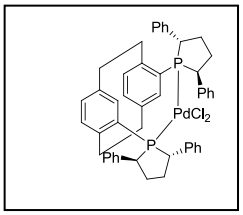


(*R*)-(-)-bis(4-piperidinylmethylphenylphosphino)-[2.2]-*para*cyclophane (90 mg, 0.093 mmol) was dissolved in CH_2Cl_2 (10 ml) and bis(benzonitrile) palladium(II)chloride (71 mg, 0.186 mmol) was added and stirred over night. The solution color changed to dark reddish brown with some precipitate over night. A ^{31}P {^{1}H} NMR showed that there was still (**53**) in the solution (42.1 ppm). More Pd precursor (25 mg, 0.065 mmol) was added in little steps until no more monopalladium peak was visible. The solution was found to result in more dark brown precipitate, as did the solution colour. The solvent was removed until a few ml left, then hexane was added, stirred for few minutes and solution filtered off via cannula filtration. The brown solid was dried under vacuum, leaving the product in quantitative yield (122 mg, 0.093 mmol). The sample was not soluble enough for a ^{1}H or a ^{31}P {^{1}H} NMR. To assure that this is indeed a di-Pd complex the sample was sent to mass spectroscopy. The MS suggests that the observed species could contain the Pd_2Cl_4 species, but the ion intensities were too low to be sure about the isotope patterns.

The results found for EA indicate a possibility of Pd coordinating to the nitrogens of pip-phanephos. Although adding only 2 equiv. of $[PdCl_2(PhCN)_2]$ was found to still give a strong picks of the (**53**) and dark precipitate in the solution. The further addition of Pd precursor resulted in more precipitate and the disappearance of the monopalladium species.

MS (MALDI): m/z calcd. for $C_{64}H_{78}N_4P_2Pd2Cl2$ [M-2Cl]$^+$: 1249.02 ; found 1249.3. Anal. calcd. for $C_{64}H_{78}Cl_4N_4P_2Pd2$: C, 58.24; H, 5.96; N 4.24 Found : C, 51.93; H, 4.99; N 4.15; adding 2 x PdCl2, 2 x CNPh, 1 x hexane :C, 51.29; H, 5.23; N, 4.27.

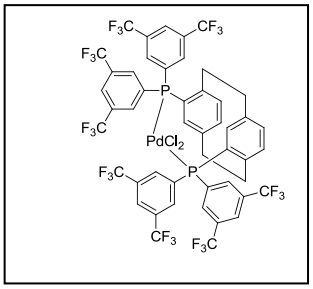
2.4.3.20 {[(*S*)-(+)-4,12-Bis((*R*,*R*)-2,5-diphenylphospholane)-[2.2]-*para*cyclophane}palladium(II) dichloride}, (**54**)



The (*R*,*R*)-2,5-diphenylphospholane-1-chloride was prepared according to literature.[22] (*R*)-4,12-dibromo-[2.2]-*para*cyclophane (46.6 mg, 0.128 mmol) was dissolved in dry Et_2O (10 ml). After the addition of *n*-BuLi (0.16 ml, 0.255 mmol, 1.6 M) the solution was left stirring for 2 hours. The (*R*,*R*)-2,5-diphenylphospholane-1-chloride (70 mg, 0.255 mmol) was dissolved in Et_2O (5 ml) and added to the lithiated cyclophane. The reaction was stirred over night at room temperature. To assure the completion of the reaction a ^{31}P $\{^1H\}$ NMR was taken. The peak of the ligand was found at 18.61 ppm. Dry MeOH (0.2 ml) was added to quench any unreacted *n*-BuLi, then the solvent was removed under vacuum and the ligand was purified via cannula filtration in hexane (15 ml). The solvent was removed yielding the crude ligand in 47 % yield (41 mg, 0.060 mmol). The ligand was then dissolved in CH_2Cl_2 (10 ml) and 1 equiv. of $[PdCl_2(PhCN)_2]$ (120 mg, 0.313 mmol) was added and stirred over night at room temperature. A ^{31}P $\{^1H\}$ NMR was taken to assure the completion to the Pd catalyst. Then the solvent was removed and the yellow precipitate was washed 3 times with hexane solution (20 ml). Then the product was dried under vacuum and yellow powdery product was obtained in 93 % yield (380.2 mg, 0.293 mmol).

^{31}P $\{^1H\}$ NMR (121 MHz, $CDCl_3$) δ_P 48.8 (s). MS -ve CI (NH_3): m/z calcd. for $C_{48}H_{46}P_2PdCl_2$ $[M\text{-}HCl]^-$: 824.2 ; found 823.9.

2.4.3.21 {{(*R*)-(-)-4,12-Bis[3,5-bis(trifluoromethyl)phenylphosphino]-[2.2]-*para*cyclophane} palladium(II)dichloride}, (**69**)



(*R*)-4,12-dibromo-[2.2]-*para*cyclophane (185.8 mg, 0.508 mmol) was dissolved in dry Et_2O (20 ml). After the addition of *n*-BuLi (0.40 ml, 0.001 mol, 2.5 M) the solution was left to stir for 3 hours. The bis[3,5-bis(trifluoromethyl)phenyl]phosphinochloride (500 mg, 1.015 mmol) was dissolved in Et_2O (2 ml) and added to the lithiated cyclophane. The reaction was stirred over night at room temperature. To assure the

completion of the reaction a ^{31}P $\{^{1}H\}$ NMR was taken. The peak of the ligand was observed at 0.89 ppm. Dry MeOH (1 ml) was added to quench any unreacted *n*-BuLi, then the solvent was removed under vacuum and the ligand was purified via cannula filtration in hexane (15 ml). The solvent was removed yielding the crude ligand in 68% yield (386 mg, 0.344 mmol). The ligand was dissolved in CH_2Cl_2 (10 ml) and 1 equiv. of $[PdCl_2(PhCN)_2]$ (120 mg, 0.313 mmol) was added and stirred over night at room temperature. A ^{31}P $\{^{1}H\}$ NMR was taken to assure the completion to the Pd catalyst. Then the solvent was removed and the yellow precipitate was washed 3 times with hexane solution (20 ml). Then the product was dried under vacuum and yellow powdery product was obtained in 93% yield (380.2 mg, 0.293 mmol).

^{1}H NMR (300 MHz, CD_2Cl_2) δ_H 2.55-2.96 (m, 8H, CH_2), 6.55-6.67 (m, 5H, $C_{Ar}H$), 6.98-7.04 (m, 2H, $C_{Ar}H$), 7.97-8.23 (m, 7H, $C_{Ar}H$), 8.29-8.32 (m, 4H, $C_{Ar}H$). ^{13}C $\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C 33.16 (s, CH_2), 36.06 (s, CH_2), 121.14 (d, J = 19.5 Hz, C_{qu}), 124.72 (t, J = 12.0 Hz, C_{qu}), 126.17 (s, $C_{Ar}H$), 136.56 (m, $C_{Ar}H$), 137.08 (s, $C_{Ar}H$), 138.32 (t, J = 4.5 Hz, $C_{Ar}H$), 140.82 (s, C_{qu}), 140.93 (s, C_{qu}), 141.02 (s, C_{qu}), 144.38 (s, C_{qu}). ^{31}P $\{^{1}H\}$ NMR (161MHz, CD_2Cl_2) δ_P 38.93 (s). Anal. calcd. for $C_{48}H_{26}Cl_2F_{24}P_2Pd$: C, 44.42; H, 2.02; Found : C, 44.52; H 1.91. MS (EI): m/z calcd. for $C_{48}H_{26}Cl_2F_{24}P_2Pd$ $[M^+]$: 1298.0; found 1298.0.

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CHAPTER III

Heterogeneous Catalysis: Immobilisation and characterisation of homogeneous catalysts by ion-exchange and their application in asymmetric catalysis.

Abstract Highly active homogeneous phanephos type Pd and Rh complexes with *nitrogen* functionalisation were prepared. These *N*-tagged catalysts were then tethered onto acidic ion-exchange polymeric supports. By simple acid-base chemistry the *N*-functionality was protonation and therefore the catalyst immobilising by simple. The catalytic activities of the chiral Rh catalysts were examined in hydrogenation reactions of MAA and the Pd catalysts investigated in asymmetric methoxycarbonylation of styrene. The catalysts were highly active and stable for recycling of up to 10 cycles. Furthermore, the *N*-functionalised Pd catalyst was tested in continuous $scCO_2$ flow methoxycarbonylation reaction of styrene, heterogenised by acidic ionic liquids onto silica (SILP).

3.1 Heterogenisation *via* ion-exchange

Catalysts can be classified either as homogeneous and heterogeneous catalysts, depending if they are in the same phase as the reactants (homogeneous) or not (heterogeneous). Homogeneous catalysts have been of great interest for commercial and academic applications, due to their high efficiency and selectivity, and their ease of preparation and characterisation and despite their disadvantages of relatively high costs in preparation and difficulty of separation from the product mixture. This can hold back their industrial implementation particularly for large scale reactions or in applications where high catalyst loadings are required. For toxic metals such as Rh and Pd, final products need to contain <5 ppm metal. In order to simplify the separation/recovery and reuse process, it is desirable from both an environmental and practical viewpoint to find simpler ways for separation.

Thus, it would be a great improvement to combine the advantages of homogeneous catalyst, namely high activity, selectivity and ease of characterisation, with the simplicity of separation provided by heterogeneous catalysts.

The immobilisation of homogeneous catalysts onto solid supports is an appealing possibility for separating and recycling metal complexes and constitutes an area of great interest and extensive study.[1] Many ingenious techniques and approaches have been developed over the years. However only a few successful examples of catalyst separation methods are applied in industry.[2] Among all types of supports, polymers and silicas are the most preferred solid systems. Of special interest for us are supports using ionic bonding for heterogenising the catalyst. This method requires the metal complex and the support to be ionic; in some examples conventional ligands in cationic metal complexes, were ionically immobilised onto the solid support. This method is very simple; however the results obtained thus far suggest improvements are required. An alternative approach is to tag the ligand such that it is, or can become, ionic which requires custom-made ligands. In *chapter I* ion-exchange resins are introduced in more detail, about their preparation, functionalisation and application in catalysis.

In this *chapter* the preparation and characterisation of new heterogenic catalytic systems, based on chiral cationic Rh(I) complexes and neutral Pd(II) complexes, are discussed. Heterogenisation of these catalysts was carried out by polymeric functionalised acidic ion-exchange resins H^+ DOWEX 50WX2-100 and acidic supported

ionic liquids phase (SILP). The heterogenised Rh catalysts were applied in asymmetric hydrogenation reactions of the model substrate methyl-2-acetamidoacrylate (MAA). The heterogenised Pd catalysts were examined in asymmetric methoxycarbonylation of styrene.

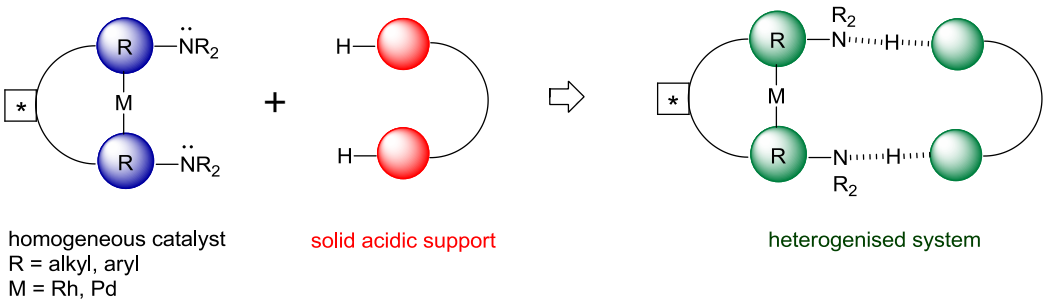


Figure 38 Immobilisation of homogeneous catalysts *via* ion-exchange. The idea of this approach is to functionalise a phosphine ligand with a tertiary amine group. By adding the homogeneous catalyst to the acidic support, the amine gets protonated and therefore becomes ionic. By simple acid base chemistry the homogeneous catalyst is heterogenised onto the acidic solid support.

Ion-exchange is a convenient method for supporting ionic complexes. Simple acid-base chemistry can immobilise a homogeneous catalyst system onto a solid support. By preparing amine functionalised diphosphines Tóth and co-workers reported about the successful immobilisation of cationic Rh(I) complexes.[3] However, this idea was never applied to neutral catalysts before, and secondly it is not obvious if this method is better than simple ion-exchange of $[Rh]^+$ in cationic catalysts, since the different approaches have not been compared under controlled conditions. To examine the ability of immobilisation purely by protonation of the amine moiety, tertiary amine functionalised alkyl diphosphine ligands were prepared and their corresponding complexes formed. These catalysts were then immobilised by protonating the nitrogen functionality with the strong acidic ion-exchange groups on the support. Therefore the catalyst becomes ionic and as a result becomes attached onto the support (Figure 38).

Since alkoxy- and hydroxy-carbonylations generally require relatively high catalyst loadings (0.2 - 20 %) immobilisation of these expensive catalysts would most certainly improve these processes. Amine functionalised chiral diphosphines are not that common and they would certainly be also of interest for a number of other applications in homogeneous catalysis

Amine functionalised chiral catalysts were prepared and then evaluated in hydrogenation and hydroxy- and methoxy-carbonylation reaction of prochiral alkenes.

Heterogenisation was done in collaboration with ou EU-network partners, NANO-HOST. Some of the catalysis experiments were carried out by myself at ICCOM-CNR Italy, Florence in collaboration with Dr. Pierluigi Barbaro. The continuous $scCO_2$ flow experiments were carried out by either Dr. Barthel Engendahl (Figure 64) or myself in collaboration with Prof. David Cole-Hamilton.

3.2 Synthesis of *nitrogen*-functionalised ligands

The first target ligands for this project were amine-functionalised enantiomerically pure 4,12-dibromo-[2.2]-*para*cyclophane. This backbone was chosen since it is readily available (and produced for commercial-scale asymmetric catalysis) and constitutes the backbone of highly active and selective catalysts in asymmetric hydrogenation reactions[4] and hydroxy- and alkoxy-carbonylation (*chapter II*).

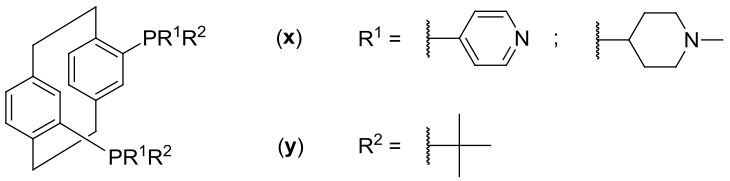
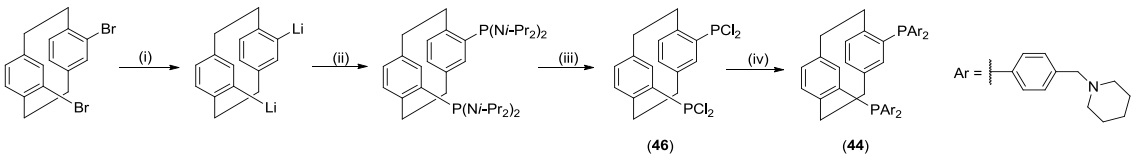


Figure 39 Possible *N*-functionalised phanephos derived diphosphine ligands.

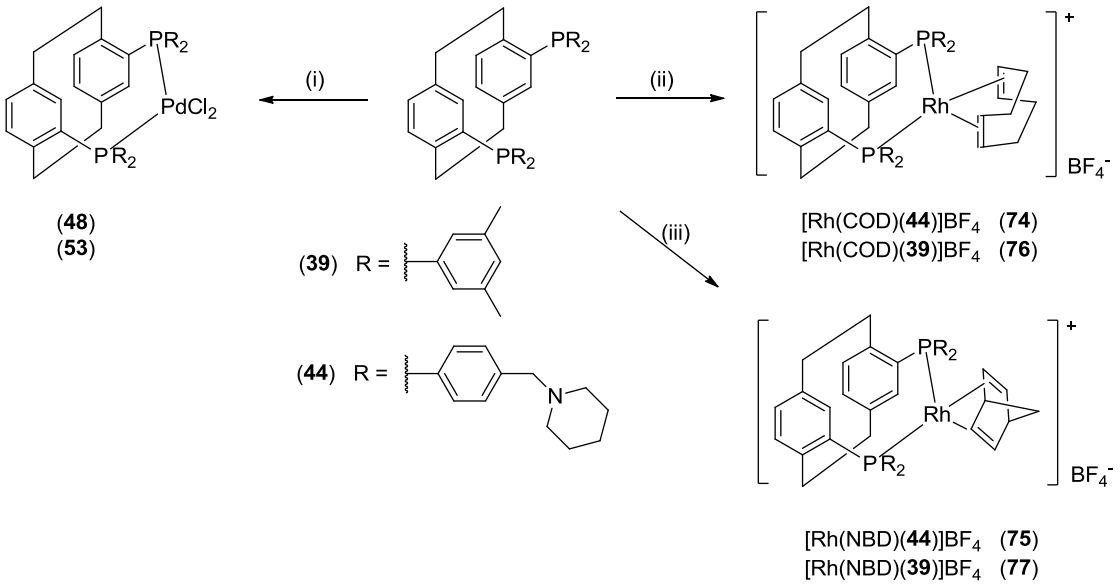
Many approaches towards this new chiral amine functionalised phosphine ligands have been investigated and are displayed in Figure 39. Due to the unsuccessful preparation attempt these were shortly summarised in the experimental for future references and the target was changed to a much simpler approach towards *N*-tagged phosphine ligands.



Scheme 36 Synthesis of *N*-functionalised phanephos ligand. Reaction condition : (i) *n*-BuLi (2 equiv.) in Et_2O for 2-3 h at r.t.; (ii) $ClP(N^iPr_2)_2$ (2.3 equiv.) added; (iii) HCl^*Et_2O (28 equiv.) in Et_2O for 24 h; (iv) MgBrR (5 equiv.) in Et_2O overnight.

In *chapter II* Scheme 1 a simpler approach towards the preparation of different phanephos derived diphosphine ligands is described and following this procedure also the *N*-functionalised ligand (**44**) was synthesised. Compound (*R*)-4,12-

bis(dichlorophosphino)-[2.2]-*para*cyclophane (**46**) was prepared (Scheme 36), and then reacted with the commercially available Grignard of 4-phenylmethyl-*N*-piperidinylmagnesiumbromide. The ligand (**44**) was obtained in 68 % yield, and the corresponding palladium and rhodium complexes were prepared (Scheme 37).



Scheme 37 Rhodium and palladium complexes prepared with phanephos ligands (**39**) and (**44**). Palladium catalyst preparation: (i) reaction carried out in CH_2Cl_2, $[PdCl_2(PhCN)_2]$ (1 equiv.) added and stirred overnight at r.t.; (**48**), (**53**) and (**61**) and their catalytic activity in homogeneous phase are discussed in more detail in *chapter II.* Rhodium catalyst preparation: (ii) in CH_2Cl_2 $[Rh(COD)_2]BF_4$ (1 equiv.) added and stirred overnight at r.t.; (iii) reaction carried out in CH_2Cl_2, $[Rh(NBD)_2]BF_4$ (1 equiv.) added and stirred overnight at r.t., after a ^{31}P $\{^1H\}$ NMR spectra was recorded of a small crude sample the compound (**75**) and (**77**) were immobilised onto the acidic resin without further purification, respectively.

The palladium complex (**53**) was obtained in 73 % yield, as already mentioned in *chapter II*. The dipalladium complex (**61**) was attempted but only resulted in a dark brown powdery insoluble solid, suggesting that the more bulky phenylmethylpiperidinyl substituents on the phosphorus might sterically hinder any further palladium dichloride merging. Another possibility is the involvement of the nitrogen lone pair coordinating to the Pd precursors.

The rhodium complex was prepared by dissolving the ligand in CH_2Cl_2, adding either $[Rh(COD)_2]BF_4$ or $[Rh(NBD)_2]BF_4$ precursor and stirring for 30 min. The solvent was removed and the precipitate washed with hexane, after drying under vacuum a reddish precipitate was obtained for compounds $[Rh(COD)(\mathbf{44})]BF_4$ (**74**) (45 % yield), $[Rh(NBD)(\mathbf{44})]BF_4$ (**75**) (86 % yield), $[Rh(COD)(\mathbf{39})]BF_4$ (**76**), $[Rh(NBD)(\mathbf{39})]BF_4$ (**77**), all of them were obtained in moderate to good yield (see *experimental III*).

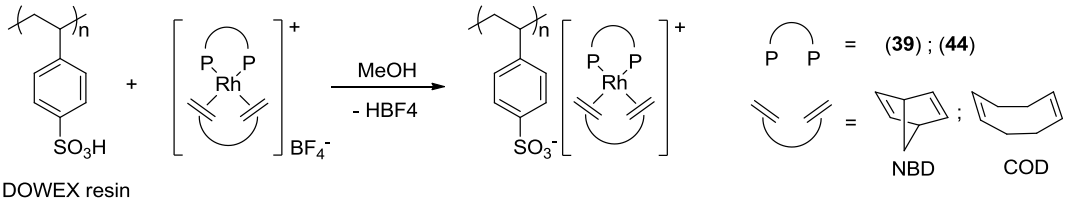
3.3 Immobilisation onto polymeric cation exchange resins

The homogeneous catalysts were immobilized by ionic interactions onto the commercially available cation-exchange resins H^+ DOWEX 50WX2-100. This is a conventional ion exchange resin, which consists of a cross-linked polymeric construction and is functionalised with sulfonic acid groups (-SO_3H), and is the solid equivalent of *p*-toluene sulfonic acid. The chemical properties of the resin are expressed in a number of ways and can be controlled to individual wishes. The capacity expresses the total number of sites available for exchange; this is expressed on a dry weight. The particle size and swelling properties are expressed in the solvent uptake and as a result determined in its wet weight. All these properties depend on the polymeric backbone and the amount of cross linkages. The swelling properties can influence catalytic behaviour dramatically, and as a consequence can improve the accessibility of the reactants to the catalytic active centre. Therefore catalysts immobilised onto a polymeric support matrix can profit from the swell ability, different to other more conventional solid supports.

The metal content of the individual heterogenised catalyst resins was determined by Energy Dispersive X-ray Spectrometry (EDX) (details see *experimental III*). This was done by calculating the average of at least 2 different resin-beads, from which a minimum of 3 different areas on the resin was examined. Mapping, to confirm the evenly dispersion of the catalyst on the resins was also carried out for all different types of resin (*experimental III*). The metal content was also determined for selected resins by Inductively Coupled Plasma optical emission spectrometry (ICP-OES) and Inductively Coupled Plasma Atomic emission spectrometry (ICP-AES).

3.3.1 Heterogenisation of homogeneous rhodium complexes

The commercially available and strong cation exchange, gel-type resin H^+ DOWEX 50WX2-100 was treated as described in the *experimental III* prior to use. The dried resin was weighed into a Schlenk flask, placed under nitrogen atmosphere and left in MeOH for swelling. Shortly after that, the homogeneous catalyst was also dissolved in MeOH and the solution added to the resin. The resin catalyst solution was gently stirred or shaken overnight at room temperature (Scheme 38).



Scheme 38 Immobilisation of homogeneous rhodium phanephos derived catalysts onto an acidic ion exchange resin H^+ DOWEX.

Image 1 shows the empty H^+ DOWEX resin in MeOH (left side) and the amine-tethered rhodium complex onto the cation-exchange resin (right side), after immobilisation of the homogeneous catalyst (**77**) after 24 hours.

empty resin in MeOH

resin containing the Rh catalyst

Image 1 (Left) H^+ DOWEX resin in MeOH; (right) after addition of homogeneous catalyst (**77**) and stirring for 24 hours. The immobilised catalyst changes the resin's colour to an intense red.

The EDX confirmed that Rh was indeed on the polymeric resin. Furthermore mapping confirmed that the Rh was evenly dispersed on the surface of the ion exchange resin. The amount of rhodium metal observed is displayed in Table 33 (after EDX and ICP measurements). The obtained numbers assure the effective heterogenisation of the complex onto the resin. ICP-AES confirmed the Rh content and the results are summarised in Table 33.

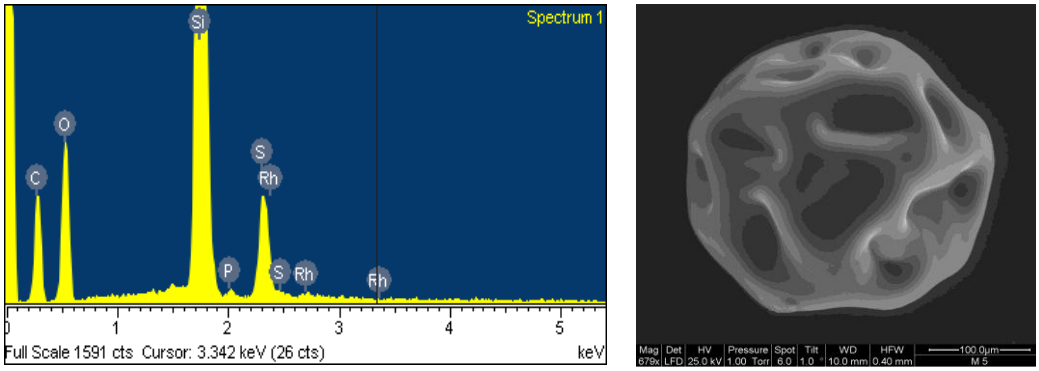
Table 33 Immobilisation of rhodium complexes on H^+ DOWEX 50WX2 resin.[a]

Homogeneous catalyst	Tethered catalyst	Rh loading (w/w)[b] (%)	Rh EDX (%)
(*R*)-[Rh(COD)(**44**)]BF_4 (**74**)	**DOWEX-74-COD-Rh**	0.84	0.70
(*R*)-[Rh(NBD)(**44**)]BF_4 (**75**)	**DOWEX-75-NBD-Rh**	n.d.	0.86
(*S*)-[Rh(COD)(**39**)]BF_4 (**76**)	**DOWEX-76-COD-Rh**	3.35	1.30
(*S*)-[Rh(NBD)(**39**)]BF_4 (**77**)	**DOWEX-77-NBD-Rh**	n.d.	0.75
(*R*)-[Rh(COD)(**44**)]BF_4 (**74**)	**Li-DOWEX-74-COD-Rh**	n.d.	0.35

[a] The resin was put into MeOH (10 ml) under inert atmosphere and a solution of the individually described homogeneous catalysts was added (4 ml). The solution was stirred for 24 hours and the resin was washed and dried as described in the *experimental III*. [b] The ICP-AES, average value over three samples.

The immobilised Rh catalyst will throughout the thesis be assigned with the resin name first, then the compound number of the tethered ligand, the used cyclodiene of the rhodium precursor and finally the metal (DOWEX-LIGAND-DIENE-Rh).

As mentioned in *chapter I*, lithiated resins have been reported to give enhanced metal loading onto the resin when non-tagged ligands are used. Barbaro and co-workers found the Li^+ DOWEX resin to give higher metal loading of the Rh catalysts by ion-exchange.[5] To investigate the exchange capacity with lithiated resins catalyst (**74**) was immobilised onto both the lithiated Li^+ DOWEX and the protonated H^+ DOWEX resin. The anchoring of the homogeneous catalyst (**74**) onto the lithiated resin was observed to be much lower, with a Rh loading of 0.35 % (according to EDX), 0.35 % lower than with the protonated resin. In the case of tertiary amine functionalised ligands, protonation is most likely quantitative and leads to a strong interaction with the support, whereas coordination of the amine to lithium is a far weaker interaction.



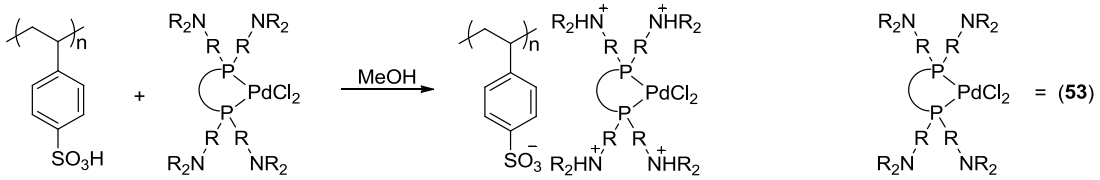
ESEM image

Figure 40 EDX spectrum (left) of DOWEX- 50XWX2 resin with heterogenised catalyst (**74**). and (right) ESEM image (backscattered electrons, 679 magnifications, 25KeV, 1 torr).

An ESEM image of the **DOWEX-74-COD-Rh** resin was obtained, presenting the dried charged resin. Theoretically 200 mg resin are used, the amount of exchangeable $-SO_3H$ groups available on the resin would be 0.96 mmol for 200 mg resin (4.8 meq/g $-SO_3H$ groups on the resin). If each *N* on catalyst (**74**) exchanges with one $-SO_3H$ group and each Rh cation exchanges as well, a total consumption of 5 x $-SO_3H$ groups/catalyst would exchange. This means a maximum exchange amount of 0.192 mmol of each Rh complex onto the resin would be theoretically possible. A maximum catalyst loading of 0.016 mmol of the homogeneous catalyst was observed onto the resin. Therefore considering each of this catalysts used 5 available $-SO_3H$ groups, this leads to a maximum usage of 8.3 % $-SO_3H$ groups only. This degree of attachment leaves many available $-SO_3H$ groups on the resin, which therefore can have in some cases important influence onto the catalytic activity of the resin.

3.3.2 Heterogenisation of homogeneous palladium complexes

The heterogenisation and characterisation of a neutral chiral palladium complex (**53**) and (**61**) onto the commercially available ion-exchange resin is described below. For comparison studies, the homogeneous catalyst (**48**), with no nitrogen moiety was also heterogenised. The same procedures used for the Rh catalyst were also applied for the Pd catalysts. The H^+ DOWEX resin was left swelling in MeOH and the homogeneous catalyst dissolved in MeOH was added. After careful stirring or shaking of the solution, the resin was washed thoroughly as reported for the Rh resin and was subsequently dried under argon or nitrogen overnight (*experimental II*).



Scheme 39 Immobilisation of a neutral palladium complex on acidic ion-exchange resin. Reaction conditions: The resin was left for swelling in MeOH before the homogeneous catalyst, dissolved in MeOH, was added; washing and drying of the catalyst resulted the desired heterogenised catalyst.

