Separation and Recycling of Phosphane Ligands from Homogeneously Catalyzed Processes

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Sythesis of Novel Ligands with Axial Chirality for Asymmetric Hydrogenation

Teil dieser Arbeit wurde beim Deutschen Patentamt zum Patent mit der Bayer AG (Lanxess FC) **2005** angemeldet.

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Abbreviations

abs.	absolute
acac	acethylacetonate
Ar	aryl
arom.	aromatic
BINAP	2.2´-bis(diphenylphosphino)-1,1´-binaphthyl
Biphemp	2,2´-bis(diphenylphosphino)-6,6´-dimethylbiphenyl
$BMIM^{+}BTA^{-}$	butyl-methyl-imidazolium-bis-triflylamide
BPPFA	N,N-dimethyl-1-[(*R*)-1´,2-bis(diphenylphosphino)ferrocenyl]-amine
BPPM	bis(para-phosphophenyl)methane
cat.	catalyst
Chiraphos	2,3-bis(diphenylphosphino)-butan
Cl-MeO-Biphep	5,5`-dichloro-6,6`-dimethoxy-2,2`-bis(diphenylphosphino)-1,1`-biphenyl
COD	1,5-cyclooctadien
cont.	content
Conv.	conversion
Cy	cyclohexyl
d	doublett
Dave-Phos	2-dicyclohexylphosphino-2´-(N,N-dimethylamino)-biphenyl
dba	dibenzylidenacetone
DEE	diethylether
DBE	dubutylether
DIOP	4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxan
DIPAMP	1,2-bis[(2-methoxyphenyl)-phenylphosphino]-ethan
DMF	N,N-dimethylformamid
DMSO	dimethyl sulfoxide
DPEPhos	bis(2-diphenylphosphinophenyl)ether
DPPF	1,1´-bis(dipehylphosphanyl)ferrocene
DtBPF	1,1´-bis(di-tert-buthylphosphanyl)ferrocene

ee	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
GC	gas chromatography
h.	hour(s)
Hz	herz
IL	ionic liquid
IR	infrared
J	coupling constant
L.	ligand
L-DOPA	L-dihydroxyphenylalanin
Lig.	ligand
m.	multiplet
$[M]^*$	metallic catalyst
Me	methyl
MeO-Biphep	6,6´-dimethoxy-2,2´-bis(diphenylphosphino)-1,1´-biphenyl
MeOH	methanol
min.	minute
mL	milliliter
mp.	melting point
MS	mass spectrometry
MTBE	methyl-*tert*-butylether
Naproxen	2-(6-methoxynaphtalen-2-yl)propanoic acid
NMP	N-methylpyrrolidon
NMR	nuclear magnetic resonance spectroscopy
Norphos	[(2*R*,3*R*)-8-9-10-trinorbon-5-ene-2,3-diyl]bis(diphenylphosphine)
PE	petrolether
PEG	polyethylenglycol-monomethylether
Ph	phenyl
$p[H_2]$	hydrogen pressure
PPh_3	triphenylphosphine

ppm	parts per million
Prod.	product
Prophos	1,2-bis-(diphenylphosphino)propane
R	substituents
R_t	retention time
q	quartet
s	singlet
S	solvent
Segphos	(4,4´-bi-1,3-benzodioxole)-5,5´-diylbis(diphenylphosphine)
S/C	Substrate/Catalyst
Sub.	substrate
Synphos	2,3,2´,3´-tetrahydro-5,5´-bi(1,4-benzodioxin)-6,6´-diyl)bis-(diphenylphosphane)
t	triplet
t	time
THF	tetrahydrofurane
TsDPEN	(1*R*,2*R*)-N-(p-tolylsulfonyl)-1,2-diphenylethylenediamine
vs.	versus
X-Phos	2-dicyclohexylphosphino-2´,4´,6´-triisopropyl-biphenyl
XantPhos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

Contents

1 Introduction

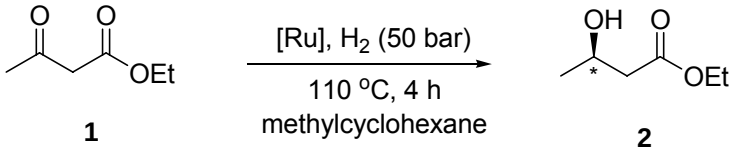
The appellation “Fine chemicals” can be heard very often in the language of modern chemistry. During the 1980s lots of leader chemical companies in the world place increased emphasis on small volume but high value products. These special chemicals contain specialized polymers, intermediates for high performance structural materials, and many biologically active compounds.

The bioactive substances usually involve complex organic structures, and often one or more chiral centers. This class of the compounds, which contains pharmaceuticals, flavors, food additives, crop protection chemicals has indicated a very significant development of the homogeneous catalysis [1].

A very fast development has continued in the use of homogeneous catalysis to produce large volume chemical intermediates and polymers. This growth has occurred despite of the fact that relatively few new large-scale processes have been brought into commercial production. For example: Monsanto acetic acid process [2], and Ruhrchemie/Rôhne-Poulenc process, or Kuraray´s hydroformylation technology for making 1,4-butanediol. For these processes homogeneous catalysts have been developed, which are extremely effective [1].

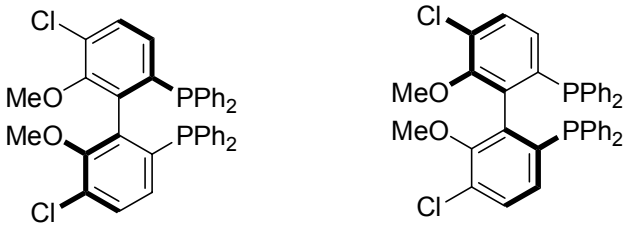
In some cases, big fine chemical companies cooperate together to achieve a common technical goal by the working in parallel. Several times these companies are stiff competitors and possess the same license from the inventor [3].

In this work two very effective reaction will be presented named as asymmetric hydrogenation [4, 5] and Buchwald-Hartwig amination [6-12], both produce pure compounds with high conversion. These processes have been described in a broad spectrum of the literature and used as standard reactions for the testing of new catalyst complexes, which are coordinated to transition metals (Ru, Rh, Pd). In this thesis, the main emphasis was placed on the asymmetric hydrogenation (Scheme 1.1), which was the ruthenium catalyzed reduction of ethyl acetoaceate (**1**) to convert to ethyl-3-hydroxybutyrate (**2**) with using Cl-MeO-Biphep ligand (**3**) [13-15].



1 **2**

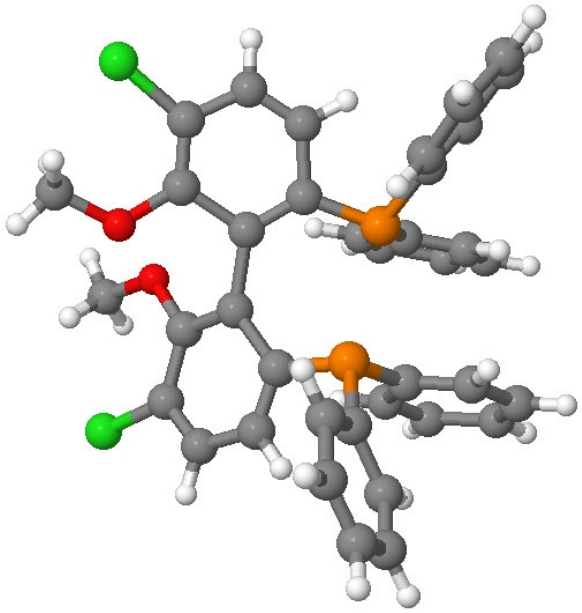
Scheme 1.1 Asymmetric hydrogenation of *β*-ketoester



(R)-Cl-MeO-Biphep (S)-Cl-MeO-Biphep

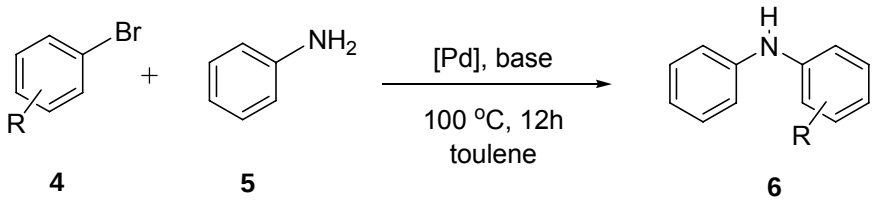
R-**3** *S*-**3**

Figure 1.1 The applied Cl-MeO-Biphep phosphine ligand, (*R/S*)-5,5`-dichloro-6,6`-dimethoxy-2,2`-bis(diphenylphosphino)-1,1`-biphenyl) (**3**)



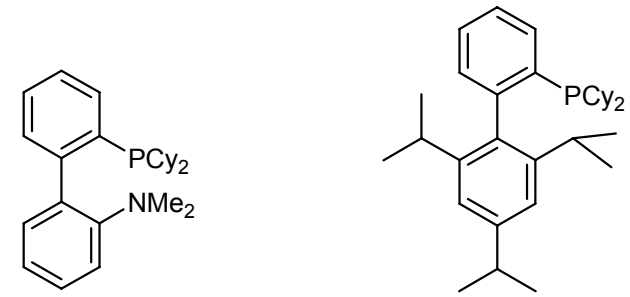
3D illustration of molecular structure of **3**

The second investigated catalytic process is the well known Buchwald-Hartwig amination reaction (Scheme 1.2) between bromobenzene (**4**) and aniline (**5**) to produce diphenylamine (**6**) with the help of Dave-Phos (**7**) [16-18] and X-Phos ligands (**8**) [18, 19].