The ability of the resin to immobilise this catalyst is merely through ion-exchange of the nitrogen lone pair on the catalysts. However, during catalysis heterogenisation *via* protonation of $PdCl_2$ by the strong acidic groups (-SO_3H), will most likely result in the formation of a cationic Pd-H species and therefore ionic interactions with the resulting cationic $[Pd\text{-}H]^+$ species cannot be entirely excluded. It is also possible that the anion of the resin could replace chloride (with formation of HCl) as another mechanism for immobilisation.

Tanaka and co-workers carried out methoxycarbonylation reactions of styrene and reported the recycling of the Pd catalyst by using a acidic polymeric Wang type resins.[6] Anchoring of the catalyst was purely by ionic $[Pd\text{-}H]^+$ SO_3^-PS interactions while recycling was indeed possible, it was undertaken for 4 cycles only and Pd leaching was not determined. Further details are reported in 3.4.2.

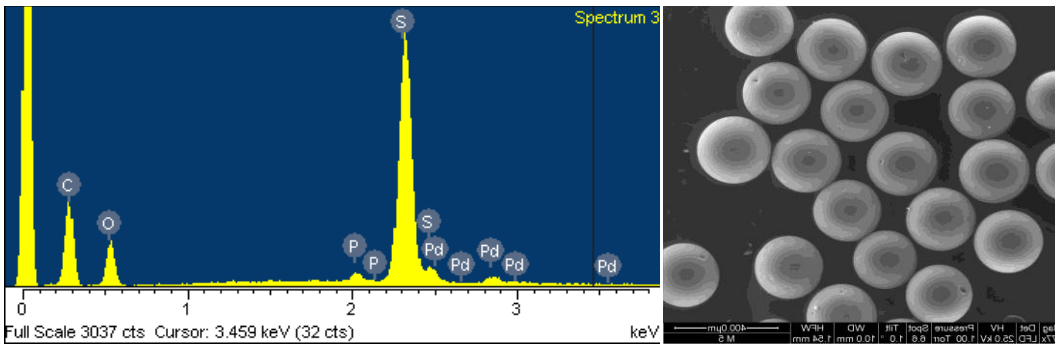


Figure 41 EDX spectrum (left) and ESEM images, image backscattered electrons, 679 magnifications, 25KeV, 1torr (right) of **DOWEX-53-Pd** of the catalyst bead.

The amount of palladium onto the resins was determined by EDX measurements and ICP-AAS was carried out to verify the accurate amount of palladium on the resin. Both, methods EDX and ICP measurements were used to confirm the total amount of metal. Numbers determined by ICP analysis were in reasonable agreement with the numbers obtained by EDX. The ESEM picture of the **DOWEX-53-Pd** resin is displayed in Figure 41.

The image of the resin differs slightly from the **DOWEX-74-COD-Rh** shown in Figure 40; this could be possibly due to inefficient drying of the resin. The metal content of the immobilised homogeneous catalysts (**48**), (**53**) and (**61**) onto the ion-exchange resin are summarised in Table 34.

Table 34 Palladium metal content on the H^+DOWEX resins with different catalyst systems.[a]

Homogeneous catalyst	Tethered catalyst	Pd loading (w/w)[b] (%)	Pd EDX[c] (%)
(*R*)- (**53**)	**DOWEX-53-Pd**	0.29	0.35
(*R*)- (**61**)	**DOWEX-61-Pd**	0.60	1.36
(*S*)- (**48**)	**DOWEX-48-Pd**	2.14	1.35

[a] The resin was put into MeOH (10 ml) under inert atmosphere and a solution of the individually described homogeneous catalysts was added (4 ml). The solution was stirred for 24 hours and the resin was washed and dried as described in the *experimental III*. [b] The ICP-AES, average value over three samples. [c] EDX measurements carried out on SEM.

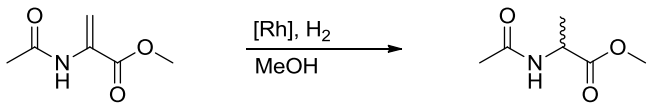
Catalyst (**61**) is troubled by solubility problems, which made characterisation difficult. Despite low solubility of complex (**61**) heterogenisation was carried out following the same procedure as for all other catalysts. (**61**) was partially dissolved in MeOH, the protonated resin added and the mixture carefully stirred for 18 hours. The resin was washed and dried following the same procedure as described before. When EDX of this resin catalyst was carried out, the metal loading observed was 5 times higher than obtained for the heterogenised catalyst (**53**). A higher catalyst loading was expected however this result was very surprising. In the EDX the resins were checked for possible unusual "lumps" visible on the resin itself, which possibly due to (**61**)'s insolubility could not be washed away. Investigations by EDX of the resin did not show any signs of "lumps", however to preclude the presence of any smaller clusters on the resin would require further tests.

3.4 Asymmetric catalysis using heterogeneous catalysts

3.4.1 Asymmetric hydrogenation

The usual model substrate methyl-2-acetamidoacrylate (MAA) for asymmetric hydrogenation alkene hydrogenation was used. No other substrates were investigated since the focus was to establish the recycling at this stage. Secondly relatively large amounts of substrate get consumed requiring a cheap, readily available substrate. Reactions were carried out in a steel autoclave in separate glass vials. The

hydrogenations were carried out with 15 bar H_2 pressure in 1.5 ml MeOH at room temperature (18-22 °C). After each reaction, the reaction solution was removed under Argon with a syringe and new substrate solution added. During all this time the catalyst was kept under H_2 or Ar atmosphere.



Scheme 40 Asymmetric hydrogenation of methyl-2-acetamidoacrylate (MAA).

In order to compare the heterogeneous to homogeneous catalyst performances, the homogeneous catalysts were conducted under various conditions first (Table 35). Entry 1-4 are the results obtained with catalyst (**74**) ([Rh(COD)(**44**)]BF_4). Entries 5 and 6 display the results obtained by the *in-situ* prepared catalyst (**38**) and (**39**) and $[Rh(COD)_2]BF_4$.

These results show how effective Rh/phanephos catalysts are for this type of substrate, and encouragingly, the new ligand (**44**) is also capable of delivering 99 % e.e. with high rates.

Table 35 Homogeneous hydrogenation reaction using different phanephos catalysts.

Entry[a]	MAA/Rh ratio	Time (min)	Temp (°C)	Pressure (bar)	Conv.[b] (%)	E.e.[b] (%)
1	**3000:1**	50	18	15	67	99
2	**1000:1**	45	18	15	77	99
3	**10 000:1**	45	18	15	38	99
4	**100:1**	>5	22	1	>99	99
5[c]	**100:1**	>5	22	1	>99	99
6[d]	**1000:1**	45	18	15	>99	99

[a] Reactions were carried out using 15 bar H_2 in 1.5 ml of anhydrous MeOH as solvent at 23 °C for 15min. [b] Enantiomeric excess and conversions determined by chiral GC, (*R*) catalysts resulted (*R*) enantiomers and vice versa. [c] Rhodium complex prepared in situ; (*S*)-(**39**) added to $[Rh(COD)_2]BF_4$. [d] Rhodium complex prepared in situ; (*R*)-(**38**) added to $[Rh(COD)_2]BF_4$.

First recycling attempts in the asymmetric hydrogenation of MAA at 1 bar H_2 pressure were carried out unsuccessfully. The heterogenised catalyst led to fast deactivation (Table 36, entry 3). Moreover, the lithiated resin, **Li-DOWEX-74-COD-Rh**, was observed to give only 85 % conversion in the first cycle after 3 hours, whereas the protonated resins reached full conversion after 55 min. The enantioselectivity obtained

with **DOWEX-74-COD-Rh** was slightly higher than with the **Li-DOWEX-74-COD-Rh**. Another drawback of the lithiated resin was that the resin catalysts could hardly reach full conversion in the first cycle resulting in loss of activity after the first cycle (Table 36, entry 2). The results are summarised in Table 36.

Table 36 First hydrogenation attempts of MAA by a supported **Li-DOWEX-74-COD-Rh** and **DOWEX-74-COD-Rh** catalyst with a S/Pd ratio of 100/1.

Entry[a]	Cycle	Resin typ	Time (min)	Conv.[b] (%)	Ee[b] (%)	Rh leached[c] (ppm)
1	**1**	**Li^+**	190	85	89	1.631
2	**1**	**Li^+**	135	70	90	n.d.
3	**1**	**H^+**	55	90	98	0.440
4	**2**	**H^+**	55	82	98	0.342
5[d]	**3**	**H^+**	10	25	99	0.418
6[e]	**4**	**H^+**	50	0	0	0.227

[a] Reactions were carried out using catalyst at 1 bar H_2 in 6ml of degassed and distilled MeOH as solvent at 20 °C. [b] Enantiomeric excess and conversions determined by chiral GC. [c] ICP-OES [d] reaction stopped due to closing of university. [e] Reaction was continued 3 days later.

However, these experiments used very low pressure and less special precautions, such as weighing the resin the catalyst under no special conditions. When handling the resin more carefully, including weighing them under inert atmosphere, the catalyst activity could be improved with up to 10 cycles (Figure 42). This activity could be achieved with much lower catalyst to substrate loadings than typically necessary for heterogenised catalyst systems.[5, 7]

Table 37 Hydrogenation of MAA by a supported (*R*)-**DOWEX-74-COD-Rh** catalyst with a S/Rh ratio of 500/1.

Entry[a]	Cycle	Conv.[b] (%)	E.e.[b] (%)	Rh leaching (ppm)
1	**1**	97	96(*R*)	0.839
2	**2**	95	89(*R*)	0.897
3	**3**	97	85(*R*)	0.342
4	**4**	94	83(*R*)	0.816
5	**5**	93	84(*R*)	1.343
6	**6**	95	84(*R*)	1.682
7	**7**	88	84(*R*)	1.345
8	**8**	85	85(*R*)	0.341
9	**9**	77	88(*R*)	0.598
10	**10**	81	87(*R*)	0.466

[a] Reactions were carried out using catalyst at 15 bar H_2 in 1.5ml of anhydrous MeOH as solvent at 23 °C for 15 min. [b] Enantiomeric excess and conversions determined by chiral GC. [c] Rhodium leaching was determined by ICP-OES.

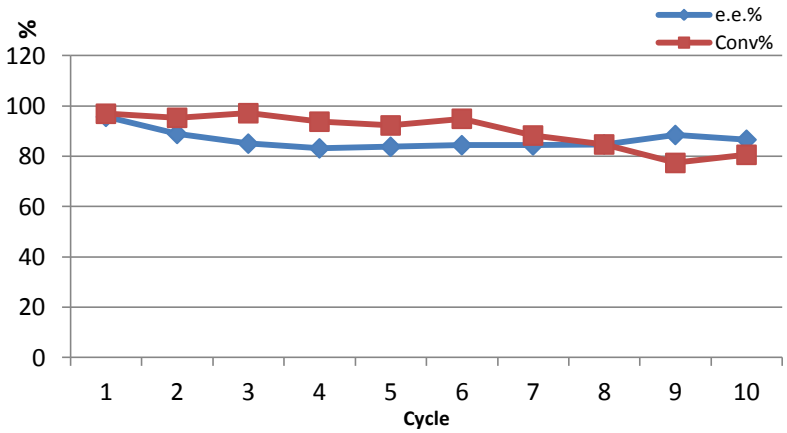


Figure 42 Hydrogenation of MAA with the heterogenised acidic resin **DOWEX-74-COD**. A substrate to catalyst ratio of 500/1 was conducted. Reactions were carried out in MeOH at 15 bar H_2 pressure and 23 °C.

The careful preparation of the catalyst and handling before and during catalysis runs is necessary in order to obtain longer catalyst activity and selectivity. As shown in Figure 42, the catalyst activity decreased slowly after 10 cycles and enantioselectivity was almost stable throughout all the cycles. Main changes in selectivity were observed in the 1st cycle, which could be due to the presence of homogeneous catalyst species that promoted the reaction at a faster rate than the heterogenised species.

An interesting observation was the colour change of the resin after the first cycle, from red to black. A possible explanation could be the formation of rhodium

nanoparticles on the resin during the hydrogenation reaction. However further investigations are necessary to support this theory (see further experiments carried out with PdNP resins in 3.4.2.4). As an alternative explanation for the slight drop in e.e. from cycle 1 to 2, traces of nanoparticles could reduce the alkene in a racemic fashion. Rh nanoparticles can furthermore be stabilised by ammonium groups, such as those contained on the **DOWEX-74-COD-Rh**. Table 37 summarises the conversion, selectivity and Rh leaching.

The washing procedure of the resin was observed to be of great importance too. Only limited metal leaching in the first cycles was found with well washed resins. Figure 43 shows one of the first attempts carried out with **DOWEX-74-COD-Rh** using the same conditions as applied for the experiment in Figure 42, with the difference of a less well purified resin. Figure 44 display the much higher Rh leaching during the first catalysis cycles due to the neglected washing process. The leaching in the first 3 cycles was high with up to 4.15 ppm. When the resin was washed thoroughly (~ 400 ml MeOH followed by ~150 ml Et_2O for 300 mg resin) leaching can be kept to a minimum, with less than 1 ppm in most cycles.

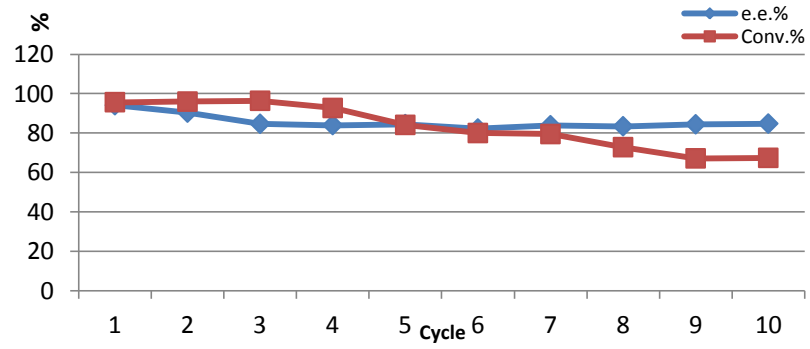


Figure 43 Asymmetric hydrogenation reaction of MAA with **DOWEX-7-COD-Rh**. The S/Rh ratio was 500/1 and reaction was carried out in MeOH with a H_2 pressure of 15 bar at 23 °C and a reaction time of 15 min per cycle.

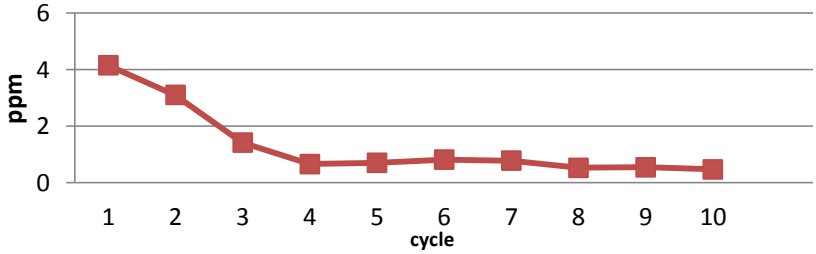


Figure 44 The rhodium leaching data of Figure 43 are presented. Cycle 1 results a high leaching up to 4.15 ppm. The exact numbers are listed in the *experimental III*.

Comparing the amine tagged ligand, (**44**), with the catalytic behaviour of the unfunctionalised Rh catalysts where the catalyst anchoring was exclusively *via* the ion-exchange of the cationic Rh species was of considerable interest to establish if the tagging improved cationic catalysts.

Ligand (**39**) is already a well established catalyst in hydrogenation reactions.[4a, 4b, 8]

The heterogeneous analogue of (**39**) was prepared by the same procedures as for the *N*-functionalised catalysts (**74**) and (**75**). Resin **DOWEX-77-NBD-Rh** was examined in asymmetric hydrogenation reaction of MAA. The results are presented in Figure 45 and catalysis details summarised in Table 38.

High activity and selectivity was achieved with the **DOWEX-77-NBD-Rh** for 9 cycles with almost no loss in activity and selectivity. The Rh leaching observed was < 1 ppm in the first 4 recycles, and then the catalyst leaching increased up to 1.379 ppm for the 9th cycle. None-the-less this is below the level required for final active pharmaceutical ingredients, nevermind chiral intermediates. The leaching of all 9 catalytic cycles was found to be <10 %. The catalyst leaching is similar to the leaching observed for the **DOWEX-74-COD-Rh**. For cationic catalysts, similar results are obtained for the auxiliary *nitrogen* supported ion-exchange heterogeneous systems as for solely ionic exchange through cationic catalyst species. The resin was able to perform for 7 cycles with high activity of >99 % and selectivity of 99 % with a minimum decrease in performance in 8th and 9th cycle.

Table 38 Asymmetric hydrogenation of MAA with (*S*)-**DOWEX-77-NBD-Rh** with a S/Rh ratio of 400/1**.**

Entry[a]	Cycles	Conv[b] (%)	E.e.[b] (%)	Rh leaching (ppm)
1	**1**	>99	99(*S*)	0.584
2	**2**	>99	99(*S*)	0.821
3	**3**	>99	99(*S*)	0.999
4	**4**	>99	99(*S*)	0.955
5	**5**	>99	99(*S*)	1.051
6	**6**	>99	99(*S*)	1.236
7	**7**	>99	99(*S*)	1.151
8	**8**	99	94(*S*)	1.194
9	**9**	99	89(*S*)	1.379

[a] Reactions were carried out using catalyst at 15 bar H_2 in 1.5ml of anhydrous MeOH as solvent at 22 °C for 15 min. [b] Enantiomeric excess and conversions determined by chiral GC. [c] Rhodium leaching was determined by ICP-OES.

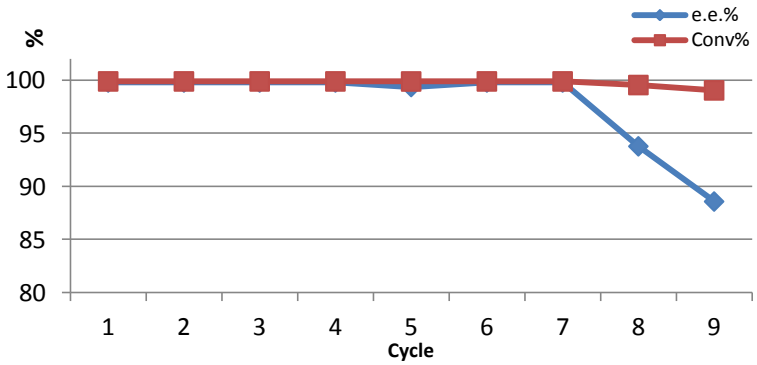
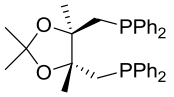


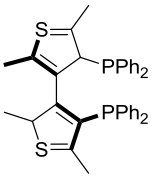
Figure 45 Asymmetric hydrogenation of MAA with (*S*)-**DOWEX-77-NBD-Rh** with a S/Rh ratio of 400/1. The reaction was carried out for 15 min at 22 °C, with a H_2 pressure of 15 bar.

For all resins handling was carried out with utmost care resulting in highly active and selective heterogenised catalysts. An interesting discovery was when the amine functionalised resin was stored for longer than 2 days; a decrease in activity was noted. With an increase in storage time, a stronger decrease in activity was observed. Interestingly, selectivity of the catalyst is not affected, only activity.

Barbaro and co-workers reported catalyst deactivation after the 2nd cycle with their heterogenised Rh catalysts, with chiral ligands ((**20**) and (**21**)).[5] However, they observed that oxidation of the phosphorus moiety was the reason for deactivation.



(**20**)



(**21**)

Figure 46 Rhodium complexes were prepared with the chiral biphosphine ligands and tethered onto Li^+DOWEX resins.

As for loss of activity for the catalyst **DOWEX-74-COD-Rh** and **DOWEX-75-NBD-Rh**, deactivation because of oxidation seems less likely, since the resin storage was done with greatest care and under argon atmosphere in a youngs flask. However, it is possible that reaction with traces of oxygen delivers an inactive Rh species. It is odd though that deactivation only occurred with heterogenised *N*-tagged catalysts.

Table 39 Storage of (*R*)-**DOWEX-74-COD-Rh** 3 months and its catalyst activity S/Rh ratio of 1000/1.

Entry[a]	Cycles	Conv.[b] %	Ee[b] %
1	**1**	87	93(*R*)
2	**2**	69	90(*R*)
3	**3**	12	94(*R*)

[a] Reactions were carried at 15 bar H_2, in 1.5 ml MeOH, **DOWEX-74-COD-Rh** (25.0 mg resin, 0.0024 mmol catalyst) and MAA (344 mg, 2.4 mmol) for 50 min reaction time for each cycle. [b] Enantiomeric excess and conversions were determined by chiral GC.

3.4.1.1 Batch reactions using S/Rh ratio of 50/1 and 1 bar H_2 pressure

Since the results had shown that more rigorous exclusion of oxygen (and higher H_2 pressure) gave better results than those obtained initially (Figure 41), lower pressures were re-examined. Furthermore due to continuous flow applications discussed in the next *chapter* (3.4.1.2) examination of catalyst stability at lower pressures was investigated. Therefore further asymmetric hydrogenation reactions of MAA were carried out in Schlenk flasks with 1 bar H_2 pressure in MeOH and a reaction time of 30 minutes for each cycle. A comparison study of the activity and selectivity for the catalyst systems **DOWEX-75-NBD-Rh** and **DOWEX-77-NBD-Rh** was conducted; the results are summarised in Table 40 and 41, respectively.

Table 40 Hydrogenation of MAA by **DOWEX-75-NBD-Rh** with a S/Rh ratio of 50/1.

Entry[a]	Cycles	Conv[b] %	Product[b] %	Ee[b] %
1	**1**	96	96	93(*R*)
2	**2**	96	96	93(*R*)
3	**3**	93	93	92(*R*)
4	**4**	90	90	91(*R*)
5	**5**	91	91	92(*R*)

[a] Reactions were carried out using catalyst at 1 bar H_2, 33.0 mg of resin (0.003 mmol catalyst on the resin) in 2.5 ml of a 0.055 M solution of MAA in MeOH. Reaction temperature was 19 °C and reaction time for each cycle was 30 min. [b] Enantiomeric excess and conversions determined by chiral GC.

The nitrogen tagged heterogeneous catalyst, **DOWEX-75-NBD-Rh**, was observed to result in stable hydrogenation for 5 cycles with almost no loss of activity or selectivity. Conversions of 96 % in the first two cycles were obtained to around 90 % for the 4th and 5th cycle (Table 40).

Table 41 Hydrogenation of MAA by a supported [Rh(NBD)(**39**)]BF_4 catalyst with a S/Rh ratio of 50/1.

Entry[a]	Cycles	Conv.[b] %	Product[b] %	Ee[b] %	Rh leached ppm
1	**1**	>99	>99	99	0.123
2	**2**	>99	>99	99	0.433
3	**3**	>99	>99	98	0.174
4	**4**	77	77	92	0.457
5	**5**	36	36	87	0.297
6	**6**	13	13	82	0.560

[a] Reactions were carried out using catalyst at 1 bar H_2, 35.2 mg of resin (0.0024 mmol catalyst on the resin) in 2.25 ml of a 0.055 M solution of MAA in MeOH. Reaction temperature was 22 °C and reaction time for each cycle was 30 min. [b] Enantiomeric excess and conversions determined by chiral GC.

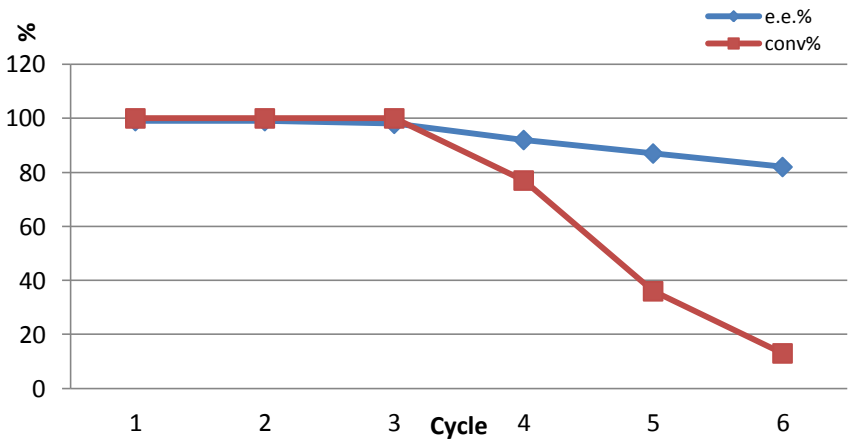


Figure 47 Batch reaction with 1 bar H_2 of **DOWEX-77-NBD-Rh.**

Surprisingly, for the heterogenised catalyst **DOWEX-77-NBD-Rh** a fast drop of activity was observed after the first 3 cycles. Until the 4th cycle high conversions of > 99 % and enantioselectivity of 99 % were obtained (Figure 47). When the Rh leaching was determined the leaching was found less than < 1 ppm per cycle, with an overall leaching of ~2 ppm. A study carried out by Sheldon and co-workers showed correlations between the activity and leaching of the heterogenised catalysts; for the Nafion resin the best swelling was observed in MeOH although in this solvent also the molecular catalyst was found very soluble therefore the resulting leaching was higher.[9] Since Rh leaching was so low the fast deactivation of catalyst **DOWEX-77-NBD-Rh** can therefore not be due to the loss of catalyst. Since there was also a drop of enantioselectivity of catalyst **DOWEX-77-NBD-Rh** observed, perhaps catalytic deactivation due to oxidation is happening. Further experiments would be necessary to confirm this possibility. Similar to the

hydrogenation reactions carried out at 15 bar H_2 pressure, both resins were observed to change colour from light red to dark grey. It is possible that using lower pressures, the relative amounts of adventitious oxygen versus hydrogen could cause some catalyst deactivation too.

While all these results obtained are very good results and point towards the simpler immobilisation method by ion exchange being sufficient, it should be noted that the substrate tested was a simple alkene.

3.4.1.2 Applications of the heterogenised resin in continuous flow

The resins were also briefly investigated in a continuous flow micro reactor. The continuous flow setup is of simple structure, consisting of: gas inlet (for low pressures only), a mixing chamber for mixing the gas and substrate solution, micro reactor which is connected *via* Teflon tubes with the mixing compartment, a pressure regulator and a HPLC pump. Before the continuous flow reactor was used, the reactor was washed with dry and degassed MeOH and brought under nitrogen atmosphere.

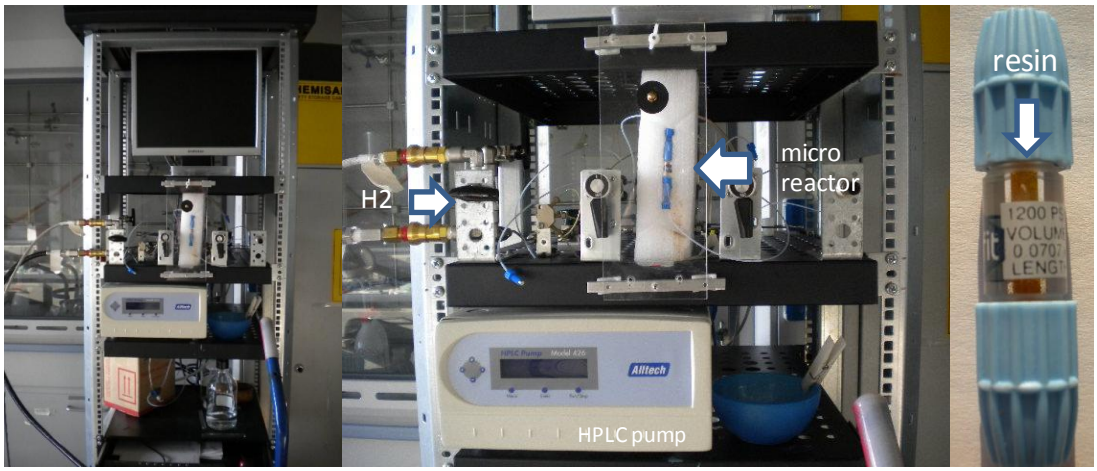


Image 2 Continuous flow micro reactor (Florence, Italy).

The heterogenised resin **DOWEX-77-NBD-Rh** was examined in asymmetric hydrogenation of MAA in the continuous flow reactor. The resin was filled into a micro reactor, which is presented in Image 2 on the right. Filling was carried out under N_2 atmosphere in a Schlenk flask. Once the micro reactor was filled, it was connected to the apparatus under nitrogen flow. The substrate solution was pumped slowly into the reactor since the resins needed time to swell. Once the reactor was filled with the solvent/substrate, mix H_2 pressure was pumped through and the reaction started. For the

catalyst system **DOWEX-77-NBD-Rh** a fast drop in activity was observed, although enantioselectivity was retained 98 % (Figure 48).

Table 42 Reaction conditions for continuous flow hydrogenation with resins.

V_{H2} = 66.89 mmol/min	
V_{MeOH} = 1.973 mmol/min	V_{Sub} = 4.40 µmol/min
p_{total} = 1 bar	Temperature 22 °C
DOWEX-77-NBD-Rh = 52.3 mg	3.73 µmol catalyst
Rh leaching = 0.081 ppm	$TOF_{max} = 70.7h^{-1}$

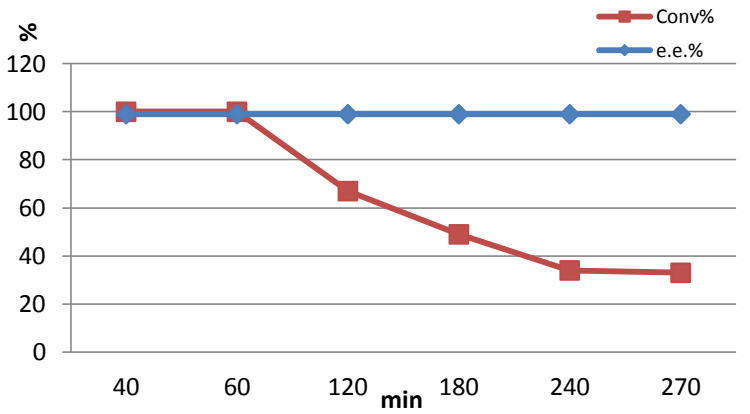


Figure 48 Asymmetric hydrogenation of MAA in continuous flow reactor using **DOWEX-2-NBD-Rh**.

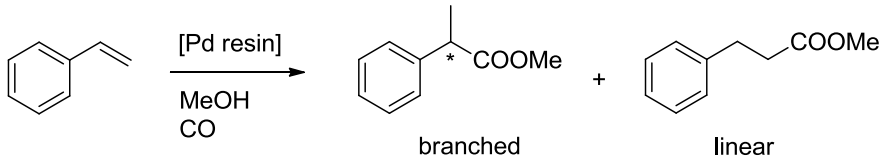
The fast decrease in activity implies that probably the catalyst was washed out of the resins. However, after collection of the combined fractions, metal leaching was found to be < 0.1 ppm. Surprisingly here no change of colour was observed during hydrogenation of MAA. However, it seems that once again low pressures of hydrogen results in some form of catalyst decomposition.

Reactions with the [Rh(COD)(**44**)]BF_4 resin were also carried out but unfortunately since the resin was stored for more than 2 months before the reaction was carried out the conversion was < 1 %, although with high e.e. of 96 %.[1] Loss of activity was already discussed earlier with nitrogen functionalised resins, however the reason for this behaviour has not been yet observed.

1 Collaborations within the network NANO-HOST. The reaction was carried out by Miss Carmen Moreno Marrodan a Ph.D. student at the ICCOM-CNR in Florence, Italy.

3.4.2 Asymmetric methoxycarbonylation reactions

Methoxycarbonylation reactions of styrene with heterogeneous catalyst are very rare and to date no asymmetric methoxycarbonylations with immobilized catalysts have been reported.[10] The reactions described in this chapter, were carried out in 1.5 ml MeOH, 30 bar CO, 60 °C reaction temperature and 20 hours reaction time for each cycle. In contrast to the homogeneous systems where both *p*-TsOH and LiCl were added, no additional promoters other than the polymeric resin catalyst were used unless otherwise stated.



Scheme 41 Asymmetric methoxycarbonylation of styrene to the linear and branched esters. The conditions applied throughout resin carbonylation reactions was 30 bar CO pressure, reaction temperature of 60 °C, for 20 hours.

As already mentioned previously, Tanaka and co-workers used polymeric acids for methoxycarbonylation instead of soluble acid promoters. The reactions were carried out using styrene, MeOH, $Pd(OAc)_2$, DBPMB (**1**) and a Wang typ resin, which is displayed in

Figure 49. The methoxycarbonylation of styrene with the polymeric acid gave high chemo- and regio-selectivity and activity (97 % conversion and B/L ratio 6.7); comparable to the homogeneous analogue, but recycling for this reaction was not reported.[6] Recycling (up to 4 times) of this sulfonated Wang resin, was however carried out for the methoxycarbonylation of vinyl acetate as substrate. Good conversions and also enhanced chemoselectivity (~82 % conversion and ~76 % ester) was observed, when comparing them to the homogeneous analogue with $MeSO_3H$.

Although recycling was reported to retain its activity for the 4 recycling processes, no Pd leaching was noted. A great advantage of this heterogenised reaction was the successful methoxycarbonylation without any need for adding more acid promoter after each cycle.

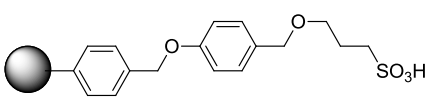


Figure 49 Wang-SO_3H resin applied in methoxycarbonylation of styrene with $Pd(OAc)_2$ and ligand (**1**).

Before studying the resin catalyst in asymmetric methoxycarbonylation reaction of styrene, the homogeneous catalyst activity and selectivity was studied, using Pd complex (**53**). The results are summarised in Table 43. Catalysis was carried out at 60 °C, a reaction time of 20 hours and 30 bar CO, unless otherwise stated. For the unfunctionalised resin, catalyst (**48**) has also been immobilised onto the resin to investigate heterogenisation *via* formation of a cationic Pd-H species. In homogeneous catalysis both catalysts (**53**) and (**48**) gave good activity, however, poor regioselectivity is a drawback for both catalysts and was further investigated in *chapter II*.

Table 43 Methoxycarbonylation of styrene by homogeneous catalysts.

Entry[a]	Catalyst	Temp. °C	Conv.[b] %	Ester[b] %	B/L[c]	Ee[c] %
Pipphanephos						
1	(*R*)-(**53**)	60	>99	>99	1.3	42(*R*)
2[d]	(*R*)-(**61**)	60	>99	>99	1.2	40(*R*)
3[e]	(*R*)-(**53**)	35	31	31	1.4	63(*R*)
Xylphanephos						
4	(*S*)- (**48**)	60	>99	>99	0.7	79(*S*)

[a] Reactions were carried out using 1 mol% catalyst at 30 bar CO in 1.5ml of anhydrous MeOH as solvent, for 24 hours unless otherwise stated. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H NMR spectroscopy. [c] Enantiomeric excess and B/L ratio determined by chiral GC. [d] Dipalladium complex formed *in-situ* by adding (**53**) and 1 equiv. [$PdCl_2(CNPh)_2$]. [e] Reaction time of 19 hours.

In *chapter II* dipalladium complexes gave, in most cases, better overall results than the monopalladium analogues. This was different for the homogeneous catalyst (**61**), which gave the same results as obtained for the catalyst (**53**). This could be due to solubility problems which can inhibit the catalyst activity and selectivity. (**61**) was essentially insoluble whereas (**53**) was soluble in most solvents. However, even using using (**53**), the catalyst appeared less soluble in the presence of *p*-TsOH. This homogeneous acid can protonate the amine moiety to give an ionic compound with lower solubility. The amphiphilic character of these catalysts should be kept in mind when comparing homogeneous and heterogeneous forms. Anyhow, catalyst (**61**) was also heterogenised on the acidic resin and its catalytic behaviour examined in methoxycarbonylation of styrene.

3.4.2.1 Methoxycarbonylation of styrene with *N*-functionalised catalyst resin

Very promising results were obtained in asymmetric methoxycarbonylations with this novel heterogeneous catalyst (Figure 50). Catalyst activity was observed to be stable throughout 10 cycles and enantioselectivity was found to be improved in comparison to the homogeneous analogue. The e.e. of **DOWEX-53-Pd** was 71 %. This is significantly higher than an e.e. of 42 % for the homogeneous counterpart at 60 °C. This is quite unusual since normally heterogenised homogeneous catalysts are observed to decrease in activity and selectivity. Also catalyst activity was fairly stable up to the 8th cycle with conversions of ~40 %, in the 9th cycle a drop of activity was observed. The regio- and enantio-selectivity was stable throughout all 10 cycles. The exact data, including Pd leaching, is presented in Table 44. The overall Pd leaching observed was < 0.2 ppm combining all 10 samples. This is the first time that a heterogeneous catalyst could be reused up to 10 times with almost no loss of activity and selectivity in combination with < 1 ppm overall metal leaching in asymmetric methoxycarbonylation. Another great feature of this heterogenised catalyst is the activity, which still provided moderate conversions with an unusually low catalyst to substrate ratio of 500/1 (compare catalyst loadings in *chapter II*).

Table 44 Methoxycarbonylation of styrene: S/Pd ratio of 500/1.

Entry[a]	Cycles	Ester[b] %	B/L[c]	Ee[c] %	Pd[d] leached(ppm)
1	**1**	45	63	59	0.1537
2	**2**	41	64	66	0.0373
3	**3**	41	63	67	0.0018
4	**4**	35	64	69	0.0052
5	**5**	35	64	71	0.0065
6	**6**	40	64	71	0.0100
7	**7**	41	64	71	0.0045
8	**8**	31	64	71	0.0030
9	**9**	20	64	72	0.0057
10[e]	**10**	32	64	71	0.0038

[a] Reactions were carried out using 0.2 mol% catalyst at 30 bar CO in 1.5ml MeOH as solvent, 1mmol styrene at 60 °C for 20 hours. [b] Ester conversions. % Product determined against tetraethylsilane internal standard using ^{1}H NMR spectroscopy. [c] Enantiomeric excess and B/L ratio determined by chiral GC; (*R*) catalyst gives the (*R*) enantiomer and vice versa. [d] Pd leaching determined by ICP-OES. [e] Reaction time was 21 hours.

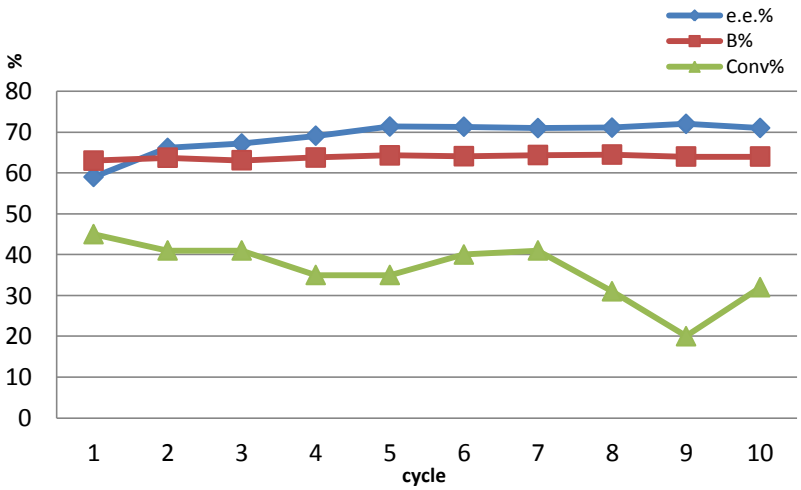


Figure 50 Methoxycarbonylation of styrene using **DOWEX-53-Pd** in a S/Pd (S = substrate) ratio of 500/1.

When decreasing the S/Pd ratio to 400/1 much higher conversions could be accomplished. As shown in Figure 51 the heterogenised catalyst could be recycled without loss of activity for 6 cycles. However, after cycle 7 the conversions decreased from 80 % to 57 % conversion. This is due to the "disturbance" between cycle 6 and 7, in which the resin was stored for 5 days under argon before carrying out further catalysis. Surprisingly, after no special conditions for the resin storage the vial with the resin was

refilled with new substrate solution and further reaction was carried out quite successfully, but with some loss of activity. After the 7th cycle was conducted the catalyst activity was observed to have regained its catalytic activity in cycle 8 and 9. It seems that once the catalyst is used on regular intervals again, catalyst activity was almost fully restored. This observation was also obtained for other catalyst systems, such as **DOWEX-61-Pd** (Figure 52).

Table 45 Methoxycarbonylation of styrene using (**53**) immobilised on resin S/Pd ratio of 400/1 (Figure 51).

Entry[a]	Cycles	Conv.[b] %	Ester[b] %	B/L[c]	Ee[c] %
1	**1**	87	87	1.1	67
2	**2**	83	83	1.3	70
3[d]	**3**	86	86	1.3	71
4	**4**	80	80	1.3	67
5[d]	**5**	86	86	1.2	72
6[e]	**6**	80	80	1.2	72
7	**7**	57	57	1.3	72
8[f]	**8**	71	71	1.4	72
9	**9**	75	75	1.2	67

[a] Reactions were carried out using 0.25 mol% catalyst (72.3 mg resin, 0.002 mmol Pd on the resin) at 30 bar CO in 1.5 ml MeOH and 1 mmol styrene at 60 °C for 20 hours. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H NMR spectroscopy. [c] Enantiomeric excess and B/L ratio determined by chiral GC; (*R*) catalyst gives the (*R*) enantiomer and vice versa. [d] 1 day in between next cycle. [e] 5 days in between next cycle. [f] 2 days in between next cycle.

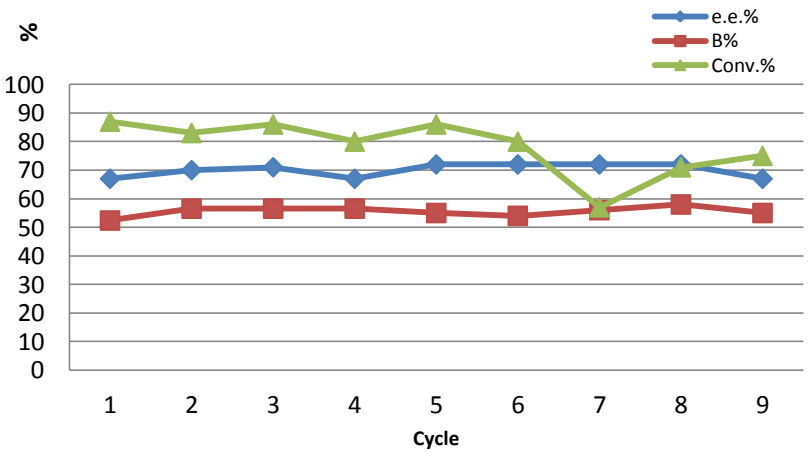


Figure 51 Asymmetric methoxycarbonylation of styrene with the hetergenised catalyst (**53**) (**DOWEX-53-Pd**). The S/Pd ratio was 400/1.

The immobilised (**61**) complex gave even greater improvements concerning enantioselectivity than was observed with the heterogenised catalyst (**53**). E.e.s up to 81 % and B/L ratios of 1.5 were achieved. However, activity of **DOWEX-61-Pd** was much lower than observed for **DOWEX-53-Pd** with a S/Pd ratio of 400/1 (Figure 51).

Table 46 Methoxycarbonylation of styrene using the catalyst resin **DOWEX-61-Pd** immobilised on resin S/Pd ratio of 110/1 (Figure 52).

Entry[a]	Cycle	Conv.[b] (%)	Ester[b] (%)	B/L[c]	Ee[c] %
1	**1**	63	1.7	1.4	76(R)
2	**2**	61	1.8	1.4	81(R)
3[d]	**3**	53	1.8	1.4	80(R)
4	**4**	43	1.8	1.6	81(R)
5[d]	**5**	50	1.8	1.4	81(R)
6[e]	**6**	43	1.7	1.3	80(R)
7	**7**	32	1.7	1.5	79(R)
8[f]	**8**	54	1.8	1.5	79(R)
9	**9**	44	1.8	1.4	79(R)

[a] Reactions were carried out using 0.9 mol% catalyst (71.8 mg resin, 0.009 mmol Pd on the resin) at 30 bar CO in 1.5 ml MeOH and 1 mmol styrene at 60 °C for 20 hours. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H NMR spectroscopy. [c] Enantiomeric excess and B/L ratio determined by chiral GC; (*R*) catalyst gives the (*R*) enantiomer and vice versa. [d] 1 day in between next cycle. [e] 5 days in between next cycle. [f] 2 days in between next cycle.

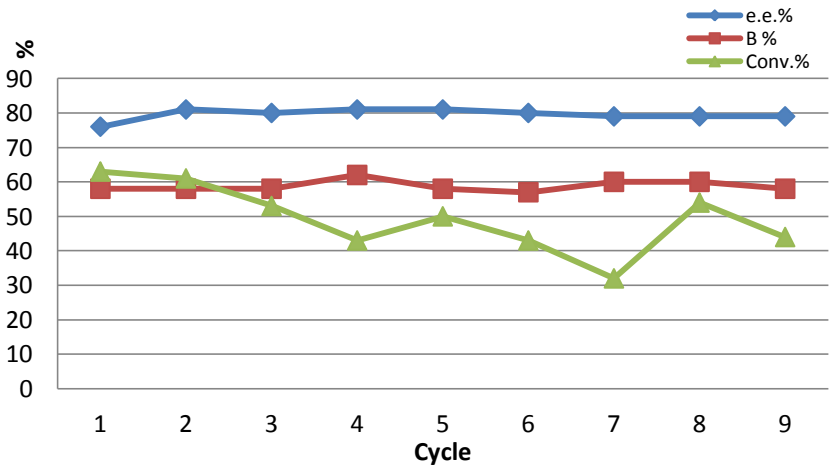


Figure 52 Asymmetric methoxycarbonylation of the heterogenised (**61**) (**DOWEX-61-Pd**) catalyst. Reaction was carried out with a S/Pd ratio of 110/1.

For the dipalladium resin **DOWEX-61-Pd** although substrate to Pd ratio was 110/1 so almost 4 times lower than were applied for the dipalladium resin but also activity was generally much lower and observed to decrease faster too (after the 6th cycle).

Similar to catalyst **DOWEX-53-Pd**, **DOWEX-61-Pd** decreased in catalytic activity after storing the resin under Argon. However, for the **DOWEX-61-Pd** the impact was more intense. Reduced catalyst activity was observed for cycle 4 and 7, which is due to the interruption of catalysis use and storage for 1-5 days. After cycle 3 the resin was stored for 1 day before further addition of substrate solution. After cycle 6 the resin was not used for 5 days and left unused under argon atmosphere. Storage of the resins was done under argon and most of the product solution is removed, however complete removal of all liquid was not possible. Also as observed for **DOWEX-53-Pd**, once the catalyst was used in catalysis again, the catalytic activity was more or less recovered. Similar to the Rh resins when applied in hydrogenation, the Pd resins changed colour during catalysis.

3.4.2.2 Methoxycarbonylation of styrene with non-functionalised resin catalyst

When comparing the nitrogen functionalised catalyst with an unfunctionalised catalyst (**48**), the value of the nitrogen moiety becomes clear. **DOWEX-48-Pd** was applied in asymmetric methoxycarbonylation with the same S/Pd ratio as for **DOWEX-53-Pd**. Figure 53 shows the fast decrease in activity after every cycle of the heterogenised catalyst (**48**) (**DOWEX-48-Pd**).

After each cycle, the reaction solution was coloured yellow, whereas the reaction solution with **DOWEX-53-Pd** always gave a clear solution. The main leaching occurred in the first 2 cycles with > 30 ppm Pd in solution. However, leaching for the following 5 cycles was much lower, but overall leaching was still > 36 ppm.

Table 47 Methoxycarbonylation of styrene: (**48**) with a S/Pd ratio of 500/1.

Entry[a]	Cycles	Ester[b] (%)	B/L[c]	Ee[c] (%)	Pd leached[d] (ppm)
1	**1**	96	0.8	72	27.61
2	**2**	72	0.7	69	3.939
3	**3**	67	0.7	49	0.768
4	**4**	60	0.8	58	1.233
5	**5**	46	0.9	70	0.810
6	**6**	45	0.9	77	0.144
7	**7**	34	0.9	73	0.881

[a] Reactions were carried out using 0.2 mol% catalyst at 30 bar CO in 1.5ml MeOH, 1mmol styrene at 60 °C for 20 hours. [b] Conversion refers to styrene consumed. % Product determined against tetraethylsilane internal standard using ^{1}H NMR spectroscopy. [c] Enantiomeric excess and B/L ratio determined by chiral GC; (*R*) catalyst gives the (*R*) enantiomer and vice versa. [d] Pd leaching determined by ICP-OES.

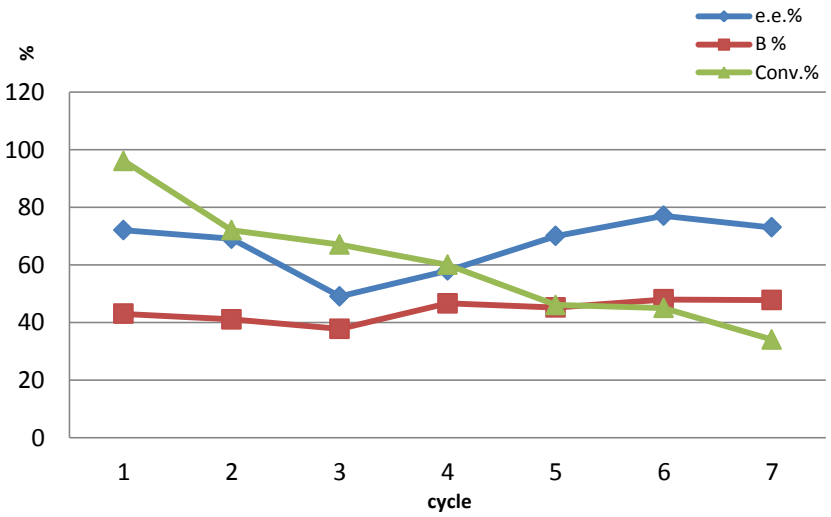


Figure 53 Asymmetric methoxycarbonylation with the heterogeneous catalyst **DOWEX-48-Pd** in S/Pd ratio of 500/1.

The non-tagged catalyst system was observed to be weakly bound to the DOWEX resin by ion-exchange; therefore a repeated reaction with increased catalyst was carried out. When a S/Pd ratio of 140/1 was applied the **DOWEX-48-Pd** catalyst could be recycled up to 10 times without any changes in activity and selectivity (Figure 54). This system has already been proven to leach Pd complex therefore no ICP measurements for Pd leaching were carried out. It was clear to see leaching was occurring since Pd black was visible in solution. However, the overall catalytic activity was higher than the

homogeneous analogue, and no additional promoters were necessary, which makes these process conditions very interesting.

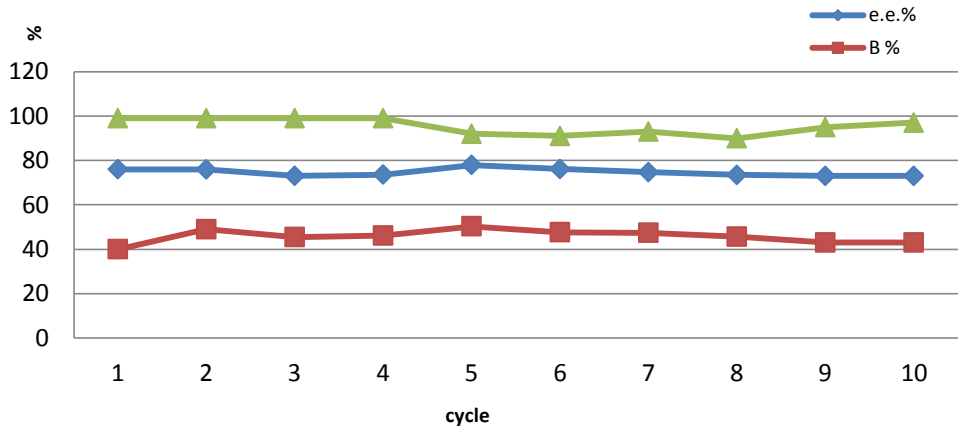


Figure 54 Asymmetric methoxycarbonylation of styrene using the heterogenised resin **DOWEX-48-Pd** with a S/Pd ratio of 140/1. Reactions were carried out using 0.9 mol% catalyst at 30 bar CO in 1.5ml MeOH, 1.00 mmol styrene at 60 °C for 20 hours; Conversion were determined against tetraethylsilane internal standard using ^{1}H NMR spectroscopy; Enantiomeric excess and B % was determined by chiral GC.

Similar to the Rh resins when applied in hydrogenation, all Pd resins changed colour during catalysis. This interesting colour change occurred after every initial application of the heterogenised catalysts in methoxycarbonylation (Image 3). This change in colour does not influence the catalyst performance of these polymeric resins, as presented above. Also their stability for recycling (~10 cycles) is of great interest, demonstrating that the polymeric support is indeed supporting the catalytic active species somehow.

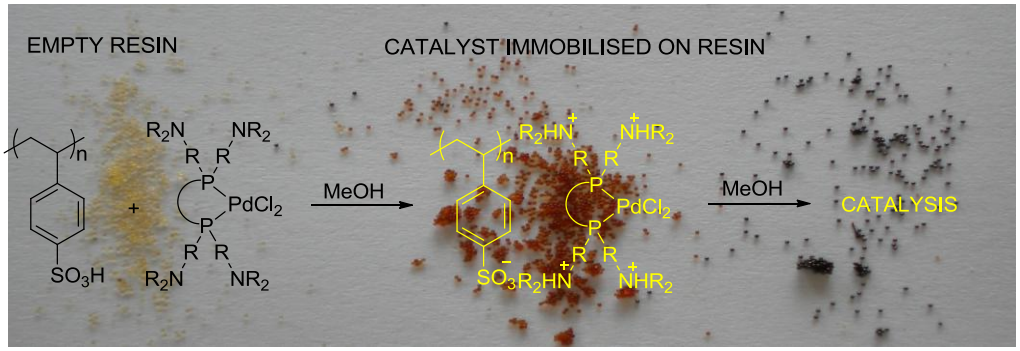


Image 3 Colour variations of the DOWEX resin at different stages; from the empty resin (yellow resin); to the immobilising catalyst (red/brown) and the colour alteration observed after the first catalysis cycle.

A theory for this change of colour is the formation of nanoparticles (NP) during the first catalysis cycle, which are stabilised onto the polymeric resin. Nanoparticles and experiments carried out to support its theory are discussed in more detail in *chapter III 3.4.2.4*.

The great value of these heterogenised catalysts not only lies in their ability to be recycled but also in their ability of not needing the addition of promoters. Typically to obtain good selectivities and activities in hydroxy- and alkoxy-carbonylation reactions of vinyl-arenes and other alkene substrates, additional promoters are necessary. Mostly high promoter concentrations are necessary to obtain reasonable activity and sometimes selectivity. This does not make these processes very environmentally friendly and can also complicate work up of product purification. By adding solid acids, which can easily be recycled by filtration or decantation, further auxiliary promoters are not required anymore. In literature and also in *chapter I* the importance of added promoters was intensively investigated, and although the concrete mechanism is still unclear, they were found to be of great importance.[11]

A short study was performed to evaluate the catalyst promoters by simply comparing the same reaction conditions with individual acid promoters, such as the H^+ DOWEX in comparison to the *p*-TsOH*H_2O/LiCl (Figure 55).

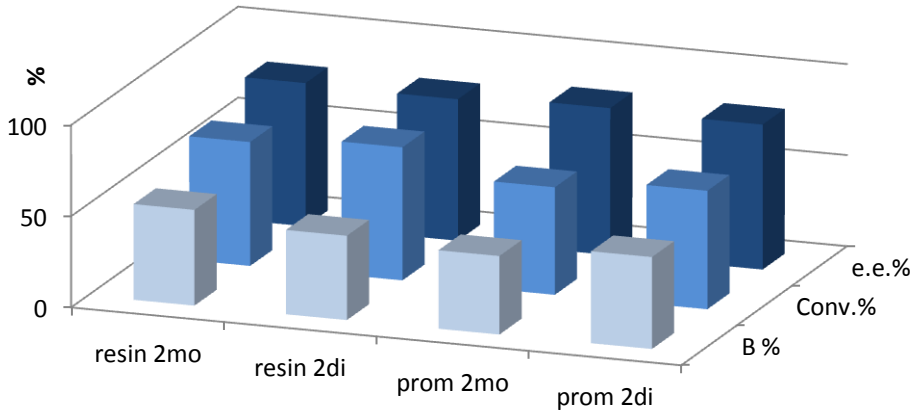


Figure 55 Methoxycarbonylation comparing different promoter systems: H^+-DOWEX (= resin) vs. *p*-TsOH*H_2O/LiCl (= prom) systems, with homogeneous catalyst (**48**). Reaction condition: reactions were carried out adding described promoter, (**48**) (1 mol%) and styrene (1.00 mmol) in a microwave vial and pressurise to 30 bar CO in 1.5ml of anhydrous MeOH as solvent, at 60 °C for 6 hours. Conversions refer to ester produced. Dipalladium catalyst (**48**) formed *in-situ* by adding (**48**) and 0.01mmol of [$PdCl_2(PhCN)_2$]. 20 mol% of LiCl and *p*-TsOH*H_2O was added.

Figure 55 visibly shows the slightly enhanced conversions and B/L ratio for polymeric acidic ion-exchange resins as the only promoter. Addition of 0.20 mmol LiCl to the resin **DOWEX-53-Pd** in styrene methoxycarbonylation was also conducted however it did not change the reaction outcome. Thus, reactions carried out by the polymeric acid as promoter and support, not only result in better activity and regioselectivity, but also provided the possibility for catalyst recovery.

Early studies by Hayashi and co-workers investigated the function of halide counter anions and proposed that these prevent the agglomeration of the molecular catalyst by simple coordination to the palladium species.[12] Aggregation of reduced palladium species would automatically lead to a deactivation of the catalytic system. Solvents and weakly coordinating anions are known to support the active catalytic species. This could be one explanation for the catalytic stability of the heterogenised DOWEX catalysts, due to their availability of many $-SO_3^-$ and $-SO_3H$ groups.

In order to exclude the importance of the influence of chloride anions, methoxycarbonylation with (**44**) and $Pd(dba)_2$ formed and heterogenised *in-situ* onto the protonated DOWEX resin, was investigated. The same reaction conditions as for all other methoxycarbonylation reactions were applied.

The first 3 cycles of this chloride free catalytic system are shown in

Figure 56. The resin catalyst shows high activity in combination with previously observed selectivity and no loss of regio- or enantio-selectivity. The same activity and selectivity was obtained for a chloride free catalyst system, as with the $PdCl_2$ palladium precursor.

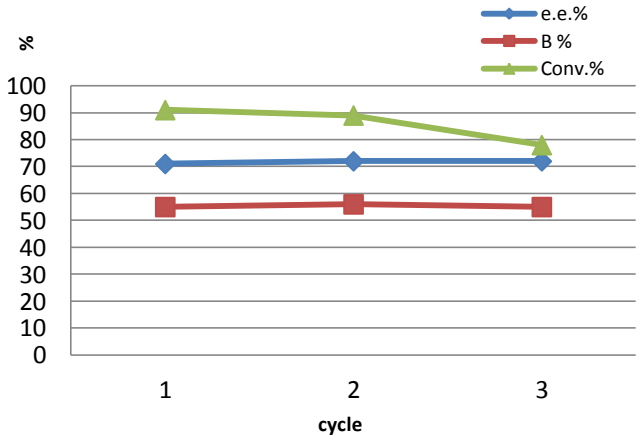


Figure 56 Asymmetric methoxycarbonylation of styrene with $Pd(dba)_2$/(**44**) prepared *in-situ*; S/Pd ratio of 200/1. Reaction was carried out in 1.5 ml of MeOH at 60 °C and 30 bar CO with the Pd resin prepared *in-situ* with resin (23.8 mg), $Pd(dba)_2$ (2.8 mg, 0.005 mmol), (**44**) (6.0, 0.005 mmol) and styrene (114 µl, 1.00 mmol). After the reaction finished the solution was removed with a syringe and new substrate solution was added (styrene (114 µl, 1.00 mmol) and MeOH (1.5 ml)).

It is very likely that the $-SO_3^-$ anion of the resin interacts with the Pd species and therefore prevents deactivation. Thus, it can be concluded that chloride is not required in the mechanism of methoxycarbonylation using these catalysts.

Overall the catalyst activity of the combination of (**48**) and solid H^+DOWEX is comparable to the homogeneous analogue. However, the homogeneous catalyst could not be reused for 9 more cycles and needs the additional promoters. The polymeric acid support and the $-SO_3H$ groups most likely stabilise the catalytically active species.
Although the solution containing the product and some leached catalyst was removed in every cycle, enough catalyst stayed attached onto the acidic ion-exchange resin to contribute to continuing high conversions. If the tagged catalyst, **DOWEX-53-Pd** is used, very little leaching occurs. All these results are very promising, giving higher activity and even enhanced selectivity than their homogeneous counterparts.