4 **5** **6**

Scheme 1.2 Buchwald-Hartwig amination reaction



Dave-Phos X-Phos

7 **8**

Figure 1.2 The applied ligands Dave-Phos (**7**) (2-dicyclohexylphosphino-2´-(N,N-dimethylamino)- biphenyl) and X-Phos (**8**) (2-dicyclohexylphosphino-2´,4´,6´-triisopropyl-biphenyl) for the Buchwald-Hartwig amination

Lots of aims have been given for the recycling of these supported ligand tags in the past few years because it is often the price of a more or less sophisticated ligand that influences the economics of a new process [20].This work has been merely financed by the Lanxess Fine Chemicals [21] in order to develop a new process for the recycling of the applied ligand after the asymmetric hydrogenation just like after the Buchwald-Hartwig amination. Aim of this work is to develop a route to recycle the catalyst.

2 General Part

2.1 Influence of the chirality on the behavior of the compounds

"I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself" stated Lord Kelvin in 1904 in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light. The term "chiral" is stemmed from the word "kheir" (greek word) meaning "hand".

Kekule [22] determined, the carbon atom has a valence of 4 in 1848. Independently J.H. van´t Hoff [23] and J. A. Le Bel [24] developed the idea of "asymmetry" in 1874. They have also recognized: if four different groups are attached to the carbon atom it will result a tetrahedral structure in which two different arrangements could appear. Louis Pasteur collected the two different forms of the tartaric acid crystal and found that the two groups of the crystals polarized the light differently, one to the left and the other to the right.

The mirror image isomers, which have similar properties (e.g. melting point, boiling point, solubility) but dissimilar optical rotations, are called "enantiomers" [25], for example the two common amino acid (*R*)- and (*S*)-alanine (Figure 2.1).

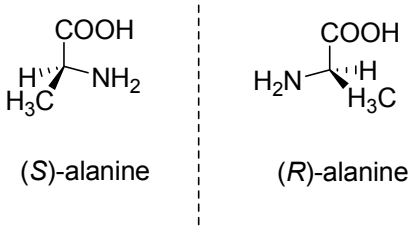
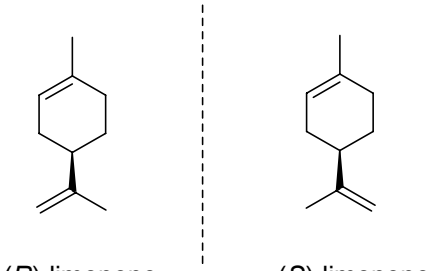


Figure 2.1 Chirality of the amino acid alanine

If alanine is produced under normal laboratory conditions, both the *R* and *S* enantiomers will be obtained as a racemic mixture. The asymmetric synthesis allows the production of an excess of one of the forms [26], therefore it is a very significant "tool" in modern

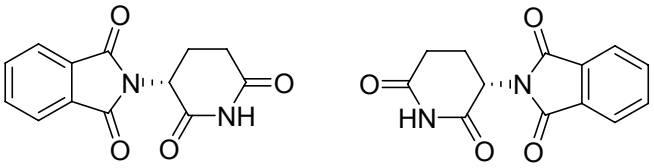
chemistry with which we are able to manufacture a chiral product from a prochiral substrate. Nature is chiral, and mainly one of the two enantiomers is used, because very often only one of the forms is of interest. Most of the drugs are chiral, but they differ from each other significantly in the properties, e.g. the (*R*)-limonene smells of oranges, while the (*S*)-limonene smells of lemons (Figure 2.2).



(*R*)-limonene (*S*)-limonene

Figure 2.2 (*R*)-limonene and (*S*)-limonene

This example is less dramatic than the difference between the two enantiomers of thalidomide drugs, which came on the market and was preserved against nausea. The *S*-(-)-thalidomide could cause foetal damage while the other enantiomer in principle is therapeutic agent (Figure 2.3).

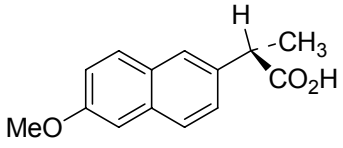


(*S*)-(-)-thalidomide (*R*)-(+)-thalidomide

Figure 2.3 Optical isomers of Contergan®

Contergan® was distributed in 1950s, but later on it was investigated in detail in 1961, because there were many birth deformities after admission to trading. Animal experiments confirmed that the (*S*)-enantiomer of the thalidomide had a fatal side effect. To avoid similar cases, one aim of pharmaceutical industry is producing numbers of products in enantiomerically pure form.

The next example is the Naproxen®, which is widely used as anti-inflammatory, but only the (*S*)-enantiomer (Figure 2.4) of it is desired while the (*R*)-enantiomer is a liver toxin. The *S*-Naproxen was produced by a conventional optical resolution of the racemate, but enantioselective hydrogenation seems to be a better solution to produce it, especially since the original patent on the drug expired in 1993. Nowadays, this drug is produced in high yield and high enatiomeric excess using Noyori´s (*S*)-BINAP-Ru($OCOCH_3$)$_2$ catalyst [27].



(*S*)-Naproxen

Figure 2.4 The anti-inflammatory enantiomer of the Naproxen®

The development of new active pharmaceutical ingredients (api) with several chiral centres requires creativity and innovation.

2.2 Enantiomerically pure compounds

As described and shown above, the production of enantiomerically pure drugs is a significant claim for the industrial application and for the economics, too. There are four general methods to prepare the desired drugs with one defined enantiomeric form.
The oldest process is the chemical or physical resolution of the obtained racemate in which the mixture of the enantiomers is reacted with enantiomerically pure auxiliaries and separated by crystallization or chromatography.
The fermentation processes are known in the field of the biocatalysis, by the utilization of the chiral synthesis potential of the microorganism. With this method, raw materials are added to microorganism culture media, and the proliferating microorganisms are allowed to produce the compound. Generally, microorganisms produce 20 kinds of amino acids and they have a mechanism to regulate the quantities and qualities of enzymes to yield amino acids only in the needed amounts.
The most effective route preparing the desired optical isomer is the asymmetric synthesis in which a chiral organic tag is usually attached to the prochiral substrate before the enantioselective step of the synhesis and than it is cleaved. By this way, almost 100 % enantiomeric excess can be reached and the desired optical isomer is variable with the chirality of the applied auxiliaries. During the last decades there were intensive researches for developing this method. Academic and industrial research groups have forced constructing chiral catalysts for two important classes of reactions in organic chemistry: hydrogenations and oxidations.

2.3 Catalysis

A catalyst is a substance that increases the rate of the reaction without being consumed itself [26]. For an industrial application, a profitable and useful catalyst must possess a high turnover number (TON = mol of product per mol of catalyst) and also high turnover frequency (TOF = TON per hour) [28]. As the production capacity depends on the activity of the catalyst, the TOF has to be at least 500 h^{-1} for the experimental scale, and more

than 10.000 h^{-1} for the large scale process [20]. Naturally, a reaction and the catalyst itself must be simple, safe and environmentally friendly. Designing suitable molecular catalysts and reactions according to these above mentioned criteria are feasible through the deep understanding of the catalytic cycle.

The cost of this auxiliaries for catalytic reaction is usually very high, for example the typical price of a diphosphanes ligands lies between 5.000 and 20.000 $/kg [29]. Therefore catalyst productivity given as substrate/catalyst ratio (S/C) or the TON value ought to be >1000 in case of the production of small-scale or high-value chemicals and >50.000 for large scale product in the industrial application. In many cases the catalyst reuse increases the productivity.

The enantiomeric excess (% *ee*) value expresses the enantioselectivity of the catalyst complex. The *ee* of the catalyst must be >99 % for the pharmaceuticals and >80 % for the agrochemicals, if no further purification is possible [20].

ee = % desired enantiomer – % undesired enantiomer

2.3.1 Homogeneous vs. heterogenenous catalysis

The two types of catalytic reactions are named as homogeneous- and heterogeneous catalysis. The main difference between them: in the homogeneous reaction the catalyst is in the same phase as the reactants, unlike in the heterogeneous reaction where these two components are in different phases.

Some examples for the heterogeneous catalysis

- Contact process for manufacturing sulphuric acid
  The sulphuric dioxide is converted into sulphuric trioxide by passing the SO_2 and oxygen over a solid vanadium(V) oxide catalyst.

$$SO_2 + 1/2\ O_2 \xrightarrow{V_2O_5} SO_3$$

- Hydrogenation of carbon-carbon double bond
  This is an example for hydrogenation reaction of the carbon-carbon double bond in the presence of Ni on heterogeneous fixed bed catalyst, which has an industrial application to produce margarine from vegetable oil.

$$CH_2{=}CH_2 + H_2 \xrightarrow{Ni} CH_3CH_3$$

Some examples for the homogeneous catalysis

The most common examples of the homogeneous catalysis are the acid (eq. a) and the basic (eq. b) catalyzed reactions following the next general schemes:

a)

$$X + HA \longrightarrow HX^+ + A^-$$

In reaction a), one of the reactant gets a proton and it reacts further. Such reactions are e.g. the transformation of keto-enol tautomers or the inversion of the saccharin.