Several examples in literature about heterogenised Pd catalysts are reported.[23, 133] Although to the best of our knowledge, up to date no other asymmetric methoxycarbonylation of styrene has been achieved to perform with stable activity over 10 recycles.

3.4.2.3 Hydroxycarbonylation of styrene with functionalised resin catalysts

Additionally asymmetric hydroxycarbonylation reactions were carried out, but the catalyst activity was very low. This was probably due to the bad swelling of the resin in H_2O as a solvent. Catalysis conducted with 2-butanone and water for improving the catalytic activity, also resulted in low conversions; therefore no further investigations of the catalytic behaviour in hydroxycarbonylation were performed. In any case, removal of the catalyst from products in hydroxycarbonylation by acid-base chemistry is more readily achieved (although recycling has not been demonstrated yet).

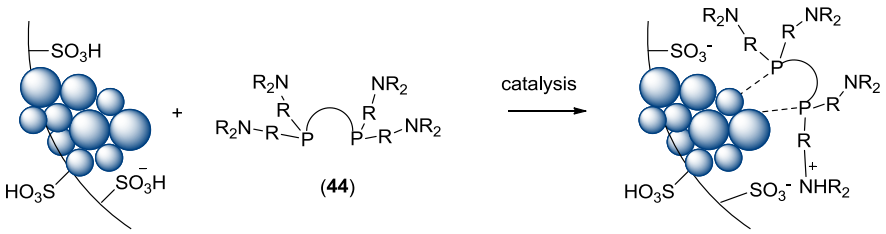
3.4.2.4 Nanoparticle resin

Metal colloids are attracting increasing interest, not only in catalytic reactions but also as biological markers, ferrofluids and many more. Metallic nanoparticles (MNP) have gained wide spread use due to their large surface areas, associated with high activity and their advantage of recyclability. All these positive contributions have promoted MNP applications in a broad range of reactions. They are highly reactive and can be immobilised onto a variety of supports, such as inorganic (silica, zeolites, alumina, clays) and organic (carbon, polymeric resins) supports or in liquid phase (colloids). Among all these supports, silicas and polymeric solids are the most investigated. Various techniques and strategies allow nowadays a controlled growth of the MNP. Immobilisation of the MNP on the solid supports provides an extra stability to avoiding agglomeration, and

makes them therefore interesting for catalyst recycling.[1c, 13] Developing metal nanoparticle processes for asymmetric catalysis are of increasing interest.[14] MNP have been applied efficiently in olefin hydrogenation reactions and C-C coupling.[15] However, asymmetric applications are still challenging and therefore effective chiral nanoparticle systems are intensively investigated.[16] In several cases nanoparticles have been observed to act as a stable reservoir for M(0) that can then form a soluble complex with a chiral ligand.[17] It is therefore arguable if genuine asymmetric catalysis on NP's has ever been observed.

The observed colour change during methoxycarbonylation of styrene with Pd resins is interesting (Image 3). Before methoxycarbonylation was performed the acidic polymeric resin consisted of a light red colour, which changed into black after the initial first catalysis cycle. A similar observation was reported by Yamashita and co-workers in 2010. They prepared Pd NP *in-situ*, by addition of acidic -SO_3H resins and $PdCl_2$ in aqueous HCl solution and bubbling through H_2 and O_2, for the direct synthesis of H_2O_2.[18] In the very initial stage of catalysis the resin colour changed from yellow to gray. Various other resins with functional groups varying from the –SO_3H, such as -SO_3Na, -CO_2H were tested, however no colour changes were observed with them. The Pd NP distribution parameter of the resin was determined by TEM after the catalysis reaction and found to have formed fairly large particles ~20.3 nm, with a narrow size distribution. This observation suggests that the catalytically active species was formed in the reaction medium, although the reason for the enhanced catalytic activity in comparison to the pre-reduced Pd NP on the same resin type is unclear.

When comparing the catalyst system of Hayashi with the resins used for methoxycarbonylation reaction of styrene, many parallels can be found. One possible explanation for the colour change during the first cycle could be the formation of nanoparticle on the resin. If and how these NPs are involved in the catalytic cycle would require more intensive investigations. One possibility could be that the immobilised *nitrogen*-functionalised ligand is attached to the resin by ionic interactions and can freely coordinate from and onto the NP to conduct the methoxycarbonylation of styrene (Scheme 42).



Scheme 42 Theory about the colour change of the heterogenised Pd resins, the colour change could be due to the formation of nanoparticles on the polymeric resin and ligand (**44**) is stabilised by ion-exchange.

First investigations concerning this heterogenised catalyst were carried out by forming resin palladium nanoparticles. The Pd nanoparticle resins were isolated as black resins, after decomposition of $Pd(dba)_2$ by H_2 (30 bar) at room temperature, the NP resin was washed and dried as described for the Rh and Pd resins.[16b] The PdNP resins were handled with similar care under inert atmosphere as previously reported. Before examining the catalytic activity, an EDX spectrum was carried out to confirm the presence of palladium metal (Table 48). Furthermore mapping carried out by EDX confirmed the homogeneous dispersion of Pd on the resins (*experimental III*).

Table 48 EDX analysis of palladium nanoparticles on polymeric resins. The resins were prepared by reduction of $PdCl_2$ precursor in MeOH. After washing and drying, the palladium amount on the resin was determined by EDX.[a]

	Palladium precursor	Pd loading EDX[b] (%)
before catalysis	$PdCl_2$	2.21
after 11 catalysis cycles	-	0.81

[a] Resin added under inert atmosphere to MeOH solution (10 ml) solution of $PdCl_2$ catalyst added in excess (4 ml). Solution stirred for 24 hours and resin washed and dried as described in *experimental III*. [b] EDX measurements carried out on SEM.

The PdNP resin and ligand (**44**) were weighed under an inert atmosphere into a vial before adding MeOH and the substrate. The autoclave was closed and pressurised as described in *experimental II*. To investigate the catalyst nature in more detail several reactions were carried out. Therefore different Pd/(**44**) ratios were prepared and examined in methoxycarbonylation reactions of styrene. Varying from 1/0.8 which investigates monopalladium (**53**) catalyst (Figure 57); 1/2 which is the theoretical equivalent to catalyst with an excess ligand (Figure 58); and 1/0.5 which is theoretically equivalent to the dipalladium complex (**61**) (Figure 59). All methoxycarbonylation

reactions were carried out in 1.5 ml MeOH, at 30 bar CO, 20 hours, 60 °C and S/Pd ratios which are provided in the individual figures.

When a Pd/P ratio of 1/0.8 was applied the methoxycarbonylation was found to give good conversions, B/L ratios and e.e.s, which are in good agreement with the immobilised molecular catalyst **DOWEX-53**.

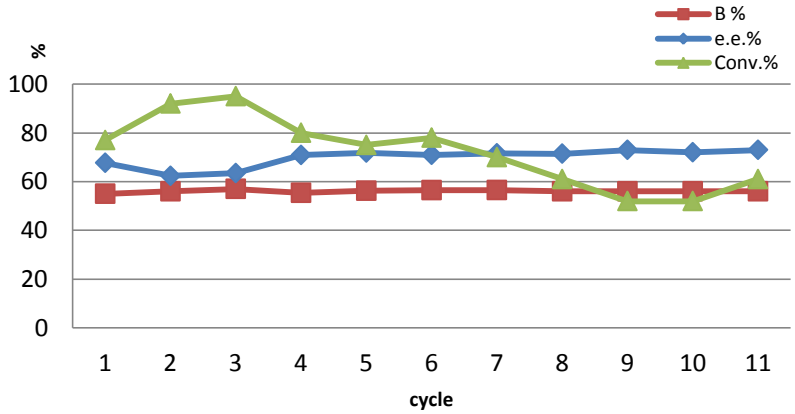


Figure 57 Methoxycarbonylation of styrene using nanoparticle resins with S/Pd/(**44**) ratio of 200/1/0.8 (= (**53**) immobilised onto resin).

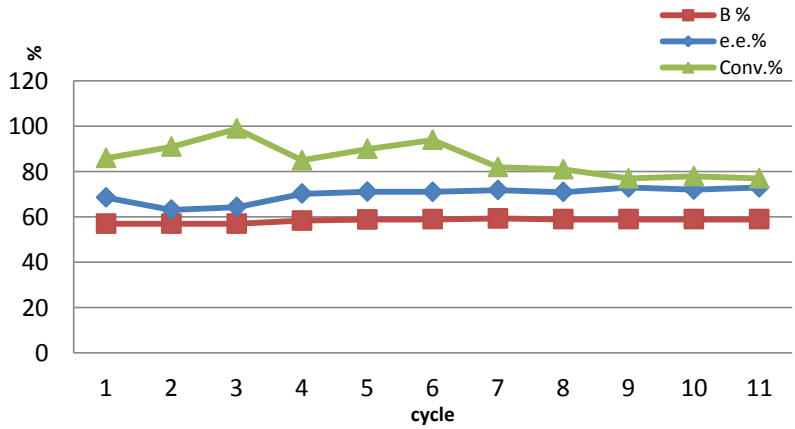


Figure 58 Methoxycarbonylation of styrene using nanoparticles resins with a S/Pd/(**44**) ratio of 200/1/2 (= excess of ligand).

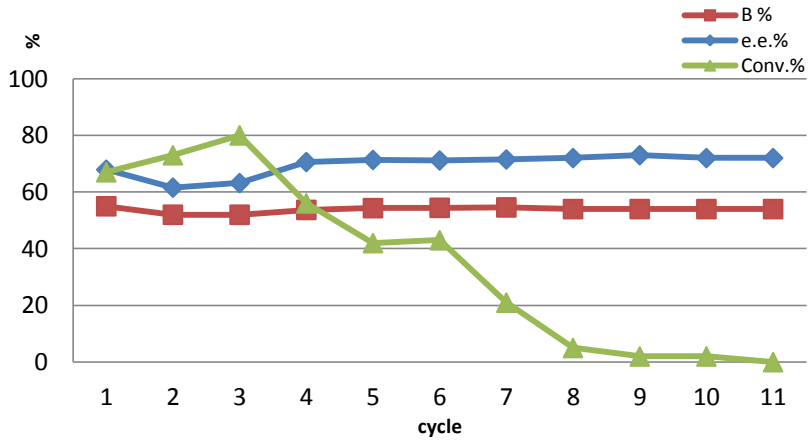


Figure 59 Methoxycarbonylation of styrene using PdNP resins S/Pd/(**44**) ratio of 200/1/0.5 (=(**61**) immobilised onto the resin).

Interestingly an excess of ligand improved the catalytic stability resulting in higher conversions and stability, than obtained for Pd/(**44**) ratio 1/0.8.

For the catalytic system with a Pd/(**44**) ratio of 1/2 of activity loss was quick. The activity with the heterogenised molecular catalyst (**61**) was already observed to be lower than (**53**) for the preformed catalyst; however *in-situ* formation of a "(**61**)" type catalyst resulted in even faster catalyst deactivation.

After every cycle the formation of a black precipitate was observed, strongly suggesting Pd leaching. EDX calculation, which was carried out after catalysis, confirmed the loss of palladium.

Ligand (**39**) was also investigated in methoxycarbonylation with PdNP resins. The heterogenised homogeneous catalyst (**48**) was investigated with a S/Pd ratio of 500/1. The conversions were found to be very high in the 1st cycles (conversion >90 %), however activity decreased fast after the 7th cycle (conversion ~40 %). For the Pd nanoparticle resin **DOWEX**-(**48**) a much lower S/Pd ratio of 330/1 was used, but conversions were decreased in comparison to the heterogenised homogeneous catalyst (Figure 60). Regarding stereoselectivity, both stereo- and enantio-selectivity gave the same selectivity as obtained for the homogeneous catalyst (**48**) and the resin **DOWEX**-(**48**).

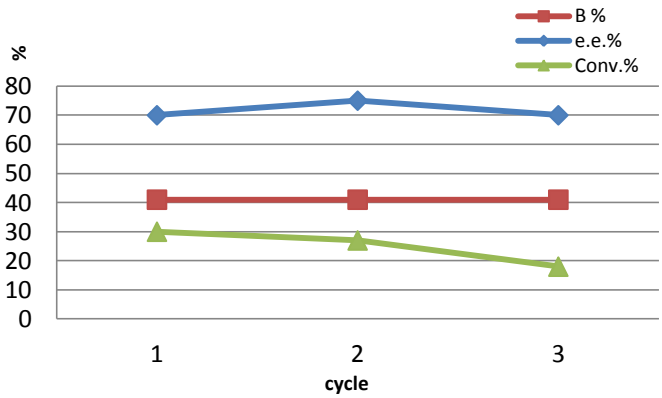


Figure 60 Methoxycarbonylation of styrene with PdNP resin and S/Pd/(**39**) ratio of 330/1/1. Reactions were carried out using nanoparticle resin (13.9 mg, 0.003 mmol Pd) and (*S*)-(**39**) (1.9 mg, 0.003 mmol) at 30 bar CO in 1.5ml of anhydrous MeOH as solvent, at 60 °C for 20 hours.

In conclusion, although some of the NP resin catalysts could be recycled up to 11 cycles with no loss of selectivity, it is still unclear if the active catalytic species is indeed the PdNPs with the ligand coordinated to the particle or a heterogenised molecular catalyst formed *in-situ* is doing the catalysis. In 2008, van Leeuwen and co-workers carried out investigations of the active catalysts true nature, and observed that when using PdNPs supported by chiral sugar-based phosphites, the actual catalytic active species was a mono-metallic, molecular catalyst.[19] As already mentioned earlier, several other papers have been published about similar behaviour, observing nanoparticles to not be the actual catalytic active species, but supply Pd species for the formation of the molecular complex. Further investigations would be necessary to confirm the catalytic active species with certainty.

3.4.3 Heterogenisation *via* supported acidic ionic liquids (SILP) for continuous $scCO_2$ flow reactions

Ionic liquids (ILs) are of great importance and have been applied widely as solvents, catalysts, lubricants, electrolytes, in photochemistry and more.[20] As their name already indicates ILs are liquids prepared from ions. The cause for this behaviour is their disruption in packing arrangement, due to bulky and asymmetric cations and flexible inorganic counter anions.

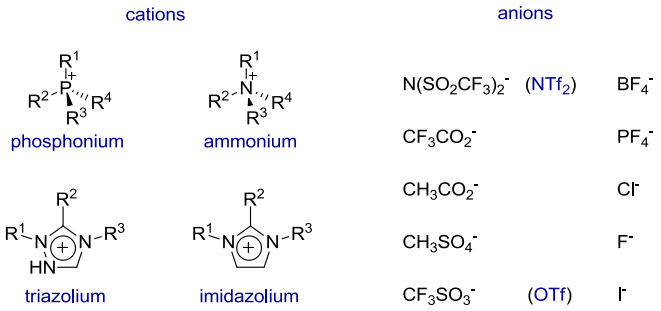


Figure 61 Some of the most common cations and anions for preparation of ionic liquids are summarised.

Their low melting point makes them ideal candidates for heterogenising homogeneous catalysts. Due to their negligible vapor pressure and high thermal stability ionic liquids have received great interest.[21] Furthermore physical and chemical properties of ILs can be modified easily by changing the length of the alkyl chain, of the cation and/or anion. Solubility of various organic solvents for example can be controlled by altering the chain lengths and the use of larger anions in the order of BF_4 < PF_6 < NTf_2.[22]

Ionic liquid systems suffer from low solubility of gases, due to the high density. However, this can be overcome by supercritical CO_2 ($scCO_2$), which is a great method to enhance the gas uptake into ILs.

$ScCO_2$ has remarkable properties; not only does it have low toxicity, rapid diffusion, low viscosity and no surface tension, but also behaves as a gas and liquid at the same time, combining the advantages of both phases. It is very useful for applications with ILs as biphasic system.[23] It was observed to decrease leaching for biphasic systems with IL/solvent, and for ILs/gas systems it provides the necessary solubility of the gas into the IL and therefore allows a wider substrate range.

ILs in continuous flow reactors have been reported for the first time in 2006 by Riisager and co-workers for methanol carbonylation.[24] By using SILP (supported ionic liquid phase) systems the molecular catalyst species was immobilised onto the surface of silica as the solid support. The catalyst is dispersed evenly onto the porous, large surface area, as a liquid phase (Figure 62). However, the first application combining ILs with $scCO_2$ in continuous flow reactors has been reported by Cole-Hamilton and co-workers in 2007 for the hydroformylation of 1-octene.[25] The application of $scCO_2$ supplies the heterogenised catalyst sufficiently with substrates and reactants.

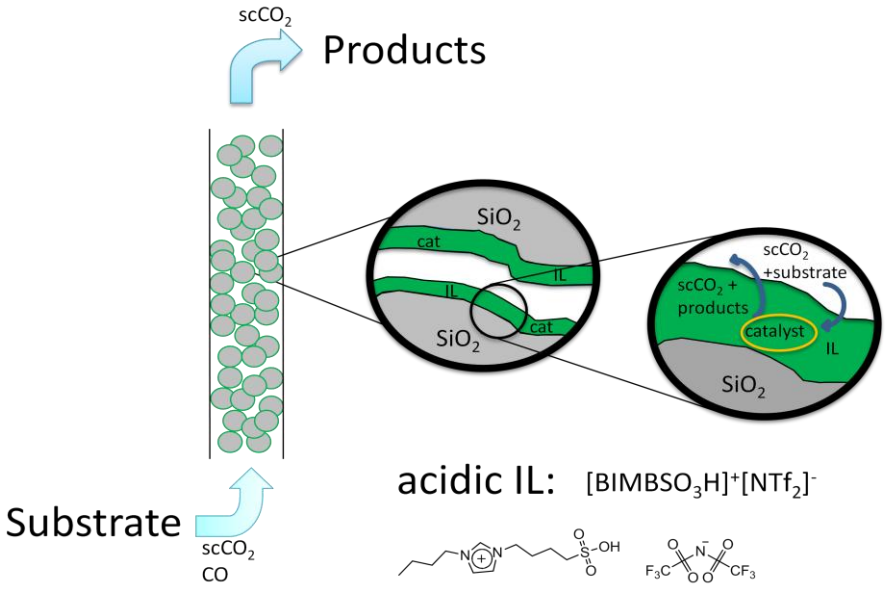


Figure 62 Concept of continuous flow reactor using SILP systems with acidic ionic liquids (Picture reproduced with permission from Mr. Ruben Duque, Prof. Dr. David Cole-Hamilton)

Not many reactions have been reported about recycling palladium catalysed hydroxy- or alkoxy-carbonylations of styrene with ionic liquids. Monteiro and co-workers reported the use of a Pd/neomenthylphenylphosphine (**3**) system with the ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($[C_4MIM][BF_4]$) and TsOH for *iso*-propoxycarbonylation of various styrene derivatives.[26] Good activity and selectivity for the branched ester was achieved, yet no recycling of the catalyst was reported.

A similar paper was published by Shaughnessy and co-workers in 2005. They reported the recycling of the $(PPh_3)_2PdCl_2$ catalyst up to five times using the similar ILs as described above, although with a fast decrease in catalyst activity.[27]

3.4.3.1 Asymmetric methoxycarbonylation in $scCO_2$ in continuous flow systems

Continuous flow reactions are a great possibility for chemical production. This is done by pumping substrates and reactants into the reactor, which is filled with a catalyst system fixed into the reactor, and simply collecting the products at the end of the reactors. Homogeneous catalysts can be supported in the reactor with same methods used to heterogenise catalysts. Heterogenisation *via* IL is a common method for anchoring homogeneous slightly modified catalysts onto solid supports. These systems can then be utilised in flow chemistry, such as continuous flow systems with $scCO_2$. Continuous flow chemistry was also observed to improve the catalyst lifetime.

The continuous flow reactor used for methoxycarbonylations is displayed in Figure 63. This reactor was designed to allow the use of 2 gases and 2 reactors at the same time, if desired 2 different reactions, which are connected in series, can be run at the same time.

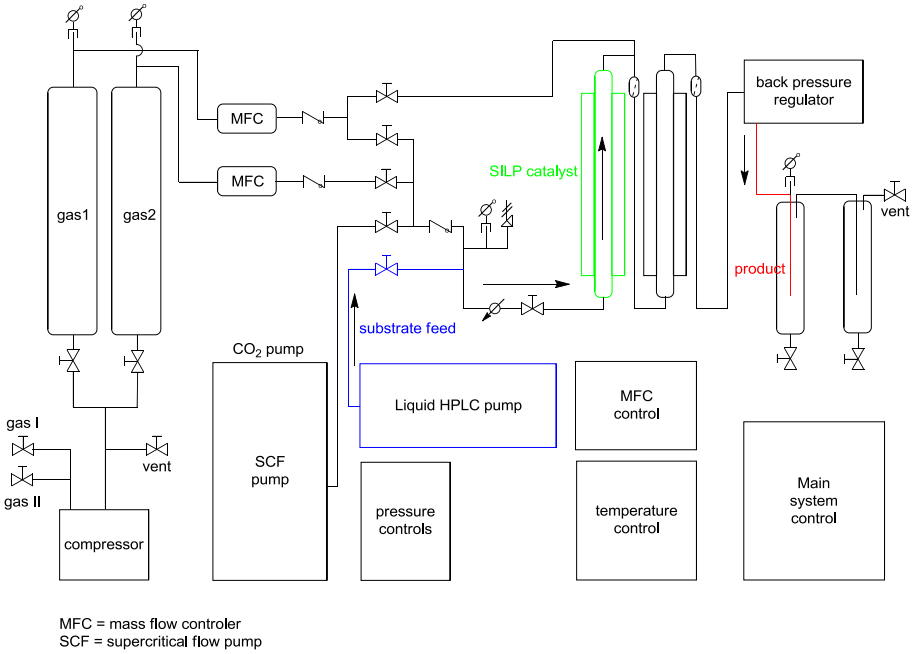
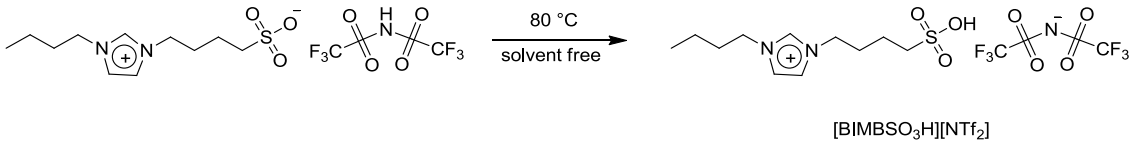


Figure 63 Continuous flow reactor used for asymmetric methoxycarbonylation reactions.[2]

The first asymmetric methoxycarbonylation reaction of styrene with the heterogenised SILP catalyst of (**53**) in continuous $scCO_2$ flow reactor is displayed in Figure 64. This reaction was carried out by Dr. Barthel Engendahl in Prof. Dr. David Cole-Hamiltons group. The homogeneous catalyst (**53**) was provided and heterogenisation of the homogeneous catalyst onto the silica was applied, following the method reported by Hanson and co-workers.[28] For the preparation of the SILP system for this particular reaction an acidic ionic liquid $[BIMBSO_3H][NTf_2]$ was used in combination with 1-butyl-3-(4-sulfomethyl) imidazolium bis(trifluoromethylsulfonyl)amide $[BMIM][NTf_2]$. The preparation is shown in Scheme 43.



Scheme 43 Preparation of the acidic ionic liquid 1-butyl-3-(4-sulfobutyl)imidazolium bis(trifluoromethylsulfonyl)amide [BIMBSO$_3$H][NTf$_2$]. Putting both solids under inert atmosphere toghether and stirred for 1 hour at 80 °C, resulted in the acidic IL in quantitative yield. (Unpublished results from the thesis of Dr. Barthel Engendahl)

Immobilisation by ion-exchange and methoxycarbonylation of styrene require acidic conditions. Using the acidic ionic liquid provides both the proton for heterogenisation of the catalyst and for the Pd-H formation.

SILP preparation is described in more detail in the *experimental III*. All reactions were carried out under inert atmosphere. The silica was dried under high vacuum and heating for about an hour, then CH_2Cl_2 is added, the catalyst, IL and the solution stirred for 30 minutes. The solvent was removed under reduced atmosphere, leaving yellow or orange coloured silica residue, which was filled into the reactor under inert atmosphere.

The reaction was found to give reasonable conversions and comparable regio- and enantio-selectivity to the homogeneous phase catalysis (Figure 64). The effect of increased e.e. and B/L ratios was not observed. The TOF_{max} was low for all reactions presented in the individual tables summarising the reaction conditions. However, the most significant and interesting finding is that the conversions are stable over the duration of the experiment. Asymmetric hydroxy- and alkoxy-carbonylation reactions are still very challenging reactions.

Table 49 Reaction conditions used with (**53**) and a MeOH/S ratio (Figure 64).[2]

V_{CO2} = 11.2 mmol/min	V_{CO} = 0.9 mmol/min
V_{MeOH} = 571 µmol/min	V_{Sub} = 16.6 µmol/min
P_{total} = 150 bar	Temperature 60 °C
Silica = 3.65 g	(**53**) = 55.1mg = 48.3µmol
$[BIMSO_3H][NTf_2]$ = 0.60 g	$[BMIM][NTf_2]$ = 1.21 g
TON_{total} = 244	TOF_{max} = 16.6 h^{-1}

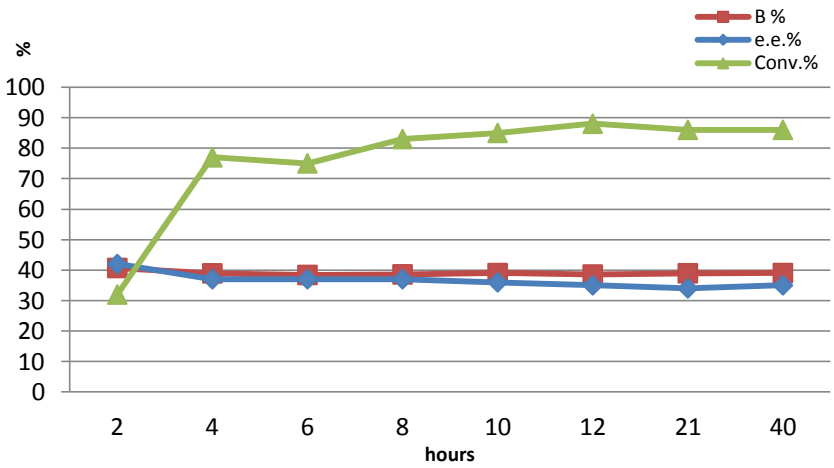


Figure 64 Asymmetric methoxycarbonylation of styrene in continuous $scCO_2$ flow. Catalyst (**53**) was heterogenised with SILP system onto silica. The reaction conditions are listed in Table 50, a MeOH/S ratio of 36/1 was applied.[2]

When (**53**) was applied for styrene methoxycarbonylation under the exact same continuous conditions, much lower conversions were observed. This was expected since this was already observed for the homogeneous and heterogenised polymeric resins. In contrast to the resin heterogenisation however the e.e. and B/L ratio were much lower, and in agreement with the results obtained for the homogeneous catalysis. The (**53**) catalyst was generally found to give much lower yields than its monopalladium analogue; therefore it was not surprising to observe a similar behavior of the heterogenised catalysts in continuous flow under $scCO_2$. Regio- and enantio-selectivity are comparable to homogeneous examples and the related monopalladium complex (**53**).

2 The continuous flow reactions in $scCO_2$ were carried out in collaboration with Prof. Dr. David Cole-Hamilton. The reaction shown in Figure 64 was carried out by Dr. Barthel Engendahl, as was the building of the rig presented in Figure 63.

Table 50 Reaction conditions for (**61**) in continuous $scCO_2$ flow (Figure 65).

V_{CO2} = 11.2 mmol/min	V_{CO} = 0.9 mmol/min
V_{MeOH} = 571 µmol/min	V_{Sub} = 16.2 µmol/min
P_{total} = 150 bar	Temperature 60 °C
Silica = 3.50 g	(**61**) = 59.98 mg = 45.5 µmol
$[BIMSO_3H][NTf_2]$ = 0.62 g	$[BMIM][NTf_2]$ = 1.18 g
Pd leaching = 0.188 ppm	TOF_{max} = 2.8 h^{-1}

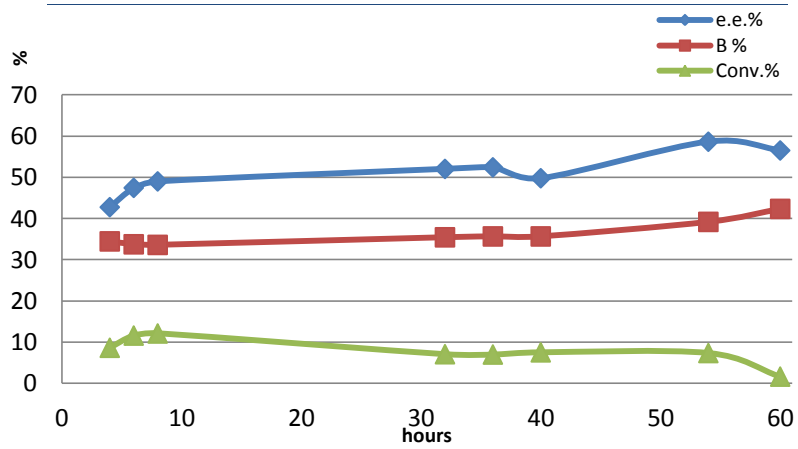


Figure 65 Asymmetric methoxycarbonylation of styrene in continuous $scCO_2$ flow with the SILP heterogenised catalyst (**61**). The same reaction conditions applied as used for the reaction in shown in Figure 64, were conducted (MeOH/S ratio of 36/1).

Furthermore, reactions were also carried out with more concentrated substrate solutions. The same conditions were applied as for the examples above, with the difference of a much higher styrene concentration; MeOH/S ratio of 20/1 instead of 36/1.

Table 51 Reaction conditions of (**53**) in CF methoxycarbonylation of styrene, results summarised in Figure 66.