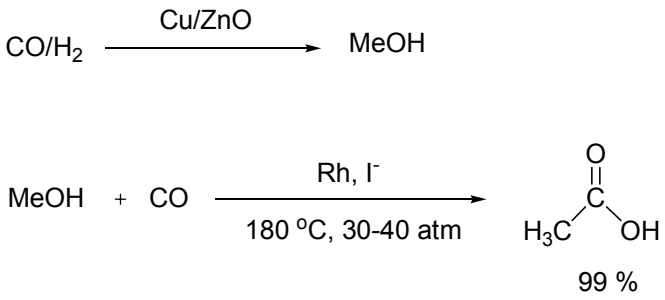
b)

$$XH + B \longrightarrow X^- + BH^+$$

In reaction b), one of the reactants gives proton to the catalyst and it reacts further. Such reactions are for example the isomerisation of some organic compounds or the Claisen-condensation [30].

Remarkable industrial homogeneous catalysis is the Monsanto acetic acid process [2], which is the major commercial production method for acetic acid. From “syn gas” (CO/H_2

mixture) prepared methanol is reacted with carbon monoxide in the presence of Rh catalyst to afford acetic acid.



Scheme 2.1 Monsanto acetic acid process

Over 1.000.000 tons of acetic acid are produced every year using this process with high selectivity and yield.

Return back to our view, the enantioselectivity is one of the main parameters to decide, which process would be more adequate from the two above mentioned reaction types. On the surface of a heterogeneous catalyst there are many different catalytically active centers, therefore the success of these catalysts is limited in enantioselective reactions. Much of selectivity observed with soluble catalysts in the homogeneous systems, which come from the process control that is attainable in the liquid phase. Some main properties of the homogeneous and heterogeneous catalysts are listed in Table 2.1.

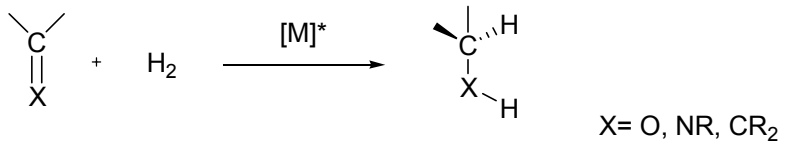
Table 2.1 Homogeneous vs. heterogeneous catalysts

Homogeneous catalysts	Heterogeneous catalysts
high activity	high activity
high selectivity	low selectivity
difficult separation	simple separation
low reaction temperature	high reaction temperature
easy control of mixing and concentration	difficult control of mixing and concentration
high adaptability	lower adaptability
high reproducibility	lower reproducibility
lower thermic and pressure stability	robust at high P, T

As a consequence, the homogeneous catalysis is able to produce high enantiomerically pure and value drugs with the utilization of the organometallic complexes. Some of the commercial applications of the homogeneous catalysis are at only the very early stage of their career. The development, the state of the art, industrial realization and most recent work will be described in the next chapters.

2.4 Asymmetric reduction

Asymmetric catalytic reduction is one of the most efficient and suitable methods to produce a wide range of enantiomerically pure compounds. For example, α-amino acids can be prepared from α-enamides, alcohols from ketones and amines from oximes or imines (Scheme 2.2).



Scheme 2.2 General scheme for asymmetric hydrogenation of ketone, imine and C-C double bond

The enantioselectivity and conversion are the most important and exciting trends of the homogeneous catalysis. The demand for the production of enantiomerically pure compounds is very high and the chiral metal complexes, which are combined with organic ligands or auxiliaries, provide the best solution. A well-designed chiral metal complex can discriminate precisely between enantiotopic groups and catalyze the formation of a wide range of natural or unnatural substances with high enantiomerical purity. Molecular hydrogen (hydrogen gas) as the source of hydrogen with transition metal can be applied as a donor of hydrogen in the asymmetric reduction [31]. By the utilization of hydrogen gas there is always a danger of an explosion of hydrogen/air mixture, therefore procedures have been developed, which use manifold hydrogen sources but avoid using of the gaseous hydrogen. For example, the well-known primary

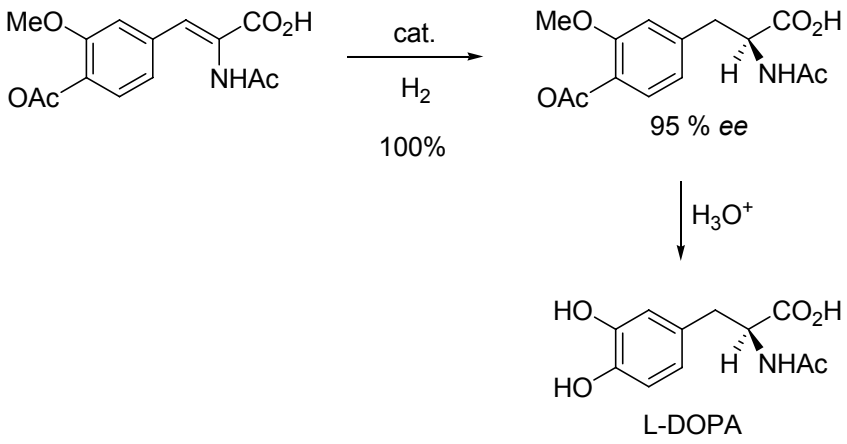
or secondary alcohols (isopropanol, benzyl alcohol) are converted to the corresponding aldehydes and ketones, whilst hydrogen gas is formed. This process is named as transfer hydrogenation reaction.

The non transition-metallic complexes are also efficient for the catalytic reduction and comparable to the metallic processes, for example the lithium aluminium hydride, sodium borohydride or borane-terahydrofurane [32] as catalysts. Among those catalysts, the chirally modified boron complexes have received great interest to be selective reducing agents for amino and phosphino alcohols [33-35].

The enzyme catalyzed reduction of carbonyl groups has also an important role in the synthesis of chiral compounds. For example, the dehydrogenases enzyme can catalyze the reduction of carbonyl groups on a practical scale with purified enzymes or with whole cells, like the more often used Bakers´ yeast system [36].

2.4.1 Enantioselective hydrogenation

The first enantioselective hydrogenation of unsaturated compounds with the help of metallic catalysts deposited on chiral supports was reported in the 1930s [37]. Osborn and Wilkinson [38] published their pioneering synthesis of a soluble transition metal catalyst $(Ph_3P)_3RhCl$) to make the catalyzed hydrogenation possible in solution. Knowles [39] and Horner [40] presented homogeneous asymmetric hydrogenation using Rh-chiral tertiary phosphine complexes. Knowles has developed the synthesis of the L-DOPA (Scheme 2.3) from enamide employing a catalytic amount of the $[Rh(R,R)DiPAMP)COD]^+BF_4^-$ complex. That was the Monsanto Process, which was the first commercialized catalytic asymmetric synthesis in 1974. The product of this process had proven to be useful in the treatment of Parkinson´s disease.



Scheme 2.3 The Monsanto synthesis of L-DOPA using [Rh(*R*,*R*)DiPAMP)COD]$^{+}$BF$_4^{-}$ catalyst complex

In the 1970s and early 1980s new catalysts were designed mainly with new optically pure chelating phosphines using Wilkinson type catalysts. For example, one of the first Kagan´s tartaric acid derived ligand DIOP [41] in 1971. This development was followed by new successful ligands, namely DIPAMP [42], prophos [43], chiraphos [44], BPPM [45], BPPFA [46], norphos [47], and BINAP [48] (Figure 2.5).