V_{CO2} = 11.2 mmol/min	V_{CO} = 0.9 mmol/min
V_{MeOH} = 819.8 µmol/min	V_{Sub} = 44.9 µmol/min
P_{total} = 150 bar	Temperature 60 °C
Silica = 3.50 g	(**53**) = 59.7 mg = 51.8 µmol
$[BIMSO_3H][NTf_2]$ = 0.62 g	$[BMIM][NTf_2]$ = 1.18 g
Pd leaching = 0.135 ppm	TOF_{max} = 26.5 h^{-1}

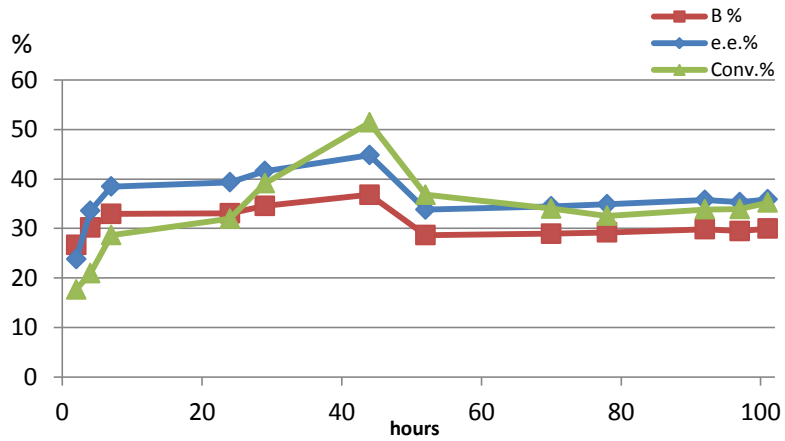


Figure 66 Asymmetric methoxycarbonylation of styrene with the heterogenised SILP catalyst (**53**) in continuous $scCO_2$ flow. The difference to reaction presented in Figure 65, is a more concentrated reaction solution. Instead of a MeOH/S ratio of 36/1, a ratio of 20/1 was used. The same reaction conditions as for the previous reactions were conducted.

The results for the more concentrated solution of MeOH/S can be found in Figure 66. The slow increase in catalyst activity in the first hours was observed in all 3 CF reactions. Due to more concentrated substrate solution the SILP catalyst does not reach conversions up to 80 %. However an increase of reactivity up to 40 hours to reach stabilised conversions rates around 35 %. Again, stabilized conversions and selectivities are indicative for a stable catalyst and are therefore an excellent proof of concept for the viability of using SILP systems containing (**53**) in continuous flow catalysis. The catalyst conditions are summarised in Table 51. Palladium leaching was performed on the collected samples and found to be < 1 ppm. A ^{19}F $\{^1H\}$ and ^1H NMR spectrum was carried out to determine possible ionic liquid leaching. ^{19}F $\{^1H\}$ NMR did show a single peak at 79.9 ppm from the ionic liquid, however ^1H NMR spectrum confirmed that the leaching of

the ionic liquid was bare minimum (< 0.1 %). Leaching was most likely occurred due to the very polar solvent MeOH used in the methoxycarbonylation reaction.

The resin heterogenised palladium catalyst was also examined in continuous $scCO_2$ flow in methoxycarbonylation of styrene. The preparation is fairly simple; the reactor was first packed with glass wool and left under vacuum for several hours to assure that everything is moisture free and under inert atmosphere. In the glove box some dried silica was filled into the reactor and then an even layer of the resin was placed. Before closing the reactor more glass wool was added to assure proper placement of the resin.

Table 52 Reaction conditions applied for methoxycarbonylation in continuous $scCO_2$ flow with acidic resin.

V_{CO2} = 11.2 mmol/min		V_{CO} = 0.9 mmol/min
V_{MeOH} = 375 µmol/min		V_{Sub} = 16.6 µmol/min
P_{total} = 150 bar		Temperature 60 °C
DOWEX-(53) = 330 mg resin	=	0.011 mmol Pd

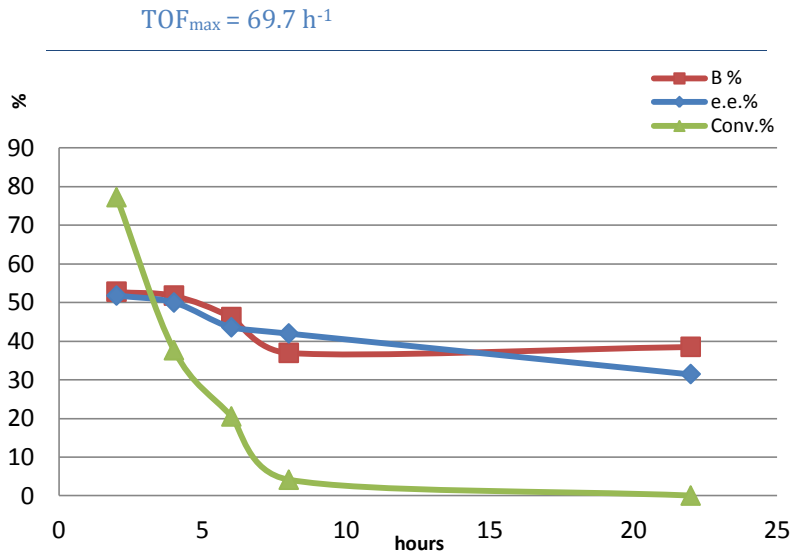


Figure 67 Asymmetric methoxycarbonylation of styrene in continuous $scCO_2$ flow with the homogeneous catalyst (**53**) immobilised onto acidic DOWEX resin. Reaction conditions are the same as discussed above, with exception to the catalyst concentration.

The reaction outcome of the resin methoxycarbonylation is displayed in Figure 67. Activity was observed to decrease fast, only in the first 2 hours high conversions were achieved, within 2 more hours activity decreased to 38 %. Also the B/L ratios and e.e. were found to slightly decrease after about 5 hours reaction time. Thus this experiment

shows the enhanced performance of SILP systems over the resin using continuous flow. It is not clear if catalytic leaching or deactivation is the cause of the decreasing conversions.

3.5 Conclusion

Palladium and rhodium homogeneous catalysts were successfully heterogenised onto acidic ion-exchange resins. The Rh catalysts exhibited high activity and enantioselectivity for the hydrogenation of MAA. Recycling of the catalyst was conducted for more than 10 cycles with high activity and selectivity. To the best of our knowledge this resin catalyst system is the most active and selective up to date, combined with lowest Rh leaching. While MAA is an easy substrate to reduce and is done in homogeneous form by Rh phanephos catalysts at ppm loadings, there are more challenging hydrogenation reactions in industry that require higher catalysts loadings or/and the cost of the ligand is significant.[29] This catalyst concept may therefore be valuable for more applied research in the future.

Interestingly, comparison of the nitrogen supported catalyst system derived from ligand (**44**) with the untagged catalyst derived from (**39**), catalyst leaching was low in both examples. However, when the batch reaction was conducted at 1 bar H_2 pressure the unfunctionalised catalyst **DOWEX-77-NBD-Rh** was observed to decrease activity after 3 cycles. This and the low pressure CF results suggest higher pressures are required with the untagged system. The results obtained at high pressures could be very useful for applications with more difficult substrates in need of higher catalyst loadings.

When the heterogenised palladium catalysts were investigated in asymmetric styrene methoxycarbonylations, good activity and enhanced selectivity were observed. An interesting observation was the improvement of enantioselectivity for the resin in comparison to the homogeneous analogue. The increase in selectivity was only observed for the nitrogen functionalized complexes (**53**) and (**61**). Possible explanations therefore are the hindered access around the catalytic sites, due to protonation of possibly all amine groups on the catalyst; the catalytically active species might be less accessible.

These methoxycarbonylation reactions are much more environmentally friendly since no additional promoters, such as chloride or acids, were required for good activity and selectivity. It was also established that there is no need of any chloride source at all for good catalyst performance, by changing the palladium precursor from a $PdCl_2$ source to a Pd(0) precursor.

The acidic polymeric resin does not only serve as the solid support but is also actively involved in the reaction, by generating the active Pd-H species, which is usually accomplished by the adding an acid promoters.

The heterogenisation onto SILP systems was also possible and these systems successfully applied in continuous flow reactions with $scCO_2$. Promising initial results were obtained for the methoxycarbonylation in continuous $scCO_2$ flow. Heterogenisation of the functionalised catalyst was performed by supported ionic liquid phase systems with acidic ionic liquids. The CF reactions of the monopalladium catalyst (**53**) gave good activity and comparable selectivity to the homogeneous analogue. Importantly, stable conversions were observed establishing this concept for continuous flow carbonylations.

These catalysts are the most active catalysts known in literature up to date for asymmetric styrene methoxycarbonylation. The heterogeneous catalyst systems presented in this chapter were observed to require less catalyst catalyst loadings than their homogeneous analogues and were found to facilitate the recycling process (for up to 11 cycles).

One of the main drawbacks of these *nitrogen* functionalised heterogenisation is that the preparation of tertiary amine ligands can be more complicated and certainly adds cost to the chiral ligand preparation. Furthermore another approach has been attempted for the functionalisation of phanephos derived catalysts on the cyclophane backbone for subsequent collaboration for new SILP catalysts with Prof. David Cole-Hamilton and coworkers. The project is summarized in more details in the *Appendix*, since the project did not reach a conclusion.

3.6 Experimental

3.6.1 Instrumentation and Chemicals

Materials H^+-DOWEX D50WX2 cation-exchange resin, $[PdCl_2(PhCN)_2]$, $[Rh(COD)_2]BF_4$, $[Rh(NBD)_2]BF_4$, styrene, bis(trifluoromethylsulfonyl)imid, silica (Kieselgel Merck type 10184 70-230 mesh, 100 °A poresize) were obtained from Aldrich and used as received. Methyl-2 acetamidoacrylate was obtained from Alfa Aesar. Carbon monoxide was obtained from BOC. Flash column chromatography was performed using Davasil silica gel 40-63µm and normal grade solvents.

ICP Catalysis leaching samples: Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES) measurements were carried out on Perkin Elmer Optima 5300 DV ICP-OES at the University of Edinburgh, School of Chemistry, by Dr. Lorna Eades. The

reaction solution was removed by syringe from the resin and the solvent evaportated. The samples were then dissolved in 1-butanol and the metal content determined. Palladium and Rhodium content on H^+ DOWEX ion-exchange resins were measured at the CNR Florence, Italy. The metal content on the solid resin was determined by Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) with a Jobin Yvon series JY24 instrument. Prior to measurement each sample of resin-supported complex (20-50 mg) was treated in a microwave heated digestion bomb with concentrated HNO_3 (1.5 ml), 98% H_2SO_4 (2 ml), 36% HCl (0.5 ml) and a pellet of a digestion aid reagent (0.5 g, 0.1 % Se in K_2SO_4). After filtration the solutions were analysed. **EDX** ESEM (Environmental Scanning Electron Microscopy) measurements were performed on a FEI Quanta200 microscope operating at 25 KeV accelerating voltage in the low-vacuum mode (1.0 torr) and equipped with an EDX Energy Dispersive X-ray Spectrometer (EDX) or carried out on the Joel JSM 5600 SEM, at St Andrews University which was equipped with an EDX Energy Dispersive X-ray Spectrometer.

3.6.2 Catalysis Experiments

3.6.2.1 General procedure for hydrogenation of methyl-2-acetamidoacrylate in autoclave

The resin catalyst (0.002 mmol) was weighed under inter atmosphere into a dry and under inert atmosphere microwave vial in a Schlenk flask. The microwave vial was closed with a crimp cap. In a different Schlenk flask, methyl-2-acetamidoacrylate (1 mmol) was dissolved in anhydrous MeOH (1.5 ml) under inert atmospheres. This solution was then added *via* a syringe to the resin and transferred into a steel autoclave which was kept under argon atmosphere. The autoclave was closed and purged 5 times with H_2 and pressurised to 15 bar H_2. An oil bath assured that a constant temperature of 22 °C was assured. After the desired reaction time the pressure was released and Argon was purged through the autoclave, to assure best possible inert conditions. The MeOH solution was removed from the resin under a constant argon flow with a syringe and new substrate solution was added. The same procedure was repeated as described above for every cycle. The conversions and enantiomeric excess was determined by GC: MEGA-DEX DMP Beta (stationary phase), 0.25 µl film thickness, 0.25 mm internal diameter, 25 m length, maximum temperature of 230 °C. t_{MAA}[substrate] = 15.2 min, t_R[(+)-*S*] = 15.5 min , t_R[(-)-*R*] = 16.0 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (d, ^{3}J = 8.0 Hz, 3H, O-CH_3), 2.03 (s, 3H, CH_3), 3.76 (s, CH_3), 4.61 (qu., ^{3}J = 8.0 Hz, 1H, CH). MS EI^{+}: m/z 145.07 (M^{+} requires 145.07), $[\alpha]_D$ = +11.40 (c = 0.16, $CHCl_3$; >99% (*R*)). {Lit.[152] $[\alpha]_D$ = +11.0 (c = 0.10, $CHCl_3$; >99.5% (*R*))}.

3.6.2.2 General procedure for hydrogenation of methyl-2-acetamidoacrylate in batch

The resin catalyst (33 mg resin, 0.003 mmol catalyst) was weighed under inter atmosphere into a dry and inert Schlenk flask. Once the resin was under inert atmosphere, a substrate solution of MAA in MeOH (2.5 ml, 0.055 M) was added and the resin left for ~5 min. to swell. Then H_2 was bubbled through at 1 bar pressure, either by H_2 generator (Florence, Italy) or by a balloon filled with H_2. (In St Andrews an oil bath assured that a constant temperature of 22 °C was assured.) After the desired reaction time the solution was removed by syringe and new MAA solution (2.5 ml) was added to the resin. The same procedure was repeated until activity was observed to decrease. Conversion and enantiomeric excess were determined by GC as described for MAA hydrogenation in autoclave.

3.6.2.3 General procedure for hydrogenation of methyl-2-acetamidoacrylate in continuous flow reactor

The resin catalyst (52.3 mg resin, 3.74 μmol) was weighed under inter atmosphere into a dry and inert Schlenk flask, which was equipped with a micro-reactor (Omni FIT reactor, Volume = 0.0707 ml). The micro-reactor was closed at the bottom end and open on the top for charging the reactor under inert conditions. The rest of the continuous flow apparatus was first washed with dry and degassed MeOH and then flushed with N_2 (flow of 2 ml/min) for about 30 min. Once the resin was filled into the microreactor, the reactor was closed on the top and inserted into the continuous apparatus under nitrogen flow. The substrate solution of MAA in MeOH (0.055 M) was passed slowly through the reactor (0.08 ml/min) and the resin observed to swell. Once the reactor was filled with substrate solution H_2 (1.50 ml/min) and substrate solution (0.08 ml/min) was started to pass through the resin filled microreactor. Starting time was taken, after visually observing the first H_2 bubble passing through. A sample was taken in regular intervals and the reaction stopped after no further conversion could be detected in the GC anymore.

Conversion and enantiomeric excess were determined by chiral GC, Lipodex E column t_{MAA}[substrate] = 10.99 min, t_R[(+)-*S*] = 10.69 min , t_R[(-)-*R*] = 11.46 min.

3.6.2.4 Methoxycarbonylation of styrene in scCO$_2$ continuous flow

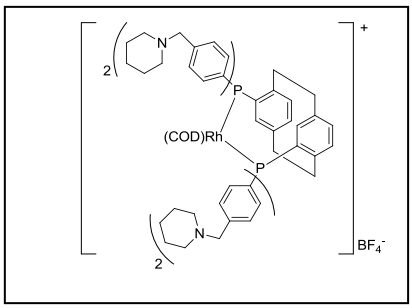
BPR	Back pressure regulator	**GB**	Gas booster	**H**	Heater 1+2
IV	Inlet valves	**LP**	Liquid pump	**R**	Reactor 1+2
BV	Ballast vessel 1+2	**PT**	Pressure transducer	**V**	Vent
CP	CO_2 pump	**HC**	Heater coil	**MFC**	Mass flow controller
		S	Substrate	**CV**	Collection vessel

Before a reaction was carried out the rig was cleaned by washing with acetone for ~2 hours. The reactor was filled with the SILP, which was prepared according to the description below. The rig was then further put under CO_2 atmosphere to assure inert reaction conditions. Then the filled reactor was connected to the rig under a flow of CO_2 and CO gases. The pre-heater was then set up to the temperature of 60 °C and switched on. The rig was then pressurised up to 150 bar total pressure and checked for leaks. Furthermore the reactor was heated to 60 °C temperature and the liquid pump was purged under N_2 with the substrate solution (MeOH and styrene). After assuring that all parameters, such as temperature, pressure (150 bar), CO (20 ml/min) and CO_2 (0.5

ml/min) flow were stable the substrate was started to be pumped into the reactor (0.025 ml/min). The products were collected in a collection vessel, after passing through a decompression chamber. Samples were collected on a regular basis and weighed to check the mass balance and analysed by chiral GC for conversions, e.e. and B/L ratio.

3.6.3 Synthesis

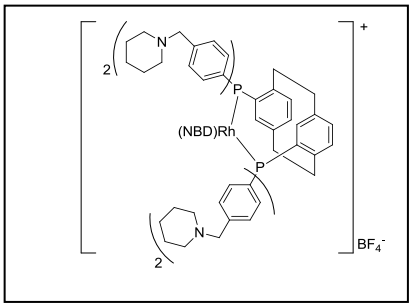
3.6.3.1 {{(*R*)-(-)-4,12-Bis[bis(4-piperidinylmethylphenyl)phosphino]-[2.2]-*para*cyclophane}rhodium(I)(COD)}tetrafluoroborane, (74)



(*R*)-(-)-4,12-Bis(4-piperidinylmethylphenyl phosphino)-[2.2]-*para*cyclophane (130 mg, 0.135 mmol) was dissolved in CH_2Cl_2 and $[Rh(COD)_2]BF_4$ (55 mg, 0.135 mmol) was added for 2 hours. A ^{31}P $\{^1H\}$ NMR was taken to assure the completion of the reaction. Then the solvent was removed until ~1 ml of CH_2Cl_2 was left and hexane was added, stirred and solution filtered off via cannula filtration. The yellow solid was dried under vacuum, leaving the product as yellow solid in 45 % (76 mg, 0.060 mmol) yield.

^1H NMR (300 MHz, $CDCl_3$) δ_H 1.41-1.56 (m, 28H, CH_2), 1.88-2.10 (m, 4H, CH_2), 2.30-2.66 (m, 24H, CH_2). 3.56-3.74 (m, 8H, CH_2), 4.07 (br s, 2H, CH), 4.31 (br s, 2H, CH), 6.30-6.34 (m, 1H, $C_{Ar}H$), 6.41-6.46 (m, 1H, $C_{Ar}H$), 7.04-7.52 (m, 16H, $C_{Ar}H$), 7.68 (d, ^3J = 7.62 Hz, 2H, $C_{Ar}H$), 8.46-8.52 (m, 2H, $C_{Ar}H$). ^{31}P $\{^1H\}$ NMR (121 MHz, $CDCl_3$) δ_P 31.39 (d, $J_{Rh\text{-}P}$= 145.7 Hz). MS (CI^+): m/z calcd. for $C_{72}H_{90}BF_4N_4P_2Rh$ $[M\text{-}BF4]^+$: 1175.5690 ; found 1175.569. MP: 220-224 °C (decomposition).

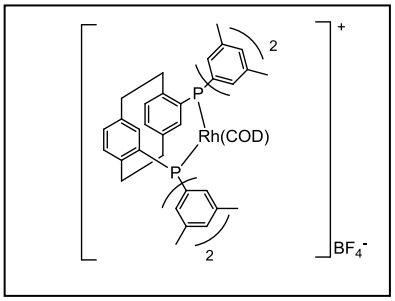
3.6.3.2 {{(*R*)-(-)-4,12-Bis[bis(4-piperidinylmethylphenyl)phosphino]-[2.2]-*para*cyclophane} rhodium(I)(NBD)}tetrafluoroborane, (75)



(*R*)-(-)-4,12-Bis(4-piperidinylmethylphenyl phosphino)-[2.2]-*para*cyclophane (180 mg, 0.186 mmol) was dissolved in CH_2Cl_2 (10 ml) and $[Rh(NBD)_2]BF_4$ (70 mg, 0.186 mmol) was added. The solution was stirred for 30 min and a small sample taken for a ^{31}P $\{^1H\}$ NMR, to assure the completion of complex formation. The solution was added to H^+DOWEX resin in MeOH and stirred over night. The resin was washed as described in the procedure below, see procedure for immobilisation of homogeneous catalysts onto ion-exchange resins.

^{31}P $\{^1H\}$ NMR (121 MHz, CD_2Cl_2) δ_P 35.36 (d, $J_{Rh\text{-}P}$= 165.8 Hz). MS (CI^+): m/z calcd. for $C_{71}H_{86}BF_4N_4P_2Rh$ $[M\text{-}BF4]^+$: 1159.5 ; found 1159.5.

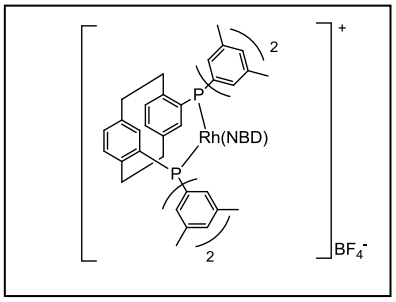
3.6.3.3 {{(*S*)-(+)-Bis[bis(3,5dimethylphenyl)phosphino]-[2.2]-*para*cyclophane} rhodium(I) (COD)}}tetrafluoroborane, (76)



(S)-(+)-4,12-Bis(3,5-dixylyl)-phosphino)-[2.2]-*para*cyclophane (36.2 mg, 0.057 mmol) was dissolved in CH_2Cl_2 (5 ml) and $[Rh(COD)_2]BF_4$ (23.2 mg, 0.057 mmol) was added. The solution was stirred for 30 min and small sample for ^{31}P {1H} NMR was taken to assure that complex formation was complete. Then the solution removed until ~ 2 ml were left and hexane was added. The solution was filtered and off and the precipitate dried under vacuum. This compound is already known and was not further characterised data in good agreement with literature.[31] The solid was further used for immobilisation onto ion exchange resins, see procedure for immobilisation of homogeneous catalysts onto ion-exchange resins.

^{31}P $\{^1H\}$ NMR (121 MHz, CD_2Cl_2) δ_P 33.12 (d, $J_{Rh\text{-}P}$ = 108.9 Hz).

3.6.3.4 {{(*S*)-(+)-Bis[bis(3,5dimethylphenyl)phosphino]-[2.2]-*para*cyclophane}rhodium(I) (NBD)}}tetrafluoroborane, (77)



(S)-(+)-4,12-Bis(3,5-dixylyl)-phosphino)-[2.2]-*para*cyclophane (200 mg, 0.2903 mmol) was dissolved in CH_2Cl_2 (10 ml) and $[Rh(NBD)_2]BF_4$ (108.6 mg, 0.2903 mmol) was added. The solution was stirred for 30 min and small sample for ^{31}P $\{^1H\}$ NMR was taken to assure that complex formation was complete. Then the solution was used immediately for immobilisation onto resins, see procedure for immobilisation of homogeneous catalysts onto ion-exchange resins. This compound is already known and was not further characterised, data is in good agreement with literature.[31]

^{31}P $\{^1H\}$ NMR (121 MHz, CD_2Cl_2) δ_P 36.77 (d, $J_{Rh\text{-}P}$ = 158.51 Hz).

3.6.4 Characterisation data of heterogenised catalysts

All preparation were carried out under inert conditions using either argon or nitrogen atmosphere unless otherwise stated. All solvents used are dry and degassed.

3.6.4.1 Preparation of the resin prior to immobilisation:

The commercially available H^+DOWEX 50WX2-100 strong cation-exchange resin, (3 g) was refluxed for 6 h with deionised water (500 ml) using a Soxhlet apparatus. Subsequently the resin was washed with degassed CH_2Cl_2 (3 x 100 ml), degassed methanol (3 x 100 ml) and dry and degassed diethyl ether (500 ml) and then dried in a stream of nitrogen over night. The obtained resin was then stored under nitrogen or argon atmosphere.

3.6.4.2 Immobilisation of the Rh(I) complexes/Pd complexes on the H^+ 50-DOWEX-100-2 resin

A dry resin H^+ D50WX2 (300 mg, 4.8 meq/g) was left swelling in MeOH (30 ml) and after around 5 minutes the [Rh(COD)(*R*)-(**44**)]BF_4 (55.6 mg, 0.044 mmol) was added and the mixture either slowly stirred of shacked over night for at least 16 hours.

The obtained resin was then washed following the procedure: MeOH (3 x 100 ml), then with hot MeOH (2 x 50 ml) and Et_2O (3 x 50 ml) before the resin was dried over night under either nitrogen or preferably an argon stream for Rh resins. The product was then kept under inert atmosphere. The washing procedure was changed to smaller solvent quantities when smaller amounts of resins were washed.

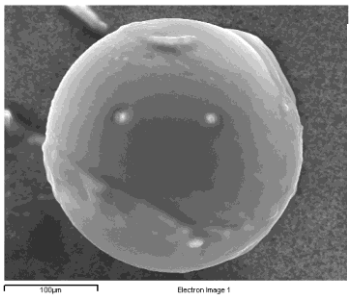
Table 53 SEM-EDX data for heterogenised catalysts and ICP analysis.

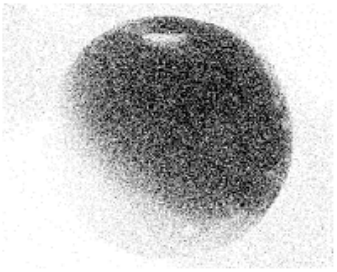
Name of resin catalyst	Homogeneous catalyst immobilised	Metal content EDX (%)	Metal content ICP (%)
DOWEX-**53**-Pd	(**53**)	0.35 (Pd)	0.29
DOWEX-**61**-Pd	(**61**)	1.36 (Pd)	0.60
DOWEX-**48**-Pd	(**48**)	1.35 (Pd)	2.14
Pd-NP	**Pd-nanoparticle**	2.21 (Pd)	n.d.
DOWEX-74-COD	(**74**)	0.70 (Rh)	0.84
DOWEX-75-NBD[a]	(**75**)	0.86 (Rh)	-
Li-DOWEX-74-COD	(**53**) **on Li^+Dowex**	0.35 (Rh)	n.d.
DOWEX-76-COD	(**76**)	1.30 (Rh)	3.35
DOWEX-77-NBD	(**77**)	0.75 (Rh)	n.d.

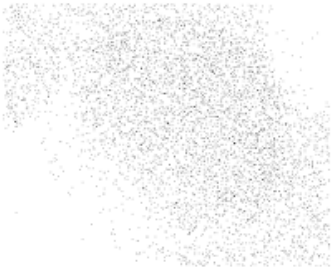
[a] Samples submitted for ICP analysis to CNRS Florence.