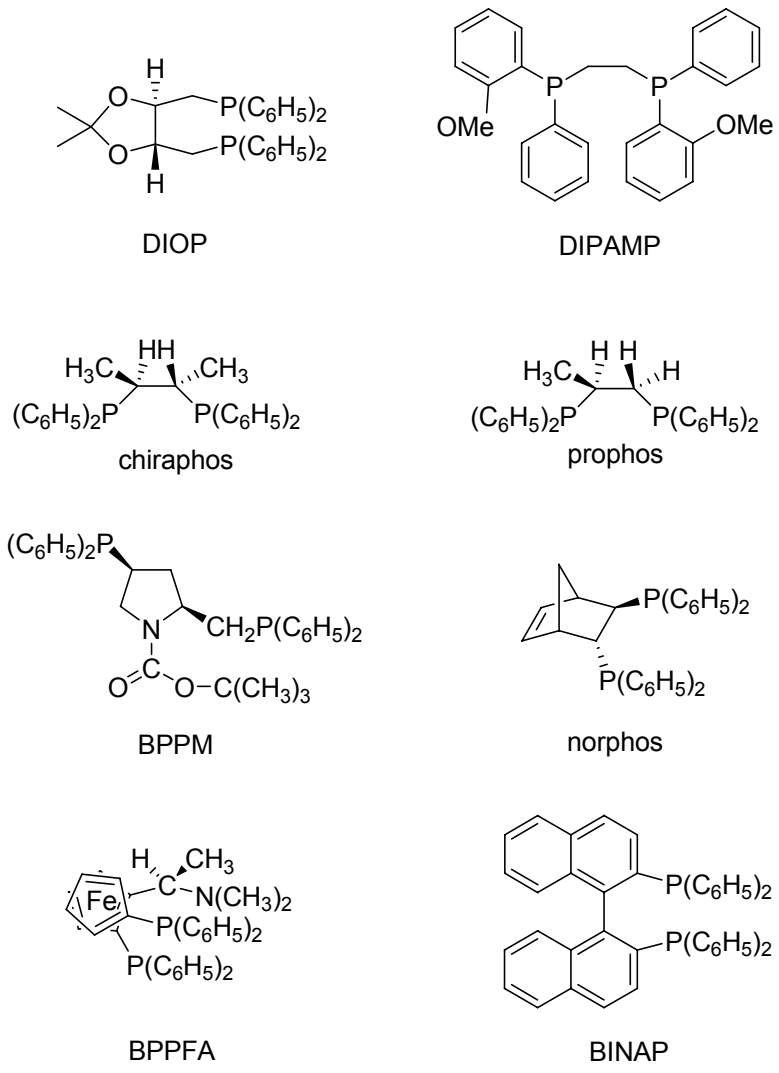
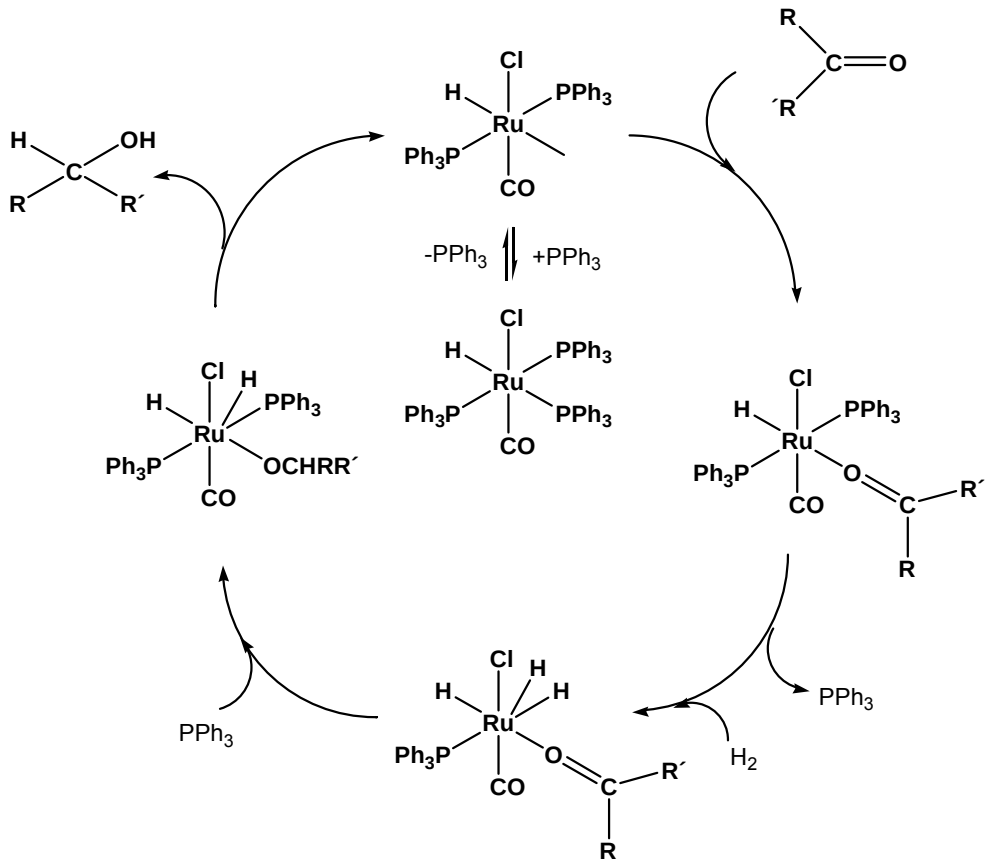


Figure 2.5 Chiral ligands for asymmetric catalysis

To the middle of 1980s the Rh-based Wilkinson type catalysts were the most used catalyst systems. Afterwards, Noyori et al. have introduced a new family of Ru-based complexes, e.g. $[Ru(BINAP)(OAc)_2]$, $[Ru(BINAP)_2Cl_4NEt_3]$, or [(arene)Ru(BINAP)I], which had wider and better applicability in the enantioselective hydrogenation of *β*-keto esters than the Rh catalysts. For example, in the hydrogenation of acetophenone using $[Rh(nbd)Cl]_2$/DIOP have reached only occasionally more than 80 % *ee*, while the Ru-based BINAP have allowed the hydrogenation of a variety of functionalized ketones in enantioselectivities close to 100 % *ee* [49, 50].

2.4.2 Mechanism of the asymmertric hydrogenation

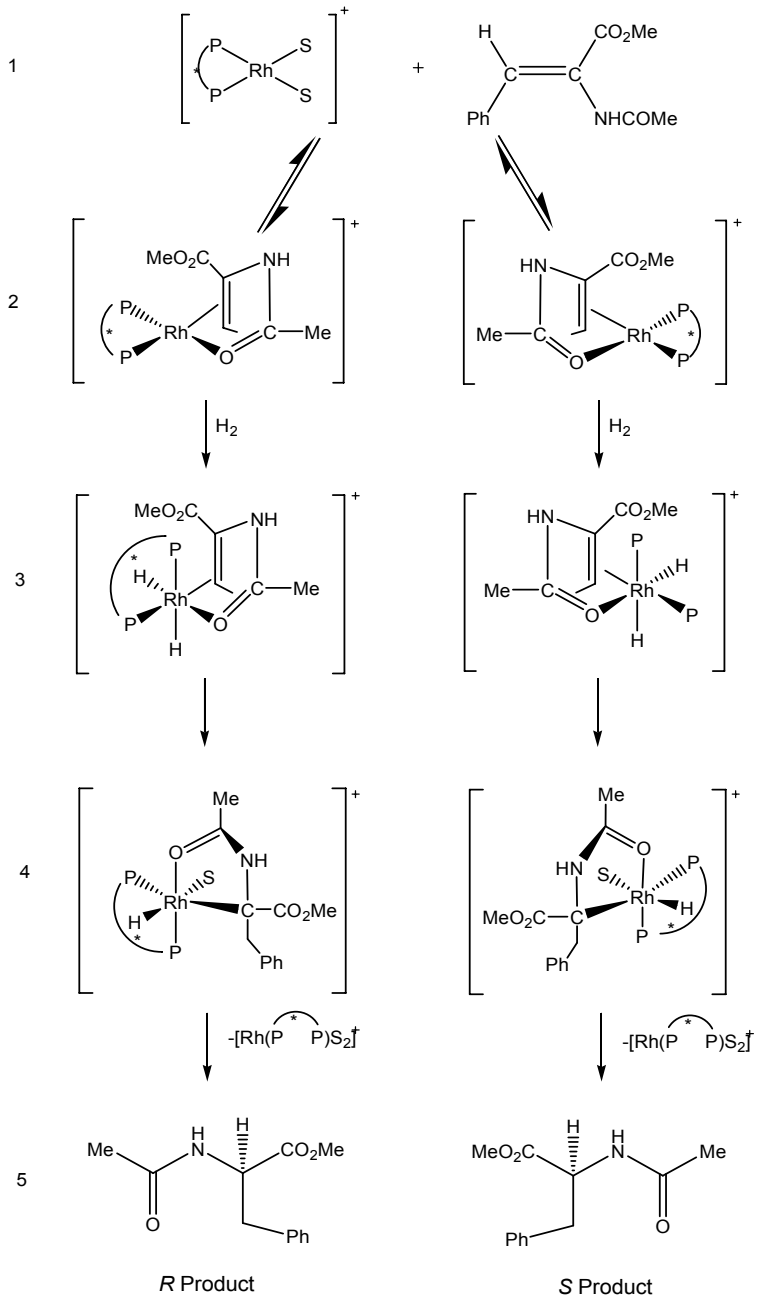
In general, the ligand modifies the properties of the metal dramatically, e.g. by stabilizing different oxidation states or by fine-tuning the electrophilic or nucleophilic properties of the metal. Probably, no element shows better this effect than ruthenium, which has the next distinctive properties that are manifested by a wide range of its complexes containing of ligands: propensity for π-back-bonding, tendency to undergo intra and intermolecular metallation and ability to form polyhydride complexes. The wide range of complexes is also a characteristic property of ruthenium, which has been studied very extensively [51]. Using [RuHCl(PPh_3)$_3$] as catalyst, very high rates of hydrogenation of terminal alkenes, alkynes or polynuclear heteroaromatic compounds was achieved. This complex catalyzes the reduction of aldehydes and ketones, however the carbonyl derivative [RuHCl(CO)(PPh_3)$_3$] is more efficient for these processes [52], which were studied by Sanchez-Delgado et al. [53, 54]. The results show the rate is first order with respect to the concentration of catalyst and substrate and second order with respect to the hydrogen pressure. A general schematic mechanism for hydrogenation of the C=O bond is shown in Scheme 2.4. The dependence of the rate on the concentration of catalyst and substrate, and on the hydrogen pressure is consistent with the mechanism.



Scheme 2.4 Mechanism of hydrogenation of the C=O bond applying $[RuHCl(CO)(PPh_3)_3]$ catalyst complex

The above mentioned mechanism operating in hydrogenation is well-known since 30 years. The famous mechanism of enantioselective hydrogenation is the hydrogenation of methyl (*Z*)-*α*-acetamidocinnamate (Scheme 2.4). The ligand is a square planar Rh^{I} complex containing a chelating phosphine ligand P*P, such as e.g. chiraphos (Figure 2.5) and two solvent molecules S, for example methanol or acetone. This species/complex reacts with the substrate, which acts as a bidentate ligand displacing the two solvent molecules, giving two diastereomeric square planar species in line 2. They contain the same optically active chelating ligand, but the metal atom is coordinated to different sides of the prochiral olefin (*re*/*si* sides).

The next step is the oxidative addition of hydrogen forming the two octahedral dihydrides, which is shown in line 3. This reaction is the rate-determining step.



Scheme 2.5 Mechanism of the hydrogenation of methyl (*Z*)-*α*-acetamidocinnamate with Wilkinson-type catalyst

The insertion of the coordinated olefin into one of the Rh-H bonds is followed, giving rise to the two diastereomeric *σ*-alkyl complexes of line 4. By reductive elimination the enantiomeric species of the product are generated (Scheme 2.5).

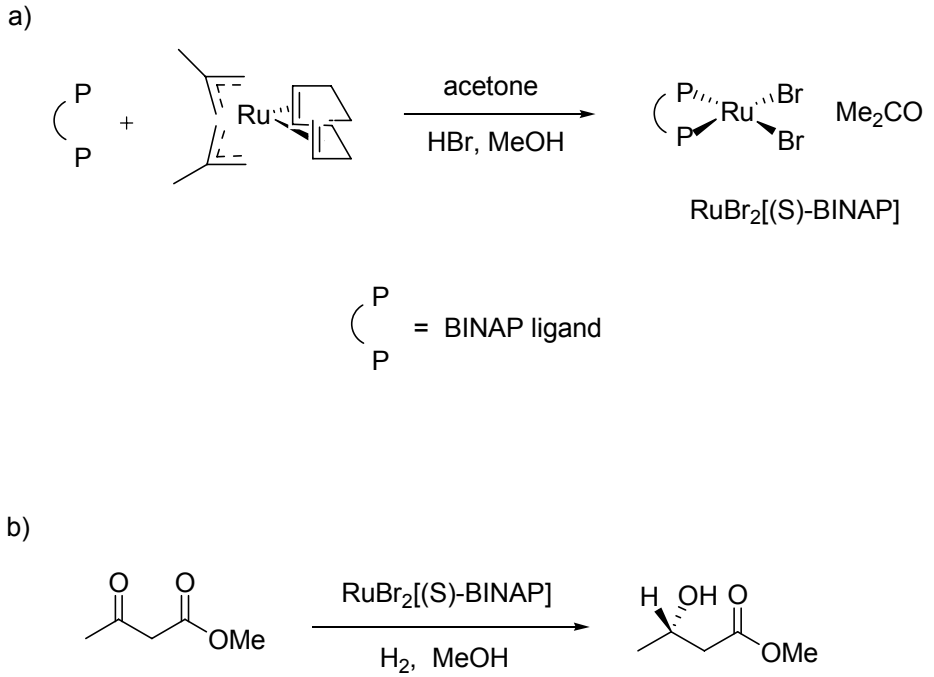
Experiments verify that the (*R*) product predominates by more than 95 % ee. Thus, the final product is not formed from the major diastereomer dominating in line 2, but from the

minor diastereomer, which presents in the equilibrium mixture to the extent of less than 5 % according to the NMR measurements [44].

2.4.3 Asymmetric homogeneous hydrogenation using metal-catalyst in industrial application

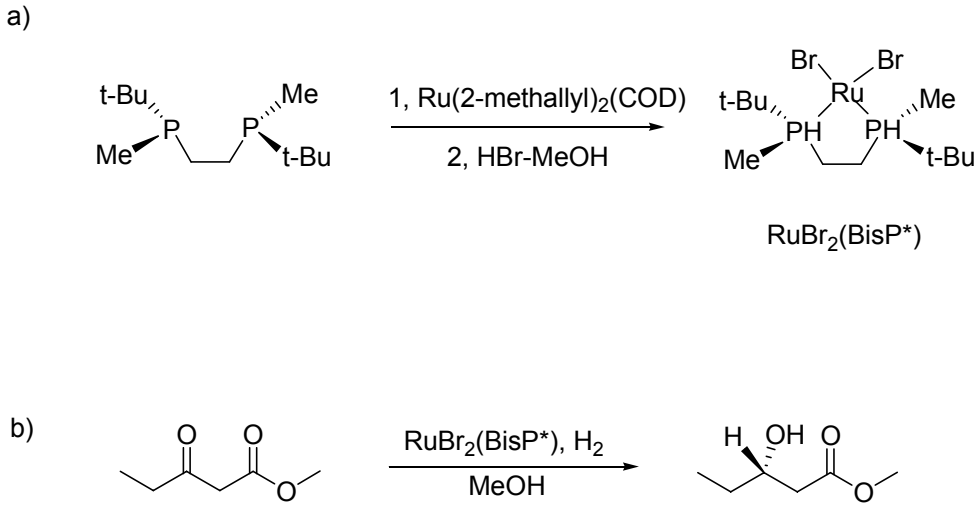
Asymmetric hydrogenation played a key role in the fundamental understanding of the catalytic reaction and offered the route from the simple to the very complex, allowing accumulation of the necessary knowledge before the next leap go to forward. Actually, the term “hydrogenation” refers to the step of the H_2-activation, because under ambient conditions H_2 is a rather unreactive molecule. The homogeneous hydrogenation allows the H_2-activation under mild conditions where powerful spectroscopic techniques can be easily used for the investigation of the reaction kinetics and the structures. Abundance of hydrogenation reaction can be examined almost step by step along the reaction coordinate and cleared the composition and structure of the reaction intermediates. The homogeneous hydrogenation, catalyzed by metal complexes offers powerful catalytic systems by the partially filled d or f electron shells of the transition metal. Due to this fact they have several interesting features, e.g. the ability to form strong bonds in a variety of oxidation states and to coordinate with several different ligands in their coordination sphere. Finally, the possibility of modifying the electronic and steric environment at the active site by the utilization of tertiary phosphine ligands is a remarkable opportunity to increase the selectivity and reactivity. Other important conditions, such as temperature, solvent, pressure, time can be modified in order to regulate the selectivity.

Few catalysts have been developed to produce alcohols from a range of ketones with absolute stereocontrol and high catalytic efficiencies. One of the best catalyst complexes for such a reaction (Scheme 2.6 *b,*) is built from 2,2´-bis(phosphino)-1,1´-biaryl (BINAP) ligand with ruthenium transition metal precursor developed by Noyori et al. This discovery was awarded by Nobel Prize. This system requires high temperature and 100 atm hydrogen pressure [55]. Genêt et al. have achieved the same result for the hydrogenation of *β*-keto-esters (Scheme 2.6) with [Ru(BINAP)Br_2](acetone) catalyst complex at atmospheric hydrogen pressure [56, 57].



Scheme 2.6 *a)* Formation of the catalyst complex; *b)* Hydrogenation of the *β*-keto-esters

The hydrogenation of (*R*)-(-)-methyl-3-hydroxypentanoate using BisP*-Ru complex (Scheme 2.7) is another example developed by Imamoto et al. [58], which can be applied to a wide range of *β*-keto-esters, *β*-keto-phosphonates and *β*-ketoamides.



Scheme 2.7 *a)* Formation of the catalyst complex; *b)* Hydrogenation of the *β*-keto-esters

In the last few years, the industrial application of the epoxidation, dehydroxylation and especially the hydrogenation have increased rapidly. Among these reactions, the enantioselective hydrogenation is the best investigated and most applied industrial reaction. Some of the most popular ligands with the preferred catalyst types and the state-of-the-art for the hydrogenation of olefins are summarized in Table 2.2 and in Table 2.3.

Table 2.2 State-of-the-art for the hydrogenation of olefins

Substrate	ee [%]	TON	TOF[h^{-1}]	Preferred catalyst types
enamides, enol, acetates, itaconates	90-98	1000-20000	200-5000	Rh/PCYCL, Rh/FERRO, Ru/BIAR, Rh/PPM
(C=C-C-OH) type of olefin	80-95	10000-50000	1000-5000	Ru/BIAR
C=C-COOH type of olefin	85-95	2000-10000	500-3000	Ru/BIAR, (Rh/PCYCL)
tetrasubstituted (C=C)	85-95	500-2000	200-500	Ru/BIAR, Rh/PCYCL, Rh/FERRO
C=C without privileged function	80-95	20-100	2-5	Ru/BIAR, Ir/P^OXAZ, Rh/PCYCL