3.6.4.3 EDX pictures and mapping data

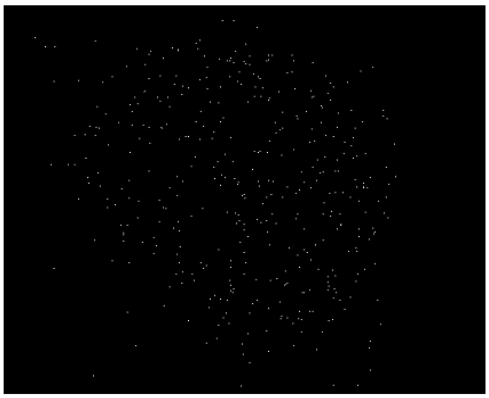
DOWEX-53-Pd

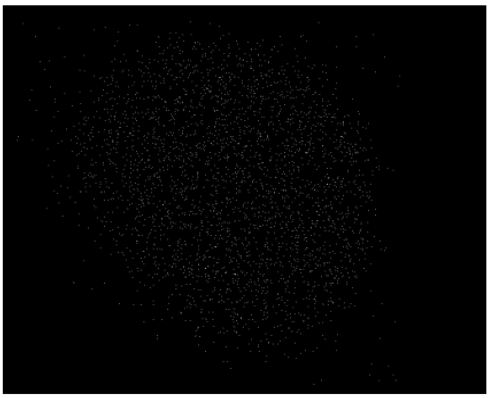



Sulfur Ka1

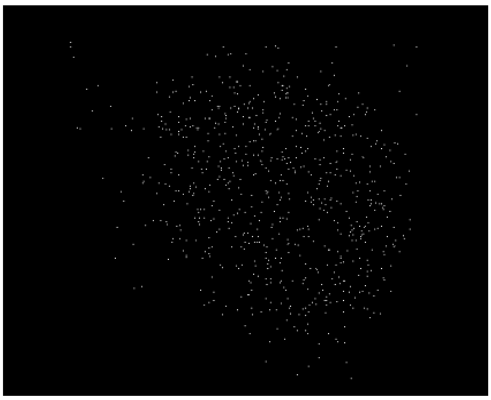

Palladium La1

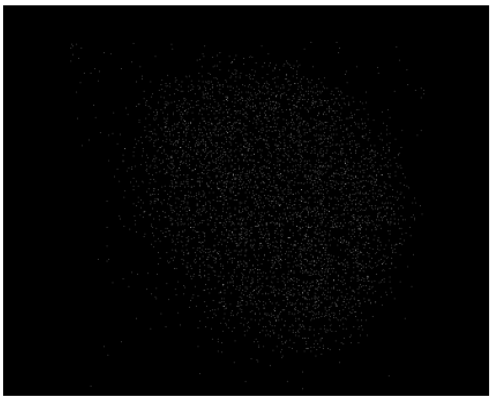
DOWEX-61-Pd


Palladium La1

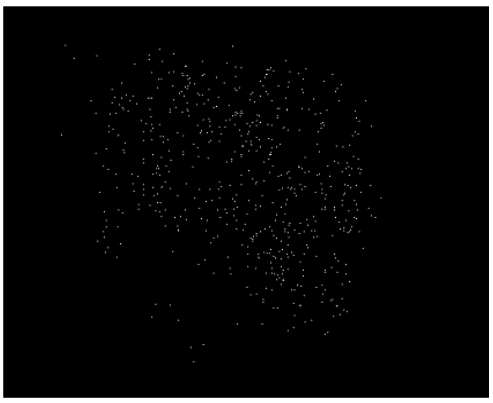

Sulfur Ka1

Pd-NP

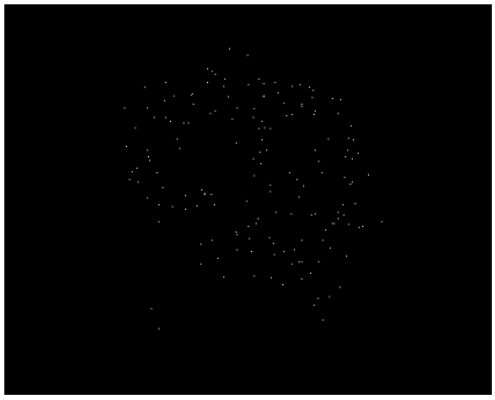

Palladium La1


Sulfur Ka1

DOWEX-48-Pd

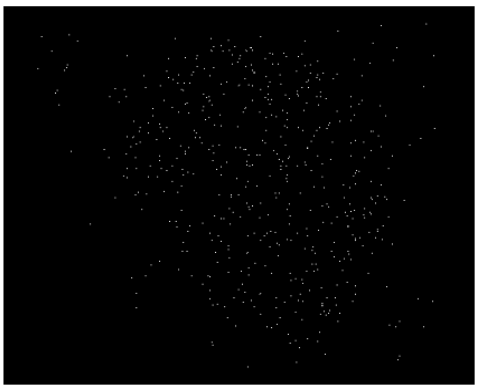


Palladium La1

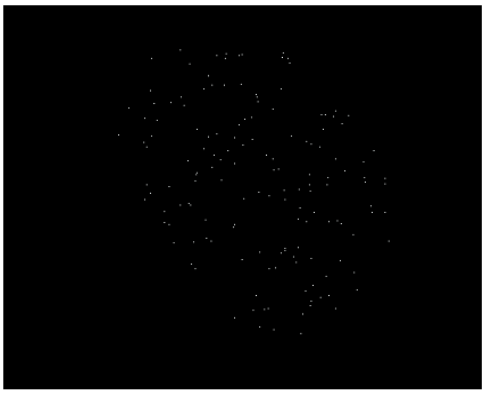


Sulfur Ka1

DOWEX-74-COD-Rh

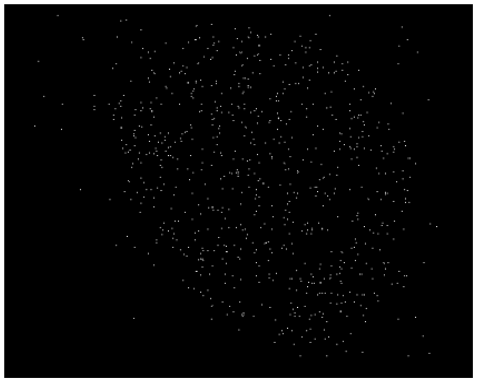


Rhodium La1

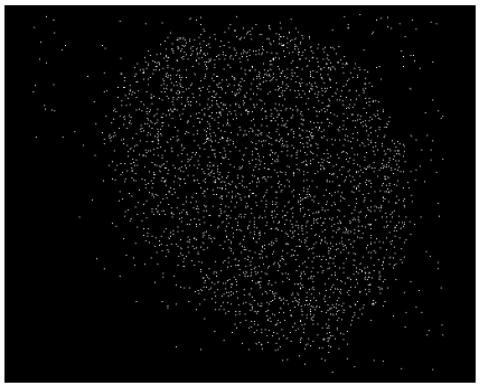


Sulfur Ka1

DOWEX-75-NBD-Rh

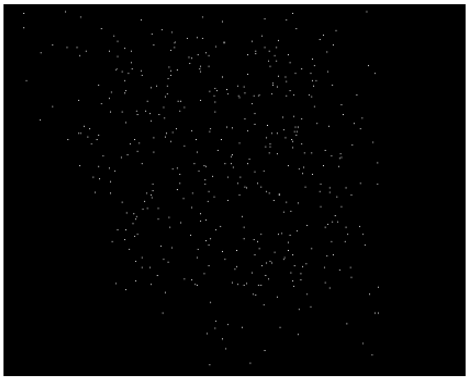


Rhodium La1

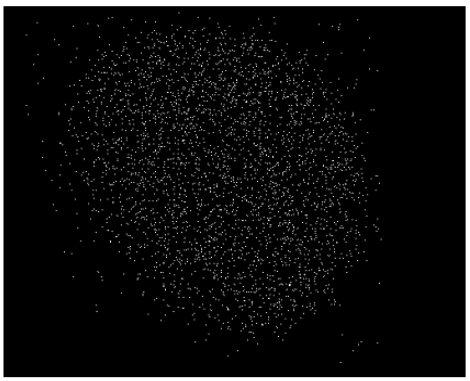


Sulfur Ka1

DOWEX-76-COD-Rh

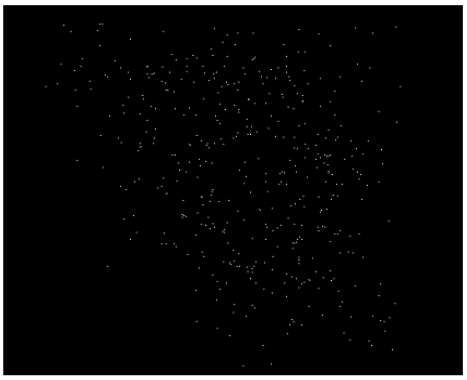


Rhodium La1

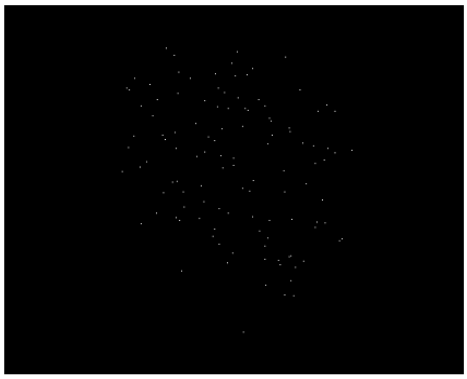


Sulfur Ka1

DOWEX-77-NBD-Rh



Rhodium La1



Sulfur Ka1

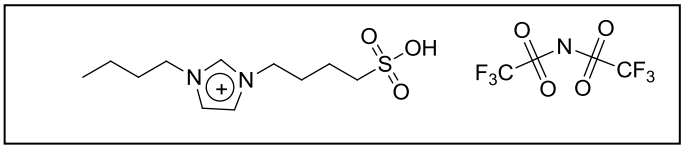
3.6.4.4 Preparation of nanoparticles

The polymeric resin H^+ DOWEX (104.3 mg) was put into a microwave vial and MeOH (3 ml) was added. $Pd(dba)_2$ (11 mg, 0.019 mmol) was partly dissolved in a MeOH/CH_2Cl_2 mix (1 ml) and added to the resin. The vial was transferred to an autoclave and the reaction mixture stirred for 2 hours at 30 bar H_2 pressure. The gas was released and the resin was washed following the general washing procedure above. The palladium content of the resin was determined by EDX. Furthermore was also $PdCl_2$ used to prepare nanoparticle immobilised resins.[16b]

3.6.5 Continuous flow methoxycarbonylation reactions in supercritical CO_2

Silica (Kieselgel Merck type 10184 70-230 mesh, 100 °A poresize) and bis(trifluoromethylsulfonyl)imid were purchased from Aldrich chemical company and used as received without further purification. [BSO_3HBIM][BTA] was synthesised by Mr. Ruben Duque from Prof. Dr. David Cole-Hamiltons group.

3.6.5.1 SILP (Supported Ionic Liquid Phase) preparation, 1-butyl-3-(4-sulfobutyl)imidazolium bis(trifluoromethylsulfonyl)amide [BIMBSO$_3$H][NTf$_2$]



[BSO$_3$BIM] (2.869 g, 11.00 mmol) was dissolved in degassed destilled H_2O (2.5 ml) and bis(trifluoromethylsulfonyl)imid (3.086 g, 11.00 mmol) was added and the solution stirred for 10 min. Then the water was removed under high vacuum and 90 °C for about an hour, leaving colourless oil in quantitative yield. (This compound is not published, compound was first synthesised from Dr. Barthel Engendahl's during his thesis.)

^{1}H NMR (400 MHz, D_2O) δ_H 0.79 (t, ^3J = 8.1 Hz, 3H, CH_3), 1.14-1.23 (m, 2H, CH_2), 1.58-1.66 (m, 2H, CH_2), 1.73 (quin, ^3J = 8.1 Hz, 2H, CH_2), 1.91 (quin, ^3J = 8.1 Hz, 2H, CH_2), 4.06-4.14 (m, 4H, CH_2), 7.39 (s, 2H, CH_2), 8.69 (s, 1H, -NH).

3.6.5.2 Preparation of the SILP

Silica (3.5 g) was put into a dry and inert Schlenk flask and dried under vacuum and heating for 1 hour. Then CH_2Cl_2 (15ml) and [(*R*)-(**61**)] (59.98 mg, 0.0455 mmol) were added and the solution stirred. By syringe [BMIM][NTf$_2$] (1.175 g, 4.219 mmol) and [BSO$_3$HBIM][BTA] (623 mg, 1.150 mmol) were added to the solution and stirred for 15 min. Then the solvent was carefully removed and the SILP dried under vacuum leaving yellow colored silica. The reactor was filled in the Glove box to assure no loss of reactivity due to oxidation, during filling of the reactor.

3.7 References

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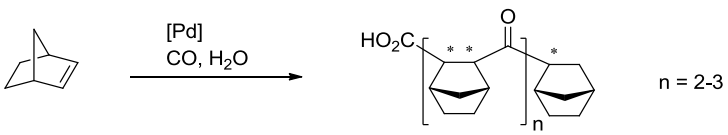
CONCLUDING REMARKS

Hydroxy-and alkoxy-carbonylation have gained increasing impact in the synthesis for commodity compounds. However, asymmetric versions of these reactions are challenging, with low activity, regio- and enantioselectivety. The objective of this work was to improve the catalytic overall performance, with special emphasis on the enhancement of regio- and enantio-selectivity for these reactions, and subsequent, catalyst recycling. Many Pd phosphine systems have been reported for asymmetric hydroxy- and alkoxy-carbonylation of prochiral aryl alkenes, with the best catalytic system reported in literature for hydroxycarbonylation of styrene with an e.e. of 43 % combined with high catalyst loadings (1.6 mol% Pd) and a B/L ratio of 0.8.

During the course of this work new phanephos derived ligands have been prepared and their Pd complexes formed. Novel dipalladium catalyst system were developed and found to be more active and selective catalysts than their monopalladium analogues. With the catalyst systems prepared in this thesis e.e.s up to 81 % for hydroxycarbonylation of styrene and 91 % for methoxycarbonylation were accomplished. By expanding the range of electronically and sterically different phanephos ligands, excellent B/L selectivity of >100:1 was obtained for hydroxy- and methoxy-carbonylations of styrene with enantioselectivities of up to 77% and good activity (>99% conversion in 20 hours at 50-60 °C). In comparison to literature these results are a promising improvement for this type of reaction.

Furthermore other prochiral alkenes have been screened and the mono- and di-palladium catalysts demonstrated that their performance is not only restricted to aryl alkenes. During the hydroxycarbonylation of norbornene an interesting by-product was observed. Electronspray MS suggest these by-products to be a co-polymerised-acid-terminated-dimer and trimer (Scheme 44). Further investigations of these by-products would help to determine the stereochemistry, since an asymmetric oligomerisation process of norbornene would be of interest.



Scheme 44 Catalytic asymmetric oligomerisation of norbornene.

Although the current system already resulted in active, regio- and enantio-selective catalysts supplementary work would be desirable, to further enhance the catalyst activity and selectivity. Also a more detailed study about the substrate scope for other prochiral

alkenes would be highly interesting. Generally mechanistic studies with these phanephos ligands would be of great interest in order to determine the true nature of this active dipalladium catalyst system. So far it is unclear how the second Pd source is influencing activity and selectivity, mechanistic studies would help to elucidate the catalytically active species is indeed a dipalladium species or if a monopalladium species is the active species with the second palladium acting as a co-catalyst. The catalytically active species could have many possibilities, e.g. one possibility would be the [(L-L)Pd_2Cl_2(μ-CO)(μ-H)] (Figure 68 Possible catalytic intermediate.).

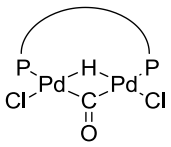


Figure 68 Possible catalytic intermediate.

Yin and co-workers observed that the addition of the co-catalyst $CuCl_2$ increased the selectivity towards the branched acid.[1] It was suggested that MCl_2 (e.g. $CuCl_2$ or $SnCl_2$) may act as chloride acceptor. In order to make a final conclusion and propose a mechanism further mechanistic investigation would be required.

Overall the Pd systems developed have given very promising results and improved the technology available for the asymmetric hydroxy- and alkoxy-carbonylations of alkenes.

The second part of the thesis investigated the recycling of homogeneous catalysts by immobilisation onto solid supports. Numerous different approaches towards immobilised catalysts have been reported in literature to combine the merits of both homogeneous and heterogeneous processes and to facilitate product separation. Catalyst recycling is particularly interesting for reactions where relatively high catalyst loadings are required. In this thesis, ion-exchange as heterogenisation method was investigated, using polymeric acidic resins as the solid support. Very promising results were obtained for the heterogenisation of the homogeneous phanephos type catalysts onto the acidic resins by two different approaches. Heterogenisation was carried out by either ionic interaction *via* the cationic metal centres (cationic Rh complexes) and/or *N*-tagged catalysts (neutral Pd complexes), which were immobilised by simple acid-base chemistry.

Investigations of the heterogenised Rh catalysts showed comparable activity and selectivity as catalyst systems in asymmetric hydrogenations of MMA when compared totheir homogeneous analogues. To determine the necessity of the *N*-tag on the Rh

complex a more detailed substrate screening could help to conclude if immobilisation by cationic metal is strong enough for Rh catalysed alkene hydrogenation reactions.

For neutral Pd complexes, however the *N*-tag was observed to be a requirement in order to recycle the catalysts with low catalyst leaching (over 9 cycles <1 ppm). The heterogenised catalysts were observed to be similarly active and even more enantioselective for asymmetric methoxycarbonylations of styrene in comparison to their exact homogeneous analogues (and similar levels to the best Ph- and Xyl Phanephos catalysts described above).

Another feature of the heterogenised Pd catalysts is that no additional promoters were required in order to obtain good results, allowing the Pd catalysed methoxycarbonylation of styrene to occur with no chloride co-catalyst and with no loss of activity or selectivity.

Heterogenisation was also carried out using acidic SILP systems continuous $scCO_2$ flow. Impressive stability over days was shown for the *N*-tagged homogeneous catalyst in methoxycarbonylation of styrene. Further improvements to catalyst selectivity would be desireable to optimise this process, which could be done by preparing a possibly more selective *N*-functionalised catalyst (see *Appendix*).

This work has greatly improved the homogeneous asymmetric hydroxy- and alkoxy-carbonylation reactions of styrene and immobilisation of these homogeneous catalysts has led to highly active and stable recyleable catalysts.

4.1 References

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APPENDIX

Catalyst Recycling by Molecular Weight Enlargement

Abstract This small chapter summarises projects that have been an important part of the thesis but did not reach a conclusion. A phanephos derived diphosphine ligand with a *N*-moiety in the backbone was designed and successfully prepared. Furthermore have molecular weight enlarged phanephos ligand and catalyst been synthesised with a POSS (polyhedral oligomeric silsesquioxane) functionalisation.

5.1 Introduction

In this *appendix* experiments are summarised that were not fully developed into completed projects, but were an important part of my PhD studies. Since catalyst (**53**) showed great catalytic activity and recycling potential, a more active and selective ligand with *N*-moiety in the backbone was designed and prepared. However, due to many difficulties during the preparation, the completion of this ligand and catalyst was not possible. None-the-less, the results obtained suggest either further optimisation or a modified route to these compounds would be an interesting target for future research.

Another important project in collaboration with Prof. Dr. Dieter Vogt at the Tu/e Eindhoven was carried out. This comprised the preparation of molecular weight enlarged (MWE) ligands and catalysts and their later application in continuous flow nano-filtration reactor. Therefore phanephos derived MWE ligands and catalysts were prepared, although could not be purified sufficiently enough for full characterisation. Optimisation of the catalyst preparation would require more time.

Furthermore chiral Ru phanephos derived (Noyori type) catalysts were successfully prepared and were investigated to see if generally larger molecular weight catalysts would also be compatibile for continuous flow membrane filtration. Preliminary results could be obtained but would require more detailed studies for any significant conclusions.

5.2 Synthesis of *N*-functionalised ligand in the backbone

N-functionalised diphosphine ligands, though more difficult in preparation, gave great results as heterogenised catalysts (*chapter III*). The asymmetric methoxycarbonylation of styrene in the continuous $scCO_2$ flow with (**53**) showed great stability and same regio- and enantio-selectivity as for homogeneous catalysis. It is however necessary to optimise this catalyst to improve the TOF and overall selectivity than achieved with (**53**).

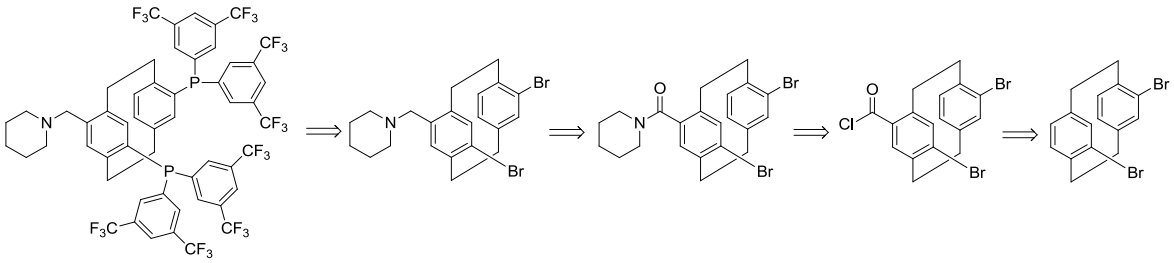
Since the *N*-functionalised catalyst was observed to enable catalyst recycling successfully, functionalisations of the ligand will be conducted again with a tertiary amine.

It would be very desireable to prepare a phanephos type catalyst that does not restrict the phosphine substituents but allows flexible individual alterations for different

reactions. Therefore of great advantage would be to place the *N*-functionality at the backbone rather than at the phosphine moiety. This provides the immobilised catalyst more freedom around the catalytic active centre, avoiding inhibiting effects of closely surrounding groups and also a hopefully more flexible preparation process for individual modifications around the phosphine substituents.

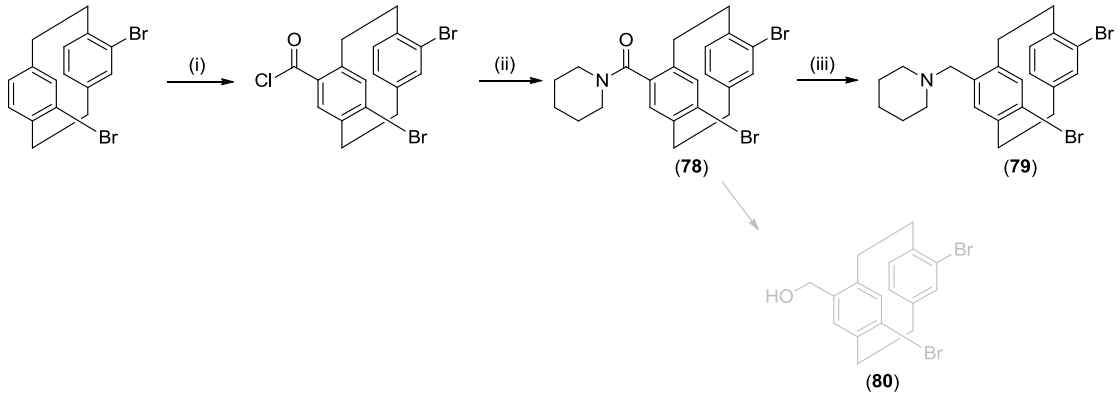
In *chapter II* various phosphine groups were intensively studied and significant improvements for asymmetric hydroxy- and alkoxy-carbonylations could be achieved by preparing phanephos derived ligands with bulky electron withdrawing -CF_3 groups in *meta* position (**70**). This catalyst gave the best overall activity, regio- and enantio-selectivity and was thus selected.

To make as little alterations as possible towards the "general" diphosphine design the piperidinyl group was decided to be attached to the backbone of the cyclophane. The phosphine moiety can therefore be modified to individual requirements by simple lithiation and addition of a variety of $ClPR_2$ (R = alkyl, aryl). The retro-synthetic approach is illustrated in Scheme 45.



Scheme 45 Synthesis pathway of a *N*-tagged ligand in the backbone. The desired phosphine ligand can be prepared from the enantiomerically pure 4,12-dibromo-[2.2]-*para*cyclophane.

The synthesis was started with the preparation of the *N*- group in the backbone first. By using a Friedel-craft-type reaction the acyl chloride was prepared.[1] Further addition of piperidine resulted in a tertiary amide, (*R*)-7-piperidinyl-1-methanone-4,12-dibromo-[2.2]-*para*cyclophane (**78**) (Scheme 46). The very reactive acyl chloride was not further isolated or characterised. Compound (**78**) was obtained in 52 % overall yield, after chromatography on SiO_2. A crystal structure of (**78**) could be obtained by letting the hexane/EtOAc evaporate slowly after the chromatography on SiO_2 (Figure 69).



Scheme 46 The synthesis of a *N*-functionalised 4,12-dibromo[2.2]-*para*cyclophane *via* a Friedels-Craft type reaction. Reaction conditions: (i) $AlCl_3$ (2 equiv.), $(COCl)_2$ (4 equiv.) in CH_2Cl_2; (ii) excess piperidine (50 equiv.) in CH_2Cl_2, column on SiO_2 (5:2 hexane:EtOAc); (iii) BH3*THF (1.3 equiv.) in THF, column on SiO_2 (95:5 CH_2Cl_2:MeOH; 90:10 CH_2Cl_2:MeOH).

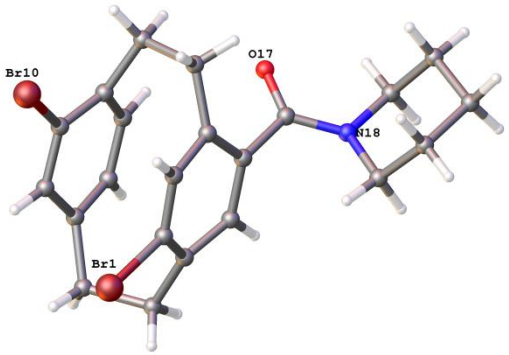


Figure 69 Crystal structure of amide (**78**). Selected bond lengths can be found in the experimental of the *appendix*.

The reduction of the amide was a more difficult task. Various attempts at amide reduction by different approaches were carried out, although with little success. Table 54 and Table 55 roughly summarises different examined reduction methods. The best overall result was achieved when almost equiv. amounts ((**78**)/BH_3 ratio of 1/1.3) of BH_3 to amide was applied. Using higher concentration of BH_3 the by-product formation of the alcohol (**80**) was the main product (Scheme 45). In order to avoid the formation of the un-desired alcohol, lower concentrations of reducing agent are used. After reduction, the product was purified by chromatograpy on SiO_2 and the amide (**78**) collected for further reduction. The amine (*R*)-(-)-4,12-dibromo-7-(methyl-*N*-piperdinyl)-[2.2]-*para*cyclophane (**79**) was obtained from the amide in 38 % isolated yield when (**78**)/ BH_3 ratio was 1/ 1.3.

Table 54 Amide reduction with BH_3*THF solution (m = microwave experiment).

Amide / BH_3	Temp. (°C)	Time (h)	Amide (%)	Amine (%)	Alcohol (%)
1 / 3(m)	100	15 min	-	-	>99
1 / 3.0	65	6	-	34	66
1 / 2.5	r.t. (16 °C)	72	>99	-	-
1 / 2.5	65	6	-	32	68
1 / 1.6	67	6	22	41	37
1 / 1.5	67	6	55	21	24
1 / 1.3	67	6	48	38	15

For more successful reduction of the amide (**78**) a just recently published method was investigated. Beller and co-workers reported an interesting article about using silanes in the presence of zinc acetate catalyst, for the reduction of various amides under very mild conditions.[2] The substrate scope included various aryl amides. However, they did not include any aryl amides with further alkyl groups on the aryl in *ortho* and *meta* position. Many conditions and variations of these zinc/silane catalyst systems were examined and are listed in Table 55. Overall very low induction was observed; in most examples almost no conversions were obtained.

Table 55 Zinc catalysed amide reduction (m= microwave experiment).

$Zn(OAc)/(EtO)_3SiH$/ amine	Temp. (°C)	Time (h)	Amide (%)	Amine (%)	Alcohol (%)
0.1/3/1	r. t.	24	>99	-	-
0.1/3/1	65	24	97	3	-
0.1/3/1	100 (m)	15	>99	-	-
0.1/3/1	100 (m)	30	>99	-	-
0.8/25/1	50	24	95	5	-

Reduction was further carried out with the (**78**)/BH_3 ratio of 1/1.3. A crystal structure of the side-product was obtained (Figure 70).

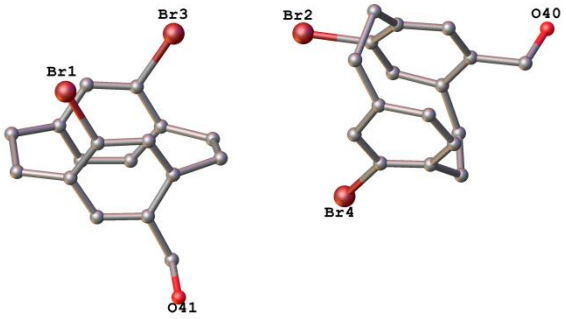


Figure 70 Crystal structure of the by-product observed for the reduction of compound (**80**). Protons removed for clarity.

The synthesis of the diphosphine ligand (**70**), with no *N*-functionalisation in the backbone was prepared *via* lithiation of 4,12-dibromo-[2.2]-*para*cyclophane and addition of the R_2PCl (R = 3,5 CF_3-C_6H_3), yielding the diphosphine (**70**) in high yields (93 %) (*experimental II*).

The (*R*)-(-)-4,12-dibromo-7-(methyl-*N*-piperdinyl)-[2.2]-*para*cyclophane (**79**) was lithiated in Et_2O for ~3 hours at room temperature (16 °C), the bis(bis(trifluoromethyl)phenylphosphine)chloride was dissolved in Et_2O and added at room temperature also. The solution was stirred overnight. ^{31}P $\{^1H\}$ NMR spectroscopy (crude NMR) displayed two single peaks at 0.58 (s) and -0.55 (s), which were assigned to ligand (*R*)-4,12-Bis(3,5-bis(trifluoromethyl)phenyl)phosphino-7-(methyl-*N*-piperdinyl)-[2.2]-*para*cyclophane (**81**). The ligand was obtained in reasonable purity according to ^{31}P $\{^1H\}$ NMR spectroscopy; however a work up was still necessary. After MeOH addition for quenching any left *n*-BuLi, the solvent was then removed and ligand (**81**) was attempted to dissolve in hexane but was insoluble. This was quite surprising since a similar behaviour never was observed for (**70**), which consists of 4 amine functionalities. After removal of hexane, CH_2Cl_2 was added and ligand (**81**) observed to neither be soluble (checked in ^{31}P $\{^1H\}$ NMR).

It was suspected that maybe the nitrogen was protonated, and therefore compound (**81**) was insoluble in organic solvents. Before immobilising onto any solid supports the theory was examined first in a 2 phase experiment. Therefore (**53**) was dissolved in CH_2Cl_2 and a ^{31}P $\{^1H\}$ NMR carried out, and was then extracted with an HCl_{aqu} solution. After phase separation another ^{31}P $\{^1H\}$ NMR was conducted of both the CH_2Cl_2 phase and HCl_{aqu} phase, with the result of compound (**53**) fully protonated in the HCl_{aqu} solution and no peak visible anymore in the CH_2Cl_2 phase.

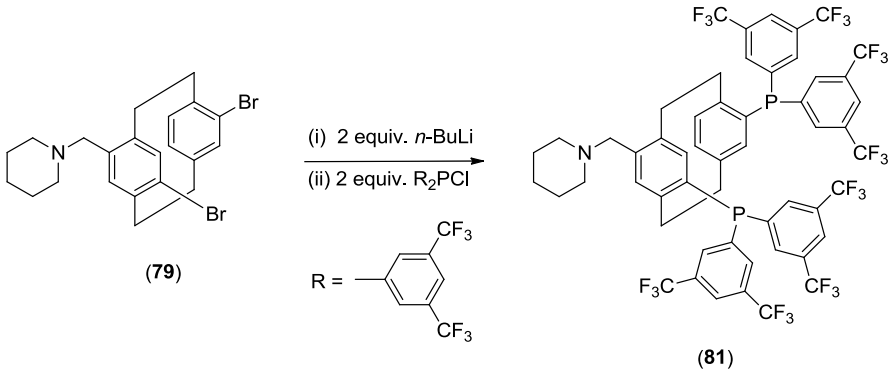
Thus further attempts to purify compound (**81**) used an extractive work up with aqueous $NaHCO_3$ solution and CH_2Cl_2. Although everything was carried out in degassed

solvents and under inert conditions, diphosphine (**81**) was oxidised, as judged by ^{31}P {^{1}H} NMR.

Even though work up was not accomplished, prior to work up, the compound was also characterised by MS, confirming the molecular species of (**81**).

Various attempts to repeat this experiment were carried out. However all preparations resulted in the formation of 2 doublets in the ^{31}P {^{1}H} NMR spectroscopy at 31.38 ppm (d) and -27.08 (d) as either the main product, or present in large amounts. These peaks can be assigned to the rearrangement product of the chlorophosphine, of the P-P=O formation. The coupling constant of these 2 doublets was observed $J_{P\text{-}P}$ = 208.10 Hz, which are characteristic for this arrangements.[3] The coupling constants $J_{P\text{-}P}$ = 211.8 Hz was observed and reported for a typical P-P=O compound.

In order to control this rearrangement product, temperature was lowered. The reaction was carried out at -78 °C and indeed found to decrease the by-product formation but only partly.

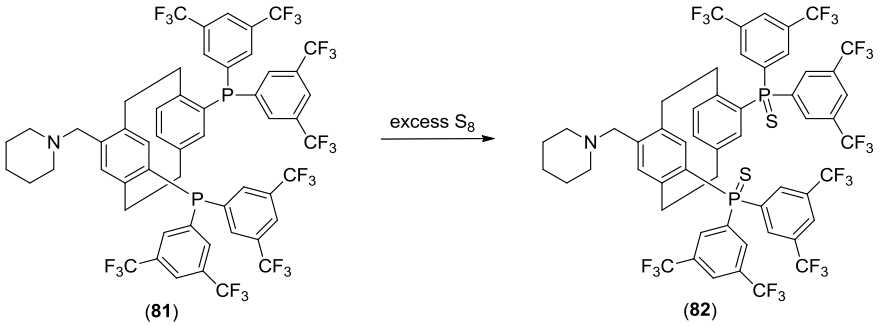


Scheme 47 Preparation of fluorinated phosphine ligand from the *N*-functionalised 4,12-dibromo-[2.2]-paracyclophane. Reaction conditions: (i) *n*-BuLi (2 equiv.) in Et_2O at room temperature; (ii) R_2PCl (2 equiv.) in Et_2O at room temperature.