Table 2.3 Explanation for the abbreviations of the preferred ligand types

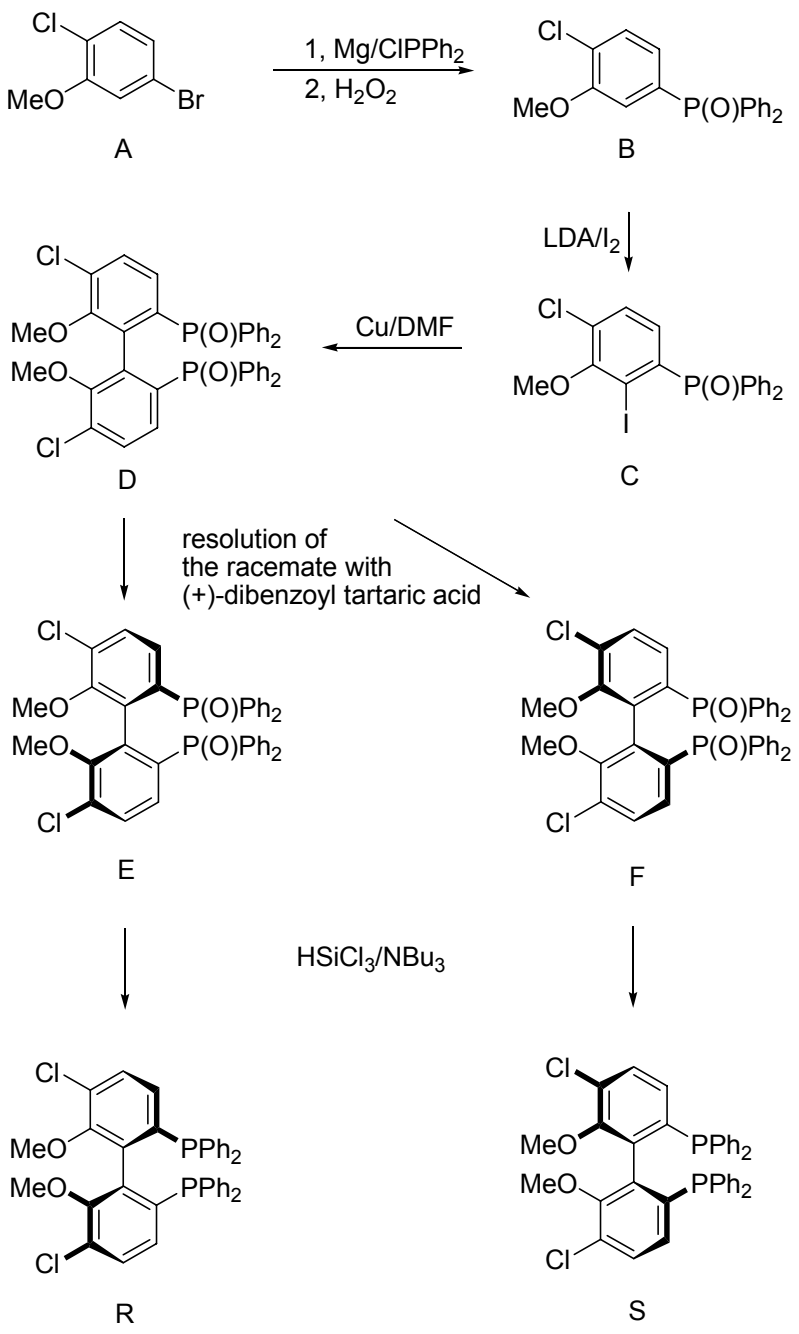
Ligand type	Family of the ligand
PCYCL	Ligands with cyclic phosphine, e.g. DuPHOS, ROPHOS
FERRO	Ferrocenyl-based ligands, e.g. JOSIPHOS, BPPFA
BIAR	Biaryl and heterobiaryl diphosphines, e.g. BINAP, Biphep
PPM	Binol-based ligands, e.g. BINOL, BINOP
P^OXAZ	Oxazoline-derivatived ligands, e.g. BISOXAZOLINE

As a consequence, there are no universal ligands for the asymmetric transformations but modifying of the properties of the new ligand by fine tuning is a versatile “tool” to create proper catalysts for specific reaction types.

The number of commercial applications will increase in the future because more and more specialized technological companies are developing the know-how and experience to produce technical quantities of the chiral ligands, which give rise to conduct of enantioselective catalytic processes with even better activity, productivity and robustness.

2.4.4 Chiral Cl-MeO-Biphep ligand

Cl-MeO-Biphep has been derived from the family of biaryl diphosphines ligands. It has been developed and patented by C. Laue at al. (Bayer AG) in 1996 [13], and commercialized for a new chiral hydrogenation technology with Ru and Rh metal complexes because of the high demand for active pharmaceutical ingredients. This ligand delivers greater more than 98.7 % enantioselectivity in asymmetric hydrogenation of carbonyl groups and carbon-carbon double bonds. Bayer AG (Lanxess FC) has contracted with the leader R&D chemicals manufacturer Strem Chemicals, Inc. to produce the ligand in research scale for promoting the development. The general synthesis of the Cl-MeO-Biphep ligand is depicted in Scheme 2.8.



Scheme 2.8 Synthesis of the Cl-MeO-Biphep biaryl based ligand **3**

First of all, bromo-aryl derivative **A** and chlorodiphenyl-phosphine were mixed in the presence of Mg and afterwards oxidized to obtain of the arylphosphine-oxide **B**. This product was iodized to **C**, which can be used as a starting material in an Ullmann coupling reaction to generate biphenyldiphosphine-oxide **D**. The racemate of the diphosphine derivative **D** was treated with (+)-dibenzoyl tartaric acid to separate the two

isomers **E** and **F** and after that it was reduced with $HSiCl_3$ in order to get the (*R*) and (*S*) isomers of biarylphosphine ligands as a pale yellow powder.
B. Drießen-Hölscher et al. [59] have developed a new synthesis route producing Cl-MeO-Biphep ligand (**3**) *via* the corresponding biphenol, which allows introducing several substituents without the necessity to separate the enantiomers of each derivative.
Bayer´s new synthesis [60] allows the introduction of a wide range of substituents (R-groups) in place of the phenyl group on the phosphorus because the racemic separation takes place before the R group is attached.
The typical price of such general ligands as the Cl-MeO-Biphep is between € 10.000-15.000 / kg and they are usually applied in ton scales per year. Due to the price, in the last few years the reuse and recycling of these ligands have become a main goal for the companies, which are interested in the catalytic and chiral technology.

2.5 Palladium catalyzed C-N bond-forming process

2.5.1 General Buchwald-Hartwig amination reaction [61]

Almost 10 years ago Buchwald [62] and Hartwig [63] have presented a new field of transition metal catalyzed cross coupling chemistry to prepare derivatized anilines and aryl ethers. These two publications have caused vast activities in academic and industrial research groups. These palladium catalyzed C-N and C-O bond-forming reactions are versatile, applicable and reliable both in academic and industrial use i.e. on small and larger scale, too. Nowadays these techniques have reached the multi-hundred kg production level in many companies, in spite of their rather rapid development and application.
Such a system as the Buchwald-Hartwig amination requires four components to prepare C-N bond. Two of them are the organic ligand and the Pd-precursor: they generate the efficient catalyst complex. This complex facilitates oxidative addition and provides sufficient bulkiness to accelerate reductive elimination. The adequate base can promote

the deprotonation of the substrate (amine) before or after the coordination to the palladium atom. Whilst these systems often possess heterogeneous characteristics, the selection of the solvent and the solubility of the base or the substrates play a more significant role than in other transition metal-catalyzed processes.

The C-N coupling reactions usually require ligands for their transformations, which show high reactivity and selectivity. Tremendous activities have been focused on this field over the last years [7, 64, 65]. Among the most frequently used ligands, the first to be mentioned are P(*o*-Tol)$_3$ and P(*t*-Bu)$_3$ [62, 66]. The chelating biphosphines BINAP, DPPF, DtBPF were used solely until Buchwald has presented the synthesis of the monodentate phosphine ligands with a biphenyl backbone. They allowed the amination of aryl chlorides and aryl halides even under mild conditions. The development of the new 2,4,6-triisopropyl-substituted ligand X-Phos [18, 67] resulted the more stable and active derivatives among the biphenyl based ligands. There were used for arenesulfonates and aqueous amination protocols, too.

In parallel, van Leeuwen [68] has developed XantPhos and DPEPhos ligands, which have specific activity for coupling reactions of amides, ureas, hydrazines and aryl halides. Verkade [69] has presented the application of triaminophosphines as electron-rich ligands with rigid framework. Pyrrole- and pyrazole-based biphenyl ligands were characterized by Singer et al. [70] in 1998. Such systems require strong base. Beller has described *N*-arylindole-substituted ligands [71] and adamantyl-based alkyl-phosphines ligands [72] for transformation of arly chlorides with high efficiency.

From the view of recycling, a solid-phase bounded derivative of biphenyl-based ligands was reported by Buchwald et al. [73] which was recyclable at least in three runs.

The possibility of the selection of a Pd-precursor is much more restricted than the choice of the ligand, which has a broad scope, as mentioned before. The most versatile Pd(0) precursors are the Pd(dba)$_2$, Pd$_2$(dba)$_3$, but the influence of the dba tag on the reaction could be remarkable. Among the Pd(II) precursors, Pd(OAc)$_2$, Pd(Cl)$_2$, Pd(acac)$_2$ should be mentioned. Reduction of Pd(II) species to Pd(0) can happen *in situ* in the presence of the ligand and base. The range of the loading of the Pd-precursors is wider than in other catalytic cross-coupling systems, thus some special reactions turned out to be successful with palladium loading down to 0.01 mol %, while a typical amount of palladium in amination reactions usually is 1-2 mol %. The impurities, whatever inorganic

or organic of the applied precursors and components have a great impact on the efficiency and reliability of these types of cross-couplings.

The subsequent major component of the Buchwald-Hartwig amination is the base e.g. Cs_2CO_3, K_2CO_3, K_3PO_4, KOH, NaOH, *t*-BuONa, which has a significant effect on the nature of the reaction by the solubility of the bases in polar (homogeneous system) or apolar (heterogeneous system) organic solvents. These are caused by the counterion and the particle size of the base. Notable side-reactions can also be remarkable by utilization of different strong bases (low functional group tolerance). Different ligands are adequate to diverse types of bases thus the base K_3PO_4 is frequently used with biphenyl-based ligands while for example the Cs_2CO_3 mostly promotes the cross-coupling reactions with the chelating biphosphine ligands.

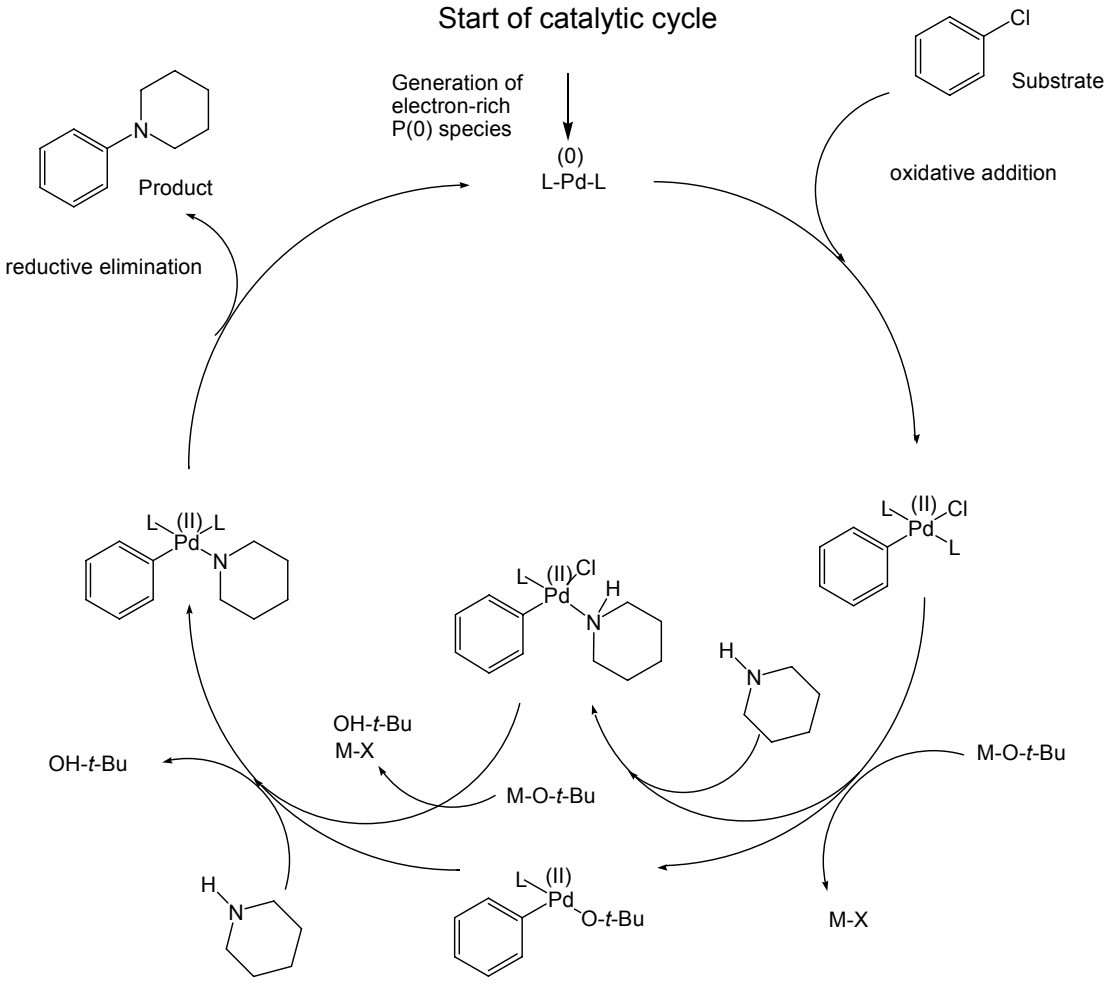
Solvent / temperature are the last factors described in the Buchwald-Hartwig amination. The solvent plays a main role in stabilizing the intermediates and in dissolving of the reaction partners, as well. The most frequently applied solvent is toluene, but for solubility reasons some polar solvents are also commonly used, e.g. DMSO, NMP, DMF. Because many catalysts are air-sensible the solvent has to be dry and the air contact has to be avoided during the reaction. In special cases using less air-sensitive ligand, the air has no influence on the yield.

These reactions are usually conducted inside a range of 70 – 140 ºC by using Pd-precursor with biphenyl-based ligands. The preparation of the catalyst is worked out sometimes *in situ* before the catalytic run allowing sufficient time for the formation of the active species. In many cases, other additives e.g. water or alcohols can be added to the mixture to facilitate the reaction and increase the conversion.

2.5.2 Proposed Mechanism of the amination reaction

Two mechanisms were discussed in details by different workgroups. The three main parts of the mechanism cycle are the oxidative addition of substrate, formation of amido complexes and the reductive elimination [64] (Scheme 2.9). In the early stage of these reaction types the whole cycle was not fully characterized but several calculated models were published giving an impression on the role of the additional phenyl group as a co-

ligand. The rate-determining step is the complexation of the amine to the catalyst. During the catalytic cycle the concentration of the active catalyst species is increasing to its steady-state concentration. According to the recent research the *σ*-substituted biphenyl based Buchwald ligands own notable role in the sequential coupling reaction of aryl chlorides [67]. The catalysts with less bulky substituents are required longer exposure to the amine to become fully activated than those bulkier based derivatives.

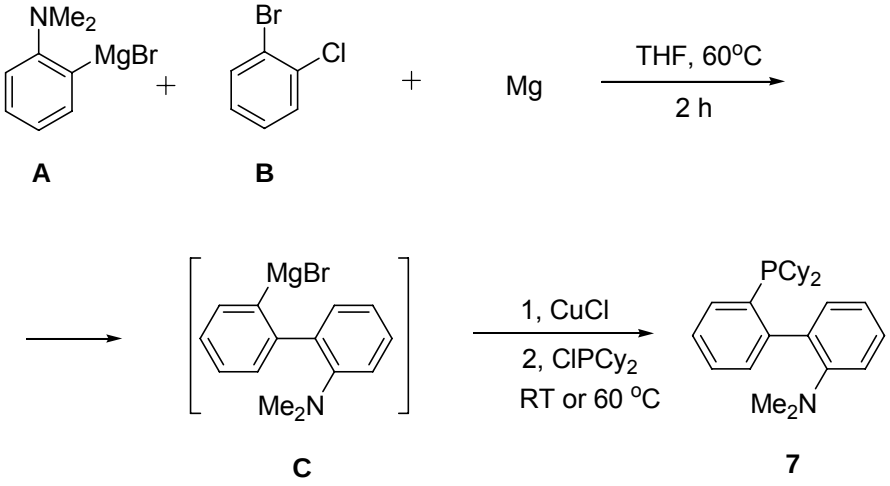


Scheme 2.9 Proposed mechanism for the catalytic cycle of the amination [61]

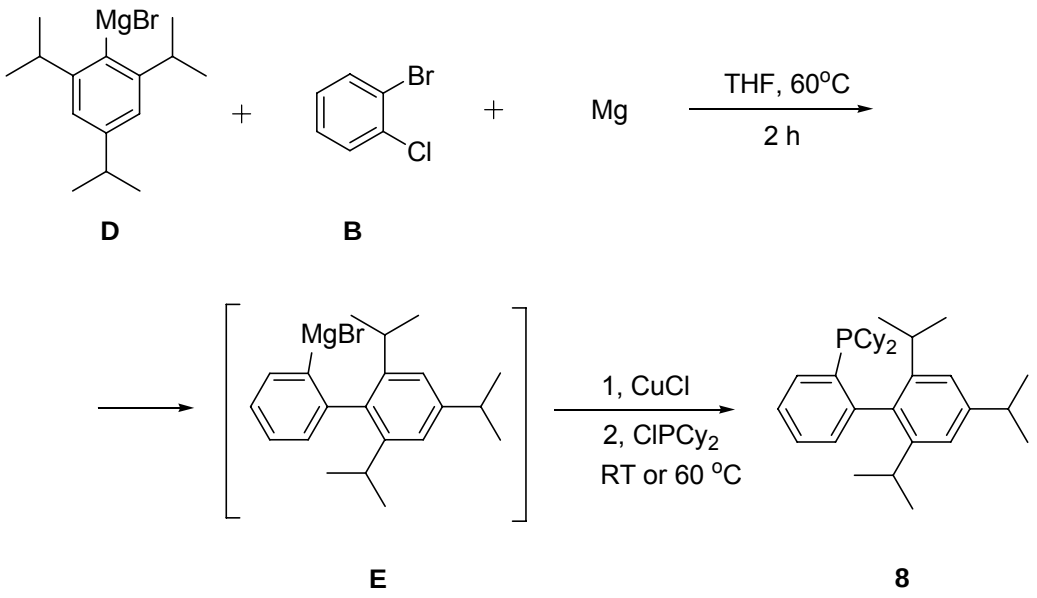
In case of less bulky or smaller ligands, the L:Pd ratio has also significant influence on the rate of catalyst activation *via* the phosphine dissociation from bisphosphine complex, while the rate dependence was influenced by the larger ligands.