To purify the crude product the phosphorus moiety needed to be protected first. Protection by BH_3 was observed unsuccessfully in early studies for nitrogen containing phosphines, therefore a different method for protection was considered. This was done by following a procedure reported by Knochel in 2007.[4] They prepared disphosphine phanephos derived ligands with two different PAr_2 groups (PPh_2, $PXyl_2$) and observed the protection and de-protection with sulfur to give good yields. Protection of the phosphine made the overall handling much easier, and allows purifying the phosphine *via* chromatography on SiO_2 under no special conditions. The crude diphosphine (**81**) was treated with S_8 overnight and two singlets at 35.59 ppm and 35.23 ppm were consistent

with the preparation of phosphine sulphide. Furthermore MS confirmed the sulfonated diphosphine compound (**82**). Purification of the diphosphine by chromatography on SiO_2 was attempted with varying solvent mixtures (columned gradually starting with very apolar to polar mixtures: hexane 100; hexane/Et_2O 70:30; hexane/Et_2O 50/50; CH_2Cl_2). However, a clean sample could not be obtained.

Due to several difficult reaction steps and their optimisation, the diphosphine ligand (**81**) could not be finished on time and would require further work.



(**81**) (**82**)

Scheme 48 Protection by sulfonation of the phosphines, was achieved by addition of S_8.

Preliminary preparation attempts failed to yield a clean enough sample of the *N*-tagged ligand for full characterisation data. Although synthetic difficulties retarded initial synthesis tries, this compound is still of great interest. Once the synthetic route is established, this backbone allowes an easy access to a wide variety of phosphine moieties.

5.3 Membrane filtration as a great opportunity for catalyst recycling[2]

In *chapter I* the approach for recycling a homogeneous catalyst by ion exchange in particular ion-exchange resins, was discussed in more detail. In *chapter III* reactions were carried out by heterogenising molecular catalysts onto acidic polymeric resins and acidic SILP systems as solid supports. Pros and cons have been discussed and experimentally investigated.

A very different approach and great alternative for homogeneous catalyst recycling is by filtration. This can easily be done *via* filtration of molecular weight enlarged (MWE) compounds using a nano-filtration membrane.

The preparation of size enlarged homogeneous catalysts has gained attention for many years, performing catalyst recovery and reuse *via* a new course by separation by

2 This work was carried out in Eindhoven TU/e in collaboration with Prof. Dr. Dieter Vogt. Due to the limited amount of the placement only preliminary results could be achieved.

size. MWE of homogeneous catalyst can be achieved by simply attaching soluble molecular weight enlargement units onto the desired catalyst. These soluble support units comprise dendrimer[5], dendron[6], polymer[7], dendronised polymer[8] and the most recent appliances are polyhedral oligomeric silsesquioxane (POSS)[9]. These MWE compounds have been investigated for many years and have been studied in homogeneous catalysis, each support providing their individual advantages and disadvantages.[10]

The design of a MWE catalyst is usually fairly simple; a well-performing ligand is choosen and equipped with a soluble support. This can be done by functionalising the ligand system and the soluble support and combining them in a preferably straight forward and clean reaction.

These catalysts can generally be recycled by precipitation, nano-filtration or ultra-centifugation, however nano-filtration has been observed to be quite useful for homogeneous catalyst recycling leading to cleaner product solutions.

Nano-filtration (size distributions between 0.5 to 8 nm) is of particular interest. Because the catalysts are in the same phase as the products, catalysis can be carried out in one phase, which allows processing the reaction in continuous flow mode.

First attempts for nano-filtration were carried out already in 1970s with enzymes in membrane reactors. The catalyst remains entrapped whereas new substrate solution can be added and products separated easily from the catalyst solution.

Silicon oxide cages, such as polysilsesquioxane (POSS) have been observed very useful for catalyst enlargement and have shown great use in continuous flow nano-filtration reactor.[11]

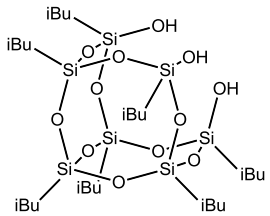


Figure 71 Poysilsesquioxane

Many more important factors such as the membrane type (ceramic or polymeric), pressure gradients onto the membrane will not be discussed in further detail, however can be found in references noted.[12]

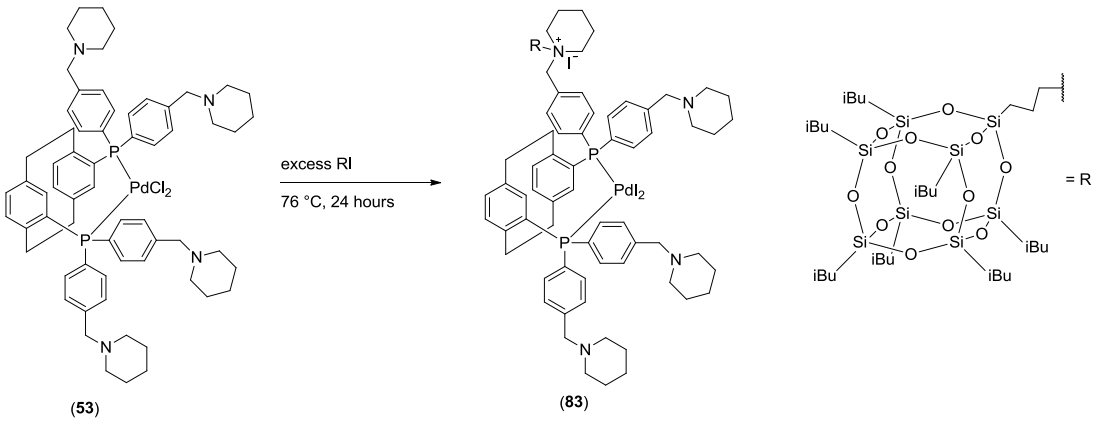
Vogt and co-workers recently showed the successful application of continuous flow nano-filtration for combining POSS ligands and nano-filtration in a loop reactor. They

successfully synthesised a POSS enlarged triphenylphosphine ligand and studied the activity and selectivity in Rh catalysed hydroformylation of 1-octene.[11] High activity, stability and retention of this POSS ligand for 13 days with no significant loss of activity or leaching of the catalyst was observed, due to the continuous application in a continuous flow membrane loop reactor. The Rh leaching was only 0.045 % which proved the catalyst was retained very well throughout the reaction. The reactor uses a TiO_2 membrane with a cut-off volume of 900 g/mol. This allows the substrate/product easy access to the catalyst and the product to be filtered off.

In this *appendix* the preparation of POSS modified phanephos catalysts are reported. Furthermore unmodified Rh and Ru (Noyori type) phanephos, with high molecular weights have been synthesised and examined briefly in the continuous flow membrane loop reactor.

5.3.1 Synthesis of catalysts with high molecular weights

The preparation of molecular weight enlarged molecules was carried out *via* 2 different approaches. 1) Alkylation of the amine functionality of catalyst (**53**) with a halide POSS compound and 2) the preparation of a PhanePOSS ligand with 4 POSS groups on the phosphine moiety.[1]



(**53**) (**83**)

Scheme 49 Preparation of POSS functionalised Pd(II) catalysts. Halogen exchange between the RI compound and $PdCl_2$ resulted a PdI_2 complex.

Alkylation of the amine functionality was conducted by adding monopalladium catalyst (**53**) and the $POSSCH_2CH_2CH_2I$ (POSS-I) compound in a catalyst/POSS-I ratio of 1/1. A halogen exchange reaction occurred between the chloride anions from $PdCl_2$ of (**53**) with the iodide anions of the POSS compound. Due to this halogen exchange reaction

no alkylation of compound (**53**) was observed, using POSS-I/(**53**) ratio's near 1. This can be attributed to the low alkylation potential of alkyl chlorides.

Table 56 Alkylation attempts of the amine functionality of homogeneous catalyst (**53**) with the POSS$CH_2CH_2CH_2I$ (POSS-I).

POSSI/(**53**)	solvent	Time (h)	Temperature (°C)	^{31}P {^1H} NMR (ppm)
1/1	toluene	24	r. t.	42.1(**53**)
1/1	toluene	1	80	42.1(**53**)
1/1	toluene	1	100	42.3(**53**)
1.1/1	toluene	10	130(mv)	42.0(**53**)
11/1	toluene	24	90	37.0(**83**)
10/1	Me-THF	24	76	35.6(**83**)

When alkylation attempts of (**53**) were conducted with higher (**53**)/POSS-I ratios, such as 10/1 the desired alkylated POSS with Pd(II)I_2 (**83**)was obtained. The compound was converted quantitatively, however due to the excess of alkylation reagent; removal of excess POSSI was more problematic. Generally, purification of MWE compounds are known for their sometimes rather difficult work up procedures. In some cases purification can even be an impossible task.

MALDI-TOF confirms the compound (**83**) as the main product, however higher molecular weights present could not be assigned to any specific compounds, such as compound **7mo** with 2 POSS, 3 POSS and so on.

The POSSification of more than one nitrogen seems unlikely, since otherwise further peaks in the ^{31}P {^1H} NMR would have been expected.

Several different work-up processes have been investigated. First attempts were carried out by separating with different solvents; however POSS compounds was observed to be soluble and insoluble in the same solvents. Generally have POSS compounds been observed to be tricky for purification, since the compound properties hardly vary at all.

Further attempts of separating the POSS compounds by filtration *via* dialysis tubing with a molecular cut off weight of smaller than 2000 Dalton was attempted. However, it did not separate the compound good enough to allow full characterisation. Furthermore size exclusion chromatography (SEC) was performed in CH_2Cl_2 under inert conditions and even though the product was columned twice the compound was still impure.

Preliminary catalytic studies in methoxycarbonylation of styrene with the impure catalyst (**83**) were conducted, results are summarised in Table 57.

The catalytic activity of POSS functionalised Pd complex (**83**) was tested in asymmetric methoxy- and hydroxy-carbonylation reaction of styrene. Although the catalyst was still impure the catalyst activity was briefly studied. It should be noted that catalyst activity could be influenced by the presence of other un-identified compounds. Overall decreased B/L ratios and activities were obtained with the MWE catalyst. The enantiomeric excess however was observed enhanced for POSS catalysts in hydroxy- and methoxy-carbonylations.

Also it is important to note that the anion in the MWE catalysts was iodide, whereas in the homogeneous catalysis chloride anions were present.

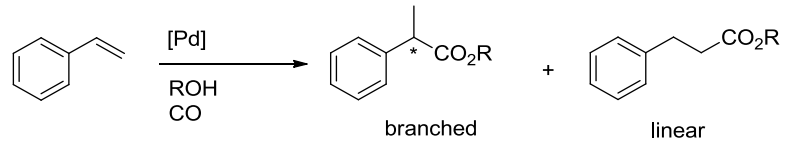


Table 57 Preliminary studies for asymmetric hydroxy- and methoxy-carbonylation reactions of styrene with MWE phanephos derived (**83**) catalyst and a S/Pd ratio of 400/1.

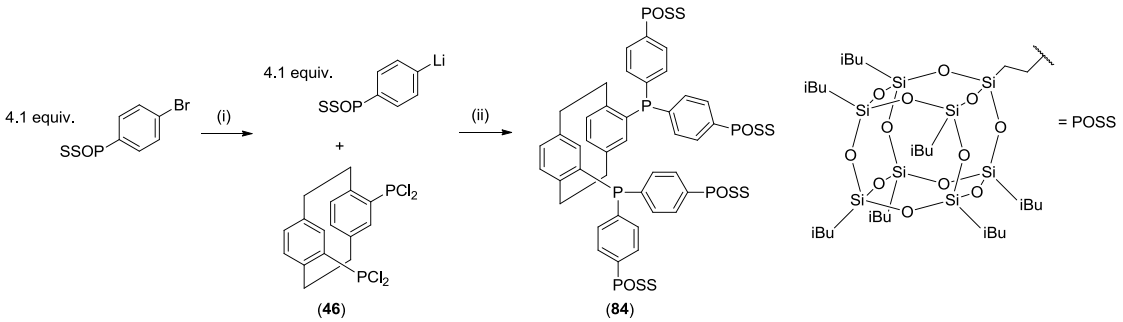
Entry[a]	Nucleophile	Time (h)	Temp. (°C)	Conv.[c] (%)	B/L[d]	e.e.[d] (%)
1	MeOH	20	60	12	0.7	54
2[e]	MeOH	24	60	>99	1.3	42
3[f]	MeOH	24	75	45	0.5	39
4[g]	H_2O	20	60	<2	0.5	44
5[h]	H_2O	22	60	>99	0.7	33

[a] Asymmetric catalysis was carried out using 0.2 mol% catalyst in 1.5 ml MeOH, 1.0 mmol Styrene with 0.20 mmol LiCl and *p*-TsOH*H_2O at 60 °C in 20 hours. [b] Catalyst amount was calculated by ^{1}H NMR due to product impurity. [c] Conversions were determined by ^{1}H NMR spectroscopy, with Et_4Si as internal standard. [d] B/L ratio and e.e. were determined by chiral GC. [e] Homogeneous phase methoxycarbonylation, Pd/S ratio was 1/100 other conditions as described for methoxycarbonylation. [f] An excess of LiCl (2.4 mmol) was added to the reaction solution. [g] Hydroxycarbonylation reaction carried out in 1.5 ml 2-butanone and 1.8 mmol H_2O. [h] Homogeneous phase hydroxycarbonylation of styrene, S/Pd ratio was 100/1 other conditions as described for hydroxycarbonylation.

Previous studies carried out in this group (*chapter I*, Figure 8) showed that when conducting catalysis with an iodide anion source instead of chloride, the overall catalyst activity and B/L ratio decreased significantly. Whereas in a study conducted by Claver

and co-workers the iodide anion, as HI, was observed to significantly increase activity and B/L ratio of the diphosphine catalyst (*chapter I*, Figure 7). Thus no trend can be noted about the reaction outcome when using different promoter sources.

For such low catalyst loadings and impurity of catalyst the activity compared to homogeneous catalyst in methoxycarbonylations of styrene would most certainly be of great interest for continuous flow reactor studies; however purification of the catalyst is necessary.



Scheme 50 The synthesis of a POSS enlarged Phanephos ligand. Reaction conditions: (i) 4-Br(C_6H_4)CH_2CH_2POSS (4.0 equiv.) was lithiated *via* *t*-BuLi (4.1 equiv.) THF at -78 °C; (ii) 4-Li(C_6H_4)CH_2CH_2POSS (4.0 equiv.) and (**46**) (4.0 equiv.) slowly added at -78 °C and stirred for 1 h.

The preparation of the MWE phanephos ligands with the POSS unit on the phosphorus moiety was carried out as shown in Scheme 50. The 4,12-bis(dichlorophosphino)-[2.2]-*para*cyclophane was prepared as described in Scheme 1 of *chapter II*. It is important to note that the procedure shown in Scheme 50 has been published before in Michele Jansen's PhD thesis, at the Tu/e Eindhoven, using the chlorophosphine of the xantphos backbone. The 4-bromophenylethylPOSS compound was reacted with *t*-BuLi in THF at -78 °C and left stirring for 1 hour. The chlorophosphine was dissolved in THF and slowly added to the lithiated POSS. After addition was finished the solution was stirred for another hour at -78 °C and then slowly warmed up to r. t. over night.

First approaches to the PhanePOSS ligand were carried out by many unsuccessful attempts to form the corresponding Grignard of the 4-bromophenylethylPOSS and so did lithiation attempts with *n*-BuLi.

In the ^{31}P $\{^1H\}$ NMR the crude product gave a shift at 4.47 ppm which is slightly downfield shifted in comparison to the phanephos ligand (**38**) which is observed at -0.53 ppm. Work up of the diphosphine ligand was similarly problematic as observed for complex (**83**). It therefore was not possible to obtain "PhanePOSS" in high purity.

5.3.1.1 Conclusions and further work

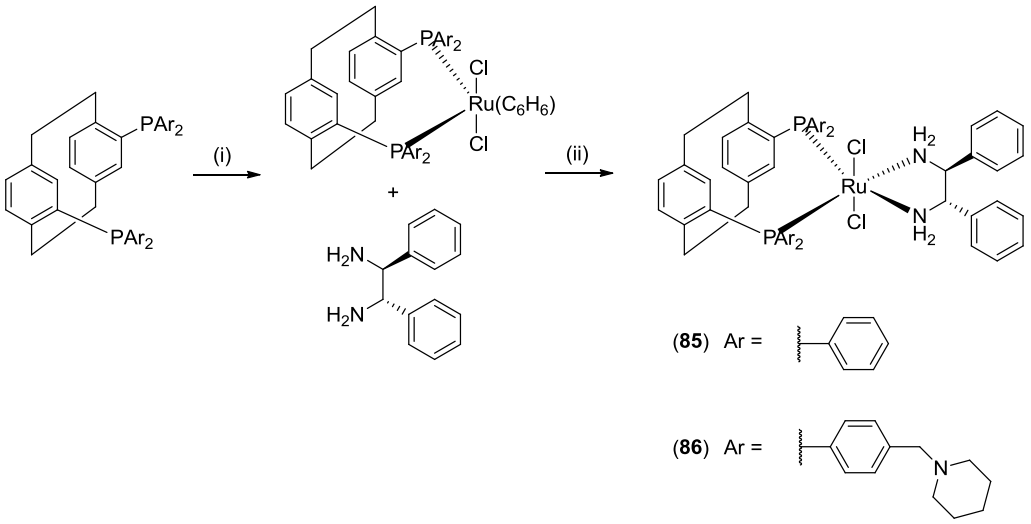
A POSS modified palladium complex (**83**) and ligand (**84**) have been prepared, but could not be purified. The POSS molecular weight enlargement catalyst (**84**) has been observed to not influence the catalytic activity in comparison to the catalyst (**53**) in methoxycarbonylation of styrene; although only preliminary reactions were carried out due to the impurity of the POSS by-products. Also further optimisation of the general catalyst design are necessary to syntheses a more active and selective catalyst for catalysis in continuous flow nano-filtration reactor. Phanephos type catalysts are very successful and highly active in many different catalytic reactions, and therefore could contribute to even better catalytic systems for recycling by nano-filtration.

5.3.2 Phanephos derived ruthenium catalyst

Furthermore of interest was the examining of chiral Ru complexes in continuous flow membrane nano-filtration reactor. Thus also phanephos derived Ru catalysts were prepared.

Since the immobilisation of the *N*-functionalised catalyst required acidic conditions to be tethered to the solid supports, reactions requiring basic conditions can therefore not be applied using these ionic solid supported catalysts. However, we envisaged that either the quaternisation reactions with POSS-I or the direct use of what is already a very large catalyst may be possible.

Phanephos type Ru Noyori type catalysts of ligand (**38**) and (**44**) were prepared as shown in Scheme 51 and examined in asymmetric hydrogenation reactions of acetophenone. Catalyst (**85**) is already known in literature.[13]



Scheme 51 The preparation of ruthenium Noyori type catalysts. Reaction conditions: (i) $[RuCl_2(C_6H_6)_2]_2$ (0.5 equiv.) in toluene/DMF in microwave (1 h, 150 °C); (ii) (*R*,*R*)-dpen (1 equiv.) in toluene added to solution and microwaved (1 h, 150 °C).

Furthermore ruthenium (Noyori type) catalysts (**85**) and (**86**) have been successfully prepared. The idea was due to their already very high molecular weight and 3-dimensionally steric structure; the catalysts might be retained by the membrane, without the use of POSS substituents.

Although only preliminary results for hydrogenation reactions in the CF membrane reactor were conducted this represents an interesting approach towards a new catalyst system.

Prior to reactions in the continuous flow reactions their kinetic status was evaluated by batch reactions carrying out a reaction profile. Based on batch experiments carried out prior to experiments in the continuous flow reactor, the reaction kinetics was calculated and the expected conversions for the reactor calculated, assuming the catalyst and reaction conditions behave ideally. Figure 72 and Figure 73 summarise briefly preliminary obtained results in CF membrane catalysis. A schematic representation of the reactor set-up is presented in Image 4.

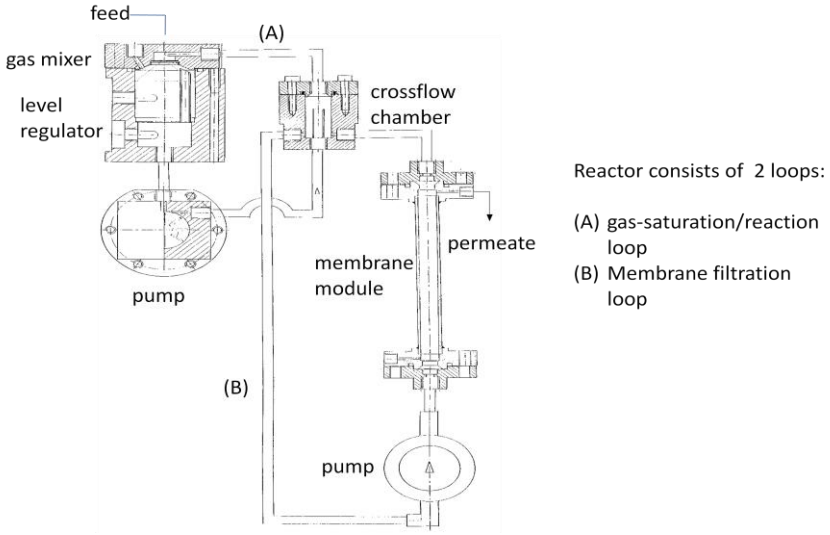


Image 4 Schematic representation of the nano-filtration continuous flow membrane reactor. (Picture from Michèle Janssen's thesis, image presented with permission) description was added.

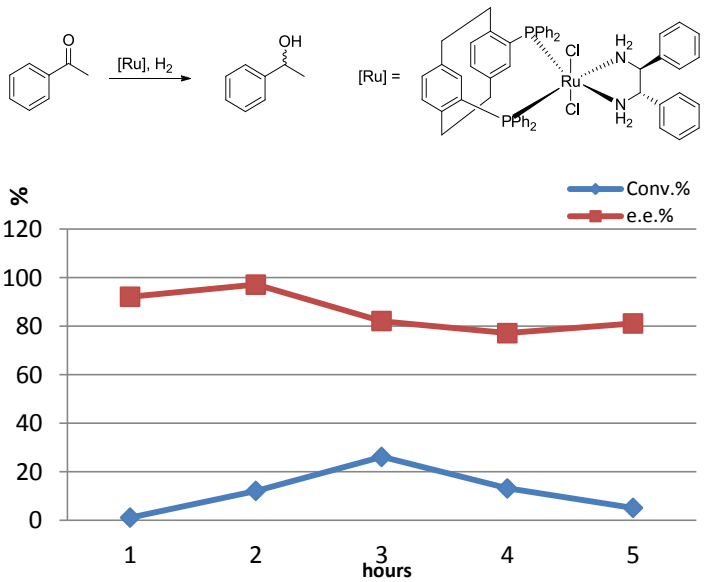


Figure 72 Asymmetric hydrogenation of acetophenone with catalyst (**85**) in a continuous flow reactor. S/Ru ratio was 35000/1.

The catalytic performance of the Ru catalyst (**85**) for asymmetric hydrogenation of acetophenone was investigated in the continuous membrane flow reactor. A substrate to catalyst loading of 35 000/1 was applied. The conversions never exceeded more than 22 % and the enantiomeric excess was observed comparable to the results obtained for batch reactions (Figure 72). Low catalyst acitivity could be due to the decreasing amounts of base in the reactor, perhaps activity could be retained by frequent addition of base into

the reactor or a higher initial concentration. Further investigations are required for any conclusions.

Also Rh catalyst (**74**) was examined in the continuous flow membrane reactor for the asymmetric hydrogenation of methyl-2-acetamidoacrylate. A substrate to catalyst loading of 10 000/1 was applied. In this initial attempt only racemic product was obtained and also conversions were only around 12% (Figure 73). The low catalyst activity and selectivity could be due to insufficiently dried and degassed solvents, and possibly more inert reactor conditions could be required. However, to make a clear statement further experiments are essential.

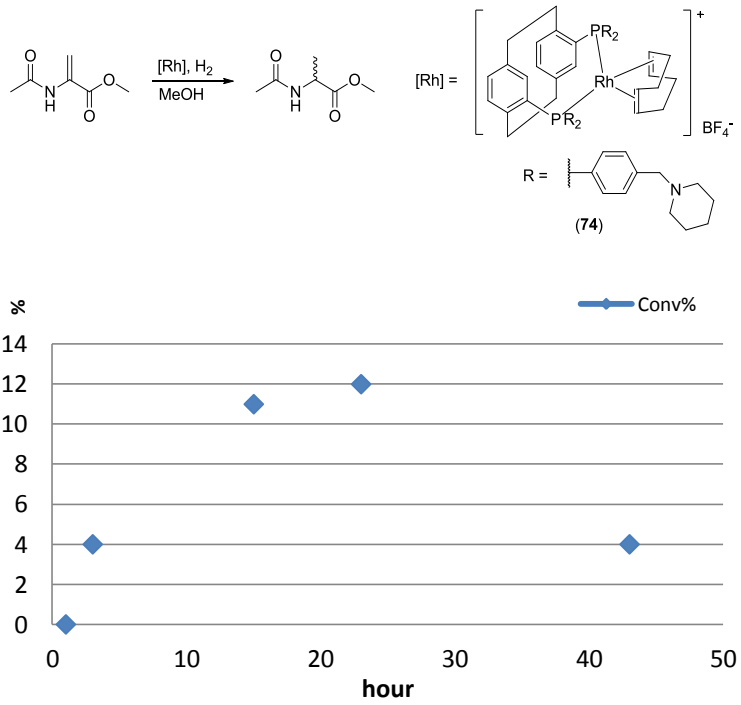


Figure 73 Asymmetric hydrogenation of MAA in a continuous flow membrane reactor with a S/Rh ratio of 10 000/1. The reaction was carried out at 10 bar H_2 and 30 °C. Enantiomeric excess was ~12 %, almost racemic.

Although first results in continuous flow membrane reactor have been less successful, further investigation for this catalytic process with this technology would be of great interest. The continuous flow membrane technique could provide an economical catalytic process for commercial applications.

5.4 Experimental Appendix

5.4.1 Instrumentation and Chemicals

Materials (*R*)- and (*S*)-4,12-dibromo[2.2]-*para*cyclophane was a donation from Chiraltech and used as received. (*R*)-4,12-Bis[diphenylphosphino]-[2.2]-*para*cyclophane ((*R*)-(+)- Ph-PHANEPHOS) were purchased from Aldrich chemical company or as a donation by Chirotech and used as received without further purification, after checking optical rotation data with the literature. $[RuCl_2(C_6H_6)_2]_2$, (1*S*,2*S*)-(-)-DPEN, acetophenone, piperidine (99.8 %), $AlCl_3$, oxalylic acid were obtained from Aldrich and used as received. 2-methylacetamidoacrylate (MMA) was obtained from Alfa Aesar. POSS compounds were a donation by Hybrid Catalysis B. V.. Flash column chromatography (eluents given in brackets) was performed using Davasil silica gel Fluorochem 60 Å particle size 40-63µm and normal grade solvents. Thin-layer chromatography (TLC) was performed on pre-coated Aldrich TLC plates, POLYGRAM SIL G/UV_{254}.

5.4.2 Catalysis

5.4.3 General procedure for hydrogenation of acetophenone

Hydrogenation reaction was carried out in a stainless steel autoclave which was equipped with temperature sensor, dropping funnel and sample outlet valve. The autoclave was evacuated and filled with argon 5 times. The catalyst solution (5 mg, 0.004 mmol) was placed into the autoclave by syring. A solution of potassium *t*-butoxide in *i*-PrOH (37 µl, 0.04 mmol, 1.0 M in *i*-PrOH) anhydrous *i*-PrOH (1.0 ml) was added *via* syringe. The dropping funnel of the autoclave when then charged with acetophenone (440 mg, 3.662 mmol). The autoclave was then charged 5 times to 10 bar of H_2 and vented 5 times before the pressure in the vessel was brought to 10 bar and 24 °C. Samples were taken in regular intervals until reaction reached full conversion.
The enantiomeric excess was determined by HPLC, using a Chiracel OD-H column, 0.5 ml/min, 95:5 hexane: *i*-PrOH; t_R[(+)-*R*] = 17.5 min, t_R[(-)-*S*] = 21.7 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.41 (d, *J* = 4.0 Hz, 3H, C*H*$_3$), 1.62 (br s, 1H, O*H*), 4.80 (q, *J* = 8.0 Hz, 1H, C*H*-OH), 7.17-7.21 (m, 1H, $C_{Ar}H$), 7.25-7.30 (m, 4H, $C_{Ar}H$). MS EI$^+$: m/z 122.15 (M^+ requires 122.07). $[\alpha]_D$ = +42.27 (c = 1.01, $CHCl_3$; 88% (*R*)). {Lit[166]. $[\alpha]_D$ = +42.0 (c = 1.04, $CHCl_3$; 87% (*R*))}.

5.4.4 General procedure for hydrogenation in continuous flow membrane reactor

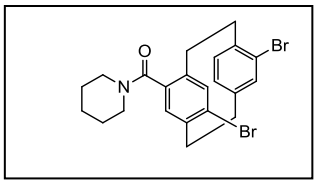
Before use, the reactor was washed with toluene and MeOH for alkene hydrogenation. Then the reactor was filled with Argon and MAA solution (0.150 M) was pumped into the reactor. The Rh catalyst (**74**) (4.2 mg, 0.003 mmol) dissolved in MeOH were filled into the dropping funnel of the reactor. The reaction was carried purged 5 times with 10 bar H_2 pressure and put to a reaction pressure of 15 bar. The catalyst solution was added to the reactor (t = 0). The reaction was carried out for 43 hours at 26 °C, after catalytic activity decreased the reactor was switched off. Conversions and enantioselectivities were determined by chiral GC described before.

5.4.5 General procedure for hydrogenation in continuous flow membrane reactor

Before use, the reactor was washed with toluene and then *i*-PrOH for ketone hydrogenation reactions. Then the reactor was filled with Argon and acetophenone solution (0.97 M) was pumped into the reactor. The Ru catalyst (**86**) (6 mg, 0.006 mmol) dissolved in *i*-PrOH/THF mix (2:1) and potassium *t*-butoxide in *i*-PrOH (2 ml, 1M in THF) were filled into the dropping funnel of the reactor. The reaction was carried purged 5 times with 10 bar H_2 pressure and the final pressure to 10 bar. The catalyst solution was added to the reactor (t = 0). The reaction was carried out for 5 hours at 30 °C and after a decrease in activity was noted the reactor was stopped. Conversions were determined by GC and enantioselectivities by chiral HPLC as described by previous methodes.

5.4.6 Synthesis

5.4.6.1 (*R*)-(-)-4,12-dibromo-7-piperidinyl-1-methanone-[2.2]-*para*cycoophane, (**78**)

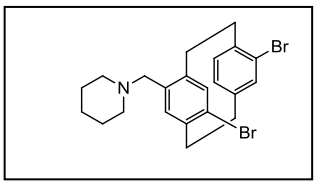


$AlCl_3$ (710 mg, 5.32 mmol) was dissolved in CH_2Cl_2 (10 ml) and stirred for 30 minutes and oxalyl chloride (0.96 ml, 11.15 mmol) was added dropwise and stirred for further 30 minutes. A solution of (*R*)-4,12-dibromo-[2.2]-*para*cyclophane (1.01 g, 2.73 mmol) in CH_2Cl_2 (8 ml) was then added slowly at 0 °C (ice bath) and stirred for 30 minutes. Then the solution was stirred for another hour at room temperature, the solvents removed and resulting residue used without further purification.

(*R*)-(-)-7-chlorocarbonyl-4,12-dibromo[2.2]-*para*cyclophane was dissolved in CH_2Cl_2 (20 ml) and solution cooled to 0 °C (ice bath) and piperidine (10 ml, 0.101 mol) was slowly added. After warming up to room temperature the solution was stirred over night. Solution turned yellow and precipitate showed in solution. The title compound was worked up by adding H_2O (30 ml) and $NaHCO_3$ aqueous solution (30 ml) and extracted 3 times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$ and solvent removed. The residue was then columned over silica with a solvent mix of hexane: EtOAc (5 : 2, R_f = 0.38). The title compound was obtained as a white solid in 52% yield (675 mg, 1.41 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.17-1.21 (m, 2H, CH_2), 1.53 (br s, 4H, CH_2), 2.59-2.69 (m, 1H, CH_2), 2.78-3.05 (m, 7H, CH_2), 3.19-3.34 (m, 2H, CH), 3.52-3.67 (m, 2H, CH_2), 6.31 (d, *J* = 1.74 Hz, 0.5H, $C_{Ar}H$), 6.34 (d, *J* = 1.74 Hz, 0.5H, $C_{Ar}H$), 6.37 (s, 1H, $C_{Ar}H$), 7.08 (s, 1H, $C_{Ar}H$), 7.16-7.21 (m, 2H, $C_{Ar}H$). ^{13}C {^{1}H}- NMR (75 MHz, $CDCl_3$) δ_C 24.97 (s, CH_2), 26.10 (s, CH_2), 26.77 (s, CH_2), 31.77 (s, CH_2), 32.32 (s, CH_2), 35.71 (s, CH_2), 35.99 (s, CH_2), 43.19 (s, CH_2), 48.08 (s, CH_2), 126.81 (s, C_{qu}), 127.71 (s, C_{qu}), 131.76 (s, $C_{Ar}H$), 132.53 (d, *J* = 6.56 Hz, $C_{Ar}H$), 133.50 (s, C_{qu}), 134.14 (s, $C_{Ar}H$), 134.96 (s, $C_{Ar}H$), 138.84 (s, C_{qu}), 139.45 (s, C_{qu}), 139.98 (s, C_{qu}), 141.03 (s, C_{qu}), 168.92 (s, -CO). Anal. calcd. for $C_{22}H_{23}Br_2NO$: C, 55.37; H, 4.86; N, 2.93; Found : C, 55.23; H 4.82, N 2.94. MS (CI): m/z calcd. For $C_{22}H_{23}Br_2NO$ [M+H]+ : 478.02; found 478.02 .$[\alpha]_D$=-200.00 (c = 0.065, $CHCl_3$). MP: 140-142 °C. IR (KBr): ν 3432 [w, sp ν(C-H)], 3017-2852 [st, sp^2 ν(C-H)], 1738 [w, ν(C=O)], 1627 [st, ν(C=C)], 1477-1360 [st, sp^2 ν(C-H)]. Crystal structure

5.4.6.2 (*R*)-(-)-4,12-dibromo-7-(methyl-*N*-piperdinyl)-[2.2]-*para*cyclophane, (79)



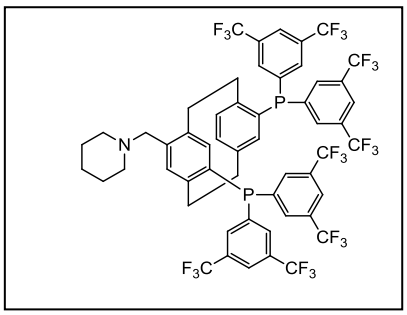
(*R*)-7-piperidinyl-1-methanone-4,12-dibromo-[2.2]-*para*cyclophane (280 mg, 0.587 mmol) was dissolved in THF and BH_3*THF solution (1.5 ml, 1.467 mmol, 1M) was added at room temperature. Solution refluxed at 67 °C for 6 hours, then cooled to room temperature and stirred over night.

Anhydrous MeOH (3 ml) was added to quench the BH_3*THF solution and solution was refluxed for 3 hours. The oily residue was columned using MeOH : CH_2Cl_2 (5 : 95, and then changing to 10:90), (in MeOH : CH_2Cl_2 mix R_f = 0.09 product, R_f = 0.44 alcohol, R_f = 0.68

starting material) giving the product as an yellowish oil in 34% yield (92 mg, 0.200 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.31-1.32 (m, 2H, CH_2), 1.49-1.51 (m, 4H, CH_2), 2.31 (br s, 4H, CH_2), 2.64-2.73 (m, 3H, CH_2), 2.85-3.01 (m, 3H, CH_2), 3.19-3.31 (m, 4H, CH_2), 3.45 (d, *J* = 9.87 Hz, 1H, CH_2), 6.35-6.39 (m, 2H, $C_{Ar}H$), 6.55 (d, *J* = 3.00 Hz, 1H, $C_{Ar}H$), 7.09 (s, 1H, $C_{Ar}H$), 7.13 (d, *J* = 1.29 Hz, 1H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 24.21 (s, CH_2), 25.73 (s, CH_2), 31.00 (s, CH_2), 32.53 (s, CH_2), 35.14 (s, CH_2), 35.58 (s, CH_2), 54.60 (s, CH_2), 61.24 (s, CH_2), 127.13 (s, C_{qu}), 131.52 (s, $C_{Ar}H$), 131.83 (s, $C_{Ar}H$), 134.05 (s, $C_{Ar}H$), 137.87 (s, $C_{Ar}H$), 138.94 (s, C_{qu}), 139.03 (s, C_{qu}), 141.27 (s, C_{qu}), 141.61 (s, C_{qu}). Anal. calcd. for $C_{22}H_{25}Br_2N$: C, 57.07; H, 5.44; N, 3.02; Found : C, 56.82; H 5.52, N 3.12. MS (CI): m/z calcd. For $C_{22}H_{25}Br_2N$ [M+H]+: 464.04; found 464.04. $[\alpha]_D$= - 126.34 (c = 0.167, $CHCl_3$).

5.4.6.3 (*R*)-4,12-Bis(3,5-bis(trifluoromethyl)phenyl)phosphino-7-(methyl-*N*-piperdinyl)-[2.2]-*para*cyclophane, (**81**)



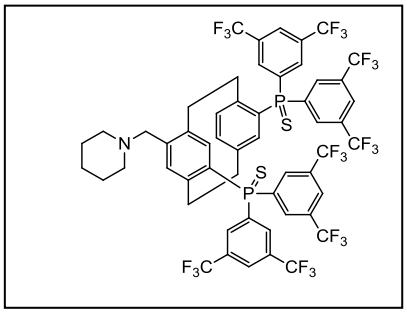
(*R*)-(-)-4,12-dibromo-7-(methyl-*N*-piperidinyl)-[2.2]-*para*cyclophane (104 mg, 0.216 mmol) was dissolved in Et_2O (15 ml) and *n*-BuLi (0.17 ml, 0.432 mmol, 2.5M in hexane) added. The solution was stirred for 3 hours at room temperature. Bis(bis(3,5 trifluoromethyl)phenyl)phosphinochloride (213 mg, 0.432 mmol) was dissolved in Et_2O (1.3 ml) and added to the lithiated solution and stirred over night. A ^{31}P {^{1}H} NMR was taken to assure the completion of the reaction.

^{31}P {^{1}H} NMR (161 MHz, CD_2Cl_2) δ_P 0.58 (s), -0.55 (s). MS (CI): m/z calcd. For $[M+H]^+$ $C_{54}H_{37}F_{24}NP_2$: 1218.2091; found 1218.2079.

Due to large amount of by-product formation, an excess of S_8 powder (1 g) was added to sulfonate the phosphorus and left stirring over night. In some cases the rearrangement of the phosphinechloride to P-P=O products was obtained as the only product. When decreasing the temperature already decrease P-P coupling was observed. After sulfonating the ligand CH_2Cl_2 (15 ml) was added to the solution and precipitate was

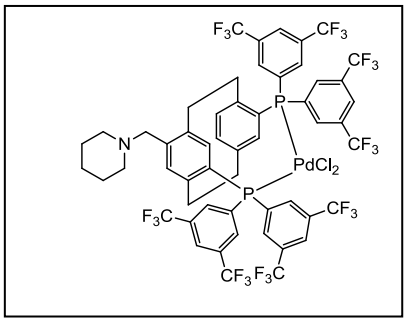
filtered off. The ligand was columned twice, however was still not obtained in good enough quality. Column: hexane 100; hexane/Et_2O 70:30; hexane/Et_2O 50/50; CH_2Cl_2.

5.4.6.4 (*R*)-4,12-Bis(3,5-bis(trifluoromethyl)phenyl)phosphinothioyl-7-(methyl-*N*-piperdinyl)-[2.2]-*para*cyclophane, (82)



^{31}P {^{1}H} NMR (161 MHz, $CDCl_3$) δ_P 35.59 (s), 35.23 (s). MS (CI): m/z calcd. For $[M+H]^+$ $C_{54}H_{37}F_{24}NP_2S_2$ 1281.92; found 1282.15.

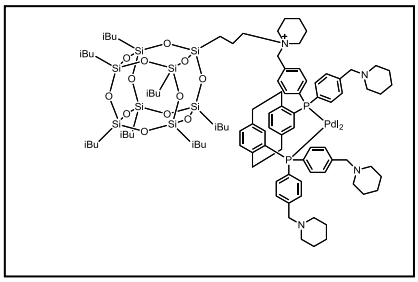
5.4.6.5 (*R*)-4,12-Bis(bis(3,5-trifluoromethyl)phenyl)phosphino-7-(methyl-*N*-piperdinyl)-[2.2]-*para*cyclophane$PdCl_2$



A small impure sample of (*R*)-(-)-4,12-Bis(3,5-bis(trifluoromethyl) phenyl)phosphino-7-(methyl-*N*-piperidinyl)-[2.2]-*para*-cyclophane was dissolved in CH_2Cl_2 and $[PdCl_2(PhCN)_2]$ was added and stirred over night at room temperature. A small sample was taken for ^{31}P {^{1}H} NMR to check the completion of the reaction. The reaction resulted as expected several unidentified peaks. To check if the Pd complex was formed a ms was carried out.

MS (CI): m/z calcd. For $[M+H]^+$ $C_{54}H_{37}Cl_2F_{24}NP_2Pd$: 1395.1; found 1396.1.

5.4.6.6 [((*R*)-(-)-Bis(4-piperidinylmethylphenylphosphino)-[2.2]-*para* cyclophane)palladium(II)]chloride alkylated with *i*BuPOSSCH$_2$CH$_2$CH$_2$I, (83)

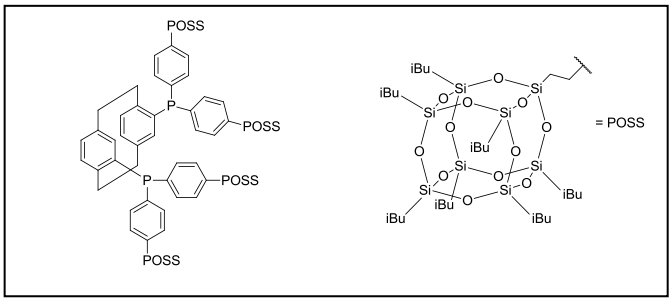


[((*R*)-(-)-Bis(4-piperidinylmethylphenylphosphino) -[2.2]-*para*cyclophane)palladium(II)]chloride (33.0 mg, 0.0289 mmol) and *i*-BuPOSSCH$_2$CH$_2$CH$_2$I (377 mg, 0.3767 mmol) were put under Argon atmosphere and

Me-THF (8 ml) was added. Solution was stirred and heated up to 76 °C for 24 hours. Then cooled to room temperature and a ^{31}P $\{^{1}H\}$ NMR was taken to check the completion of reaction. Solvent was removed under vacuum and crude product was columned by SEC using Sephadex size exclusion column. The compound was columned under inert atmosphere and the red fraction collected and solvent removed to give the product and still further impurities. SEC was repeated however the compound was still not pure enough. A different method for separation of high molecular weight compounds is by Dialysis tubing. Everything was carried out under inert conditions. The impure product dissolved in CH_2Cl_2 was filled into the tubing (MWCO ~2000 g/mol), the dialysis tubing was quickly put into a flask with CH_2Cl_2 and left there stirring for 24 hours. Compound was recovered and a ^{31}P $\{^{1}H\}$ NMR taken, most of the product was oxidised.

^{31}P $\{^{1}H\}$ NMR (161 MHz, CD_2Cl_2): δ_P 35.65 ppm (s). MS (MALDI-TOF): PipPhanePhosPd+$CH_2CH_2CH_2POSS$*i*-Bu: 1921.6 found 1921.6; PipPhanephosPdI_2+ $CH_2CH_2CH_2POSS$*i*-Bu: 2184.1, found 2183.6.

5.4.6.7 PhanePOSS, (84)

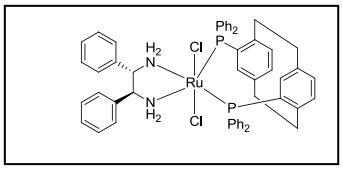


4-Br(C_6H_4)CH_2CH_2POSS*i*-Bu (1.95 g, 1.951 mmol) weight into a dry Schlenkflask and evacuated 5 times. Then the compound was dissolved in dry THF (30 ml) and solution cooled to -78 °C using an acetone/dry ice bath. *t*-BuLi (1.3 ml, 2.00 mmol, 1.5 M solution in pentane) was added dropwise to the POSS solution. The solution was stirred for 2 hours at -78 °C. In another dry Schlenkflask was (*R*)-bis(dichlorophosphino)paracyclophane (200 mg, 0.488 mmol) dissolved in THF (4 ml). This solution was added dropwise to the lithiated POSS solution turning into a yellowish colour. After addition finished stirred for another 10 minutes und cold conditions, then warmed up slowly to room temperature and solution stirred over night. A ^{31}P $\{^{1}H\}$ NMR was taken to assure the reaction has gone to completion, showing a single peak at 4.47 ppm. (Ph-Phanephos ^{31}P $\{^{1}H\}$ NMR (161 MHz, $CDCl_3$) δ_P -0.53 ppm (s))[16]

Work up of compound under inert conditions: Solvent was removed and crude compound dissolved in hexane. Then the hexane phase was washed 3 times with degassed water. After extracting the water phase 3 times with hexane, the organic layers layers were combined, dried over $MgSO_4$ and filtered off. The solvent was removed under vacuum and crude product obtained as yellowish sticky solid. This solid was then dissolved in Et_2O and crushed out with dry acetonitrile (not soluble in acetonitrile). The white precipitate was collected and the solution removed to another dry inert Schlenkflask. The procedure was repeated 5 times to assure most of the product is recovered. The compound was obtained as a white powder but was not completely pure. POSS impurities prevent full characterisation of this compound.

^{31}P $\{^1H\}$ NMR (161 MHz, $CDCl_3$) δ_P 2.57 ppm (s). (oxidised PhanePOSS ^{31}P $\{^1H\}$ NMR) δ_P 34ppm). MALDI-TOF m/z [$C_{160}H_{298}O_{48}P_2Si_{32}$] 3950.73; found 3950.73. [oxidised PhanePOSS MALDI-TOF m/z [$C_{160}H_{298}O_{50}P_2Si_{32}$] 3982.2; found 3982.2.

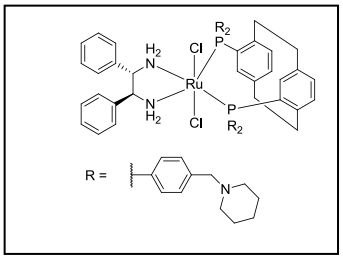
5.4.6.8 [((*R*)-(+)-4,12-Bis(phenylphosphino)-[2.2]-*para*cyclophane)ruthenium(II)dichloride(*S*,*S*)-(-)DPEN], (85)



(*R*)-(-)-4,12-Bis(phenylphosphino)-[2.2]-*para*cyclophane (417 mg, 0.723 mmol) and $[RuCl_2(C_6H_6)_2]_2$ (180.8 mg, 0.3616 mmol) were weighed into a dry microwave vial and stirrer. The vial was quickly sealed with a microwave cap and put under argon via purging 5 times with vacuum and argon. Dry toluene (4 ml) and anhydrous DMF (0.2 ml) were added via a syringe and solution was microwaved for 1 hour at 150 °C. A solution of (1*S*,2*S*)-(-)-DPEN (153.5 mg, 0.723 mmol) dissolved in toluene (1 ml) was added to the microwave vial and microwaving was continued for another hour at 150 °C. The solvent was removed from the resulting solution and the product obtained in quantitative yield (691.0 mg, 0.723 mmol), as a dark red solid. This compound is already known in literature and was therefore not further characterised.[15]

^{31}P $\{^1H\}$ NMR (121 MHz, $CDCl_3$) δ_P 46.0(s).

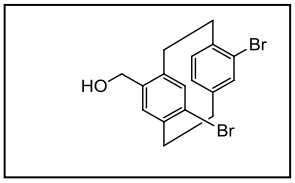
5.4.6.9 {{(*R*)-(-)-4,12-Bis[bis(4-piperidinylmethylphenyl)phosphino]-[2.2]-*para*cyclophane}ruthenium(II)dichloride((*S*,*S*)-(-)-DPEN)}, (86)



(*R*)-(-)-4,12-Bis[bis(4-piperidinylmethylphenyl)phosphino]-[2.2]-*para*cyclophane (324 mg, 0.336 mmol) and $[RuCl_2(C_6H_6)_2]_2$ (80 mg, 0.168 mmol) were weighed into a dry microwave vial and stirrer. The vial was quickly sealed with a microwave cap and put under argon via purging 5 times with vacuum and argon. Dry toluene (2.5 ml) and anhydrous DMF (0.1 ml) were added via a syringe and solution was microwaved for 1 hour at 150 °C. A solution of (1*S*,2*S*)-(-)-1,2-diphenyl-1,2-diaminoethane ((1*S*,2*S*)-(-)-DPEN) (71.2 mg, 0.336 mmol) dissolved in toluene (1ml) was added to the microwave vial and microwaving was continued for another hour at 150 °C. The solvent was removed and the product obtained in quantitative yield (453.4 mg, 0.336 mmol), as a purple solid.

^{1}H NMR (300 MHz, CD_2Cl_2) δ_H 1.32-1.54 (m, 28H, CH_2), 2.37 (br s, 20H, CH*2*), 3.33-3.49 (m, 10H, CH_2), 6.28-6.38 (m, 2H, $C_{Ar}H$), 6.87-7.28 (m, 25H, $C_{Ar}H$), 7.34 (d, *J* = 8.2 Hz, 4H, $C_{Ar}H$), 7.47 (d, *J* = 8.2 Hz, 4H, $C_{Ar}H$), 8.16 (t, *J* = 8.2 Hz, 1H, $C_{Ar}H$). ^{31}P {^{1}H} NMR (121 MHz, $CDCl_3$) δ_P 46.05 (s). MS (CI): m/z calcd. for $C_{79}H_{102}Cl_2N_5P_2Ru$: 1354.60 ; found 1354.60. Anal.calcd. for $C_{79}H_{102}Cl_2N5_4P_2Ru$: C 69.42, H 7.02, N 6.23 Found : C 67.58, H 6.83, N 6.47. MP: 208 °C (decomposition). $[\alpha]_D$= +53.75 (c = 0.08, $CHCl_3$).

5.4.6.10 (*R*)-4,12-dibromo-7-methanol-[2.2]-*para*cylcophane, (80)



This compound was obtained as a side product during the amide reduction with BH_3*THF.

^{1}H NMR, (300 MHz, $CDCl_3$): δ 2.62-2.78 (m, 2H, CH_2), 2.84-3.13 (m, 4H, CH_2), 3.28-3.38 (m, 2H, CH_2), 4.25 (d, *J* = 13.0 Hz, 1H, CH_2), 4.53 (d, *J* = 13.0 Hz, 1H, CH_2), 6.32 (d, *J* = 1.59 Hz, 0.5H, $C_{Ar}H$), 6.34 (d, *J* = 1.6 Hz, 0.5H, $C_{Ar}H$), 6.39 (s, 1H, $C_{Ar}H$), 6.53 (d, *J* = 7.9 Hz, 1H, $C_{Ar}H$), 7.09 (s, 1H, $C_{Ar}H$), 7.13 (d, *J* = 1.8 Hz, 1H, $C_{Ar}H$). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ_C 30.33 (s, CH_2), 32.52 (s, CH_2), 34.90 (s, CH_2), 35.70 (s, CH_2), 63.82 (s, C-OH), 125.96,

127.21, 131.73 (d, *J* = 16.5 Hz), 133.54, 134.22 (d, *J* =2.25 Hz), 138.82, 139.30, 139.55, 140.18, 141.58. Anal. calcd. for $C_{16}H_{17}Br_2O$: C, 51.55; H, 4.07 ; Found : C, 51.66; H, 4.02. MS (EI): m/z calcd. For $C_{16}H_{17}Br_2O$: 396.1; found 396.1. Crystal structure

5.5 References

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5.6 Crystal structures

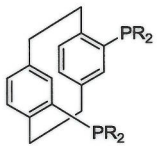
Table 58 Selected crystallographic data for catalysts (**47**), (**48**), (**50**) and (**51**).

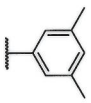
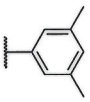
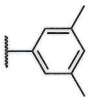
	(**47**)	(**48**)	(**50**)	(**51**)
Formular	$C_{40}H_{34}Cl_2P_2Pd$	$C_{48}H_{50}Cl_2P_2Pd$	$C_{77}H_{109}Cl_2O_4P_2Pd$	$C_{40}H_{22}Cl_2F_{12}P_2Pd$
FW (g.mol^{-1})	753.97	866.18	1337.96	969.86
Crystal system	orthorhombic	orthorhombic	monoclinic	tetragonal
Space group	$P2_12_12_1$	$P2_12_12_1$	C 1 2 1	$P4_2$
a (Å)	11.16(1)	13.85(4)	24.85(4)	24.88(6)
b (Å)	17.99(3)	20.54(3)	10.70(4)	24.88(6)
c (Å)	18.65(9)	21.17(9)	15.49(2)	10.66(5)
α (°)	90	90	90	90
β (°)	90	90	106.4	90
γ (°)	90	90	90	90
Z	4	4	2	2
D_{calc}(g cm^{-3})	1.475	1.481	1.111	1.610
μ (Mo-k_α)(nm^{-1})	0.812	1.015	0.385	0.759
T (K)	93	93	93	93
Total reflections	6805	10960	6521	11898
wR_2 (F^2)	0.0755	0.2540	0.2196	0.2549
λ	0.71075	0.71075	0.71075	0.71075
R_1 (F)	0.0276	0.1005	0.0781	0.0893
F 000	1704.0	2720.0	1408.0	3196
Volume (Å^3)	3747	6028	3953	6604

	(**56**)	(**57**)	(**78**)	(**80**)
Formular	$C_{48}H_{50}Cl_4P_2Pd_2$	$C_{40}H_{58}Cl_4P_2Pd_2$	$C_{22}H_{23}Br_2NO$	$C_{17}H_{16}Br_2O$
FW (g.mol^{-1})	1043.51	955.49	477.23	396.12
Crystal system	monoclinic	orthorombic	monoclinic	orthorombic
Space group	P 1 2_1 1	$P2_12_12_1$	P 1 2_1 1	$P2_12_12_1$
a (Å)	9.43(7)	10.80(5)	9.28(0)	8.16(3)
b (Å)	17.07(5)	12.51(4)	9.41(9)	14.96(3)
c (Å)	13.62(7)	33.40(9)	11.48(0)	24.84(9)
α (°)	90	90	90	90
β (°)	100.7	90	108.5	90
γ (°)	90	90	90	90
Z	2	4	2	4
D_{calc}(g cm^{-3})	1.606	1.655	1.665	1.049

μ (Mo-k_α)(nm^{-1})	1.190	1.371	4.282	2.686
T (K)	93	93	93	125
Total reflections	7568	8233	3107	6159
wR_2 (F^2)	0.3010	0.1914	0.0653	0.1878
λ	0.71075	0.71070	0.71075	0.71075
R_1 (F)	0.0965	0.0714	0.0402	0.0654
F 000	1056.0	2288.0	480.0	968.0
Volume ($Å^3$)	2157.6	4517.4	951.8	3035.1

Chapter II



		Mono-palladium complexes		Di-palladium complexes	
R =		(38)		(47)		(55)
		(39)		(48)		(56)
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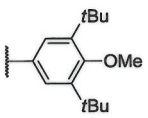
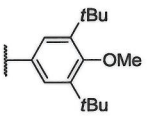
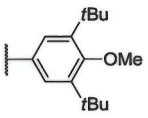
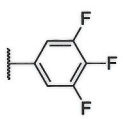
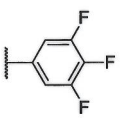
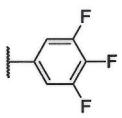
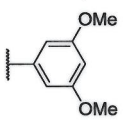
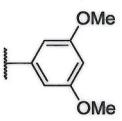
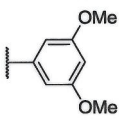
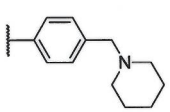
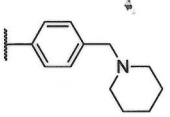
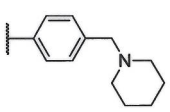
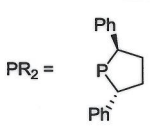
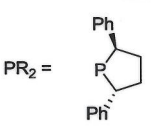
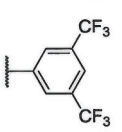
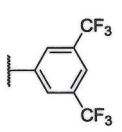
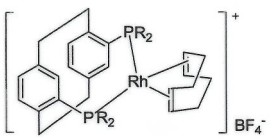
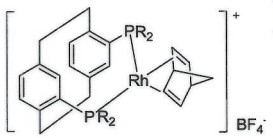
		(41)		(50)		(58)
		(42)		(51)		(59)
		(43)		(52)		(60)
		(44)		(53)		(61)
PR_2 =		(45)	PR_2 = 	(54)		
				(69)		(70)

Chapter III



[Rh(COD)(**44**)]BF_4 (**74**)
[Rh(COD)(**39**)]BF_4 (**76**)

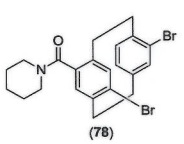


[Rh(NBD)(**44**)]BF_4 (**75**)
[Rh(NBD)(**39**)]BF_4 (**77**)

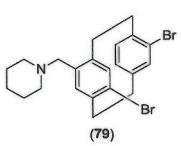
Rh catalyst	Resin catalyst
(*R*)-[Rh(COD)(**44**)]BF_4 (**74**)	**DOWEX-74-COD-Rh**
(*R*)-[Rh(NBD)(**44**)]BF_4 (**75**)	**DOWEX-75-NBD-Rh**
(*S*)-[Rh(COD)(**39**)]BF_4 (**76**)	**DOWEX-76-COD-Rh**
(*S*)-[Rh(NBD)(**39**)]BF_4 (**77**)	**DOWEX-77-NBD-Rh**
(*R*)-[Rh(COD)(**44**)]BF_4 (**74**)	**Li-DOWEX-74-COD-Rh**

Pd catalyst	Resin catalyst
(53)	**DOWEX-53-Pd**
(61)	**DOWEX-61-Pd**
(48)	**DOWEX-48-Pd**

Appendix



(**78**)



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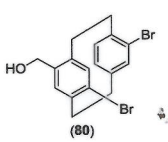
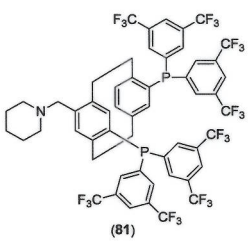


(**80**)



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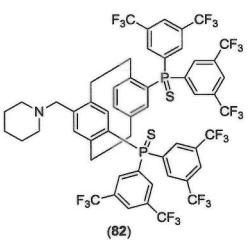

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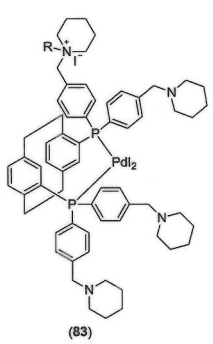

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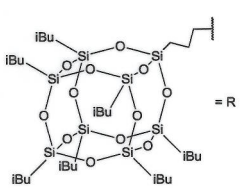

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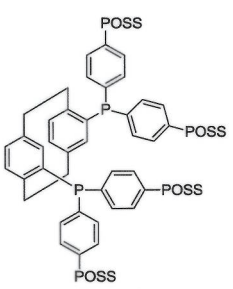

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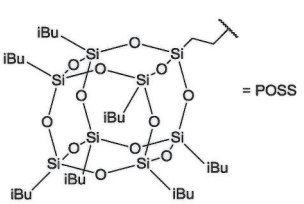

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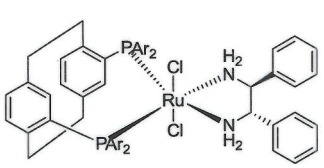

(**85**) Ar =

(**86**) Ar =