2.5.3 Dave-Phos and X-Phos ligands applied in C-N formation

The Buchwald-Hartwig C-O and C-N coupling transformations has been proven to be robust, reliable and useful to produce nitrogen-containing ligands as well as natural products and their analogues for the synthesis of heterocycles even on an industrial scale. Therefore the scope of this technique is enormous. The biphospine BINAP dominate this field of reactions because this ligand is easily available and widely examined. The utilization of this ligand does not require any extensive and lengthy optimization. Naturally, the development of new ligands also continues with high activity, e.g. the use of Buchwald´s biaryl ligands by Lakshmann [74]. This subsection focuses on two newly evolved ligands named as Dave-Phos (Scheme 2.10, **7**) and X-Phos (Scheme 2.11, **8**). The synthesis of their can be seen from Scheme 2.10. and Scheme 2.11.



Scheme 2.10 Synthesis of Dave-Phos ligand (**7**)



Scheme 2.11 Synthesis of X-Phos ligand (**8**)

Their synthesis has been reported on a lab scale using a Grignard strategy. The first amount of magnesium was added together with 2-bromo-N,N-dimethylaniline (**A**) (at synthesis of Dave-Phos Scheme 2.10) or 1-bromo-2,4,6-triisopropylbenzene (**D**) (at synthesis of X-Phos Scheme 2.11) until formation of Grignard reagent was complete. The second crop of Mg and 2-bromochlorobenzene (**B**) were also added to the mixture [75, 76]. In the last step CuCl and $ClPCy_2$ were reacted with the mixture to get the ligands (**7**, **8**).

Using the Buchwald´s ligand Dave-Phos, two patents were reported by Pfizer on a 3-kg scale for the synthesis of CP 529,414 [77, 78]. Efficient scale-up procedure was also completed with X-Phos ligand for the large scale Pd-catalyzed hydrazonation of aromatic chlorides by Mignani et al. [76]. Because of the competition among the industrial groups the number of examples not published openly may be much larger in this field of research.

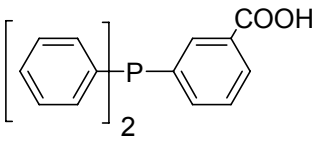
2.6 Biphasic systems for reuse and recycling of the catalyst complexes

As described before, the price is a very determining parameter in the catalysis and chiral business. After the asymmetric hydrogenation, used catalysts are usually difficult to recycle because of accumulated contaminations. Immobilization methods e.g. with ionic liquid, silica, alumina or clay could solve these problems and in this manner reused catalysts are also at least as selective and active for up to 15 times without leaching like the brand new synthesized complexes. The homogeneous catalysis, in this sense could be attainable with aqueous “heterogenized”, “immobilized” or “anchored” catalyst complexes.

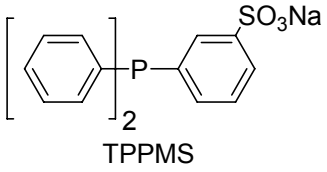
2.6.1 Immobilization by aqueous catalysts

One of the most employed and important method in this field is the immobilization technique of the aqueous catalyst. That mode uses a homogeneous catalyst, dissolved in water as a “mobile” phase (mobile support). In this manner, the catalyst and the reactants are easily separable just after the reaction, at approximately the same temperature and without any chemical stress. In this relation the catalyst is not “anchored” but “immobilized” as well as “heterogenized” on “liquid supports”. Those systems belong to type of the immobilization by aqueous catalysts in which the procedure does not contain any additional steps (except for temperature control) to promote the phase separation. It makes possible a new start of the catalytic runs immediately in the same phase without any additional reaction. Many papers review the fundamentals and limitations of the aqueous-phase homogeneous catalysis and the special role of the water [79, 80, 81]. The solubility of the ligand in water is increased by introduction of highly polar substituents, for example -SO_3Na, -NH_2, -OH, or -COOH and by variation of the nature and the number of them and/or by the condition (e.g. pH) of the aqueous phase. By that way, almost any desired ratio of hydrophobic and hydrophilic properties can be obtained. For example, the solubility of hydroxyl phosphines depends on the nature of the parent phosphine and on the number of

hydroxy substituents. A special case is the triphenylphosphine ligand with one (mono-, M) two (di-, D) or three (tri-, T) meta-positioned sulfonic acid groups. These derivatives differ in their hydrophilicity and their hydrophobicity following the next series with increasing in hydrophilic characteristic: TPPMS<TPPDS<TPPTS. The last ligand contains three meta-positioned sulfonic acid groups. A review about the synthesis of water-soluble ligands has been published in detail by Herrmann and Kohlpainter [82]. Some of such water-soluble ligands are listed in Figure 2.9.

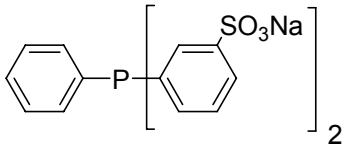


1945 Gilmann, Brown



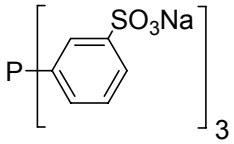
TPPMS

1958 Ahland, Chatt
1975 Joó, Beck
1978 Wilkinson



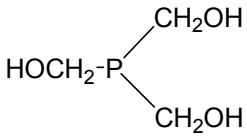
TPPDS

1975 Kuntz / Rhône Poulenc
1987 Kuraray Corp.



TPPTS

1975 Kuntz / Rhône Poulenc
1982 Cornils / Ruhrchemie

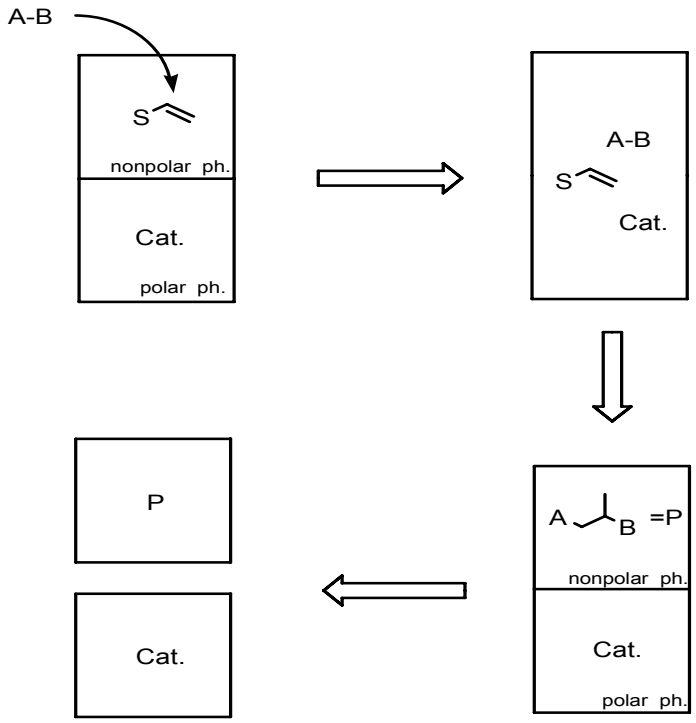


1973 Chatt et al.
1989 Harrison et al.

Figure 2.9 Water-soluble ligands used for oxo homogeneous catalysts

The great advantages of the ligands listed in the previous table are, that they are able to overcome the basic problem of homogeneously catalyzed processes: the separation of the product phase from the catalyst itself. Several times, the separation processes

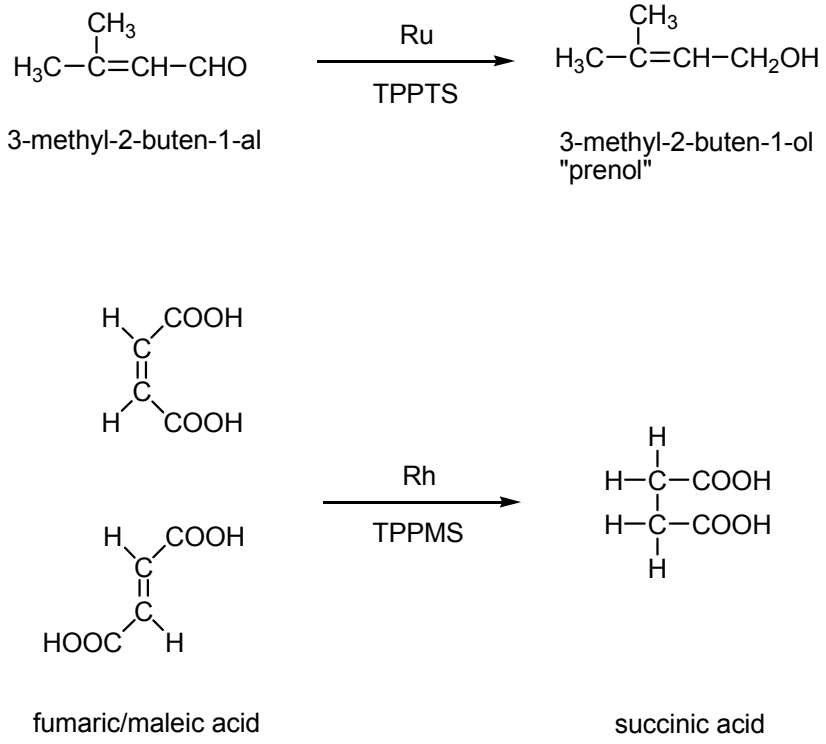
include thermal operations such as distillation or rectification, which may lead to decomposition of the catalyst complex and/or can decrease the lifetime and productivity of the catalyst, due to the thermal stress on the catalyst. The separation processes are easier in biphasic systems in which the water-soluble catalysts and the aqueous biphasic system are incorporated. The next figure shows a general example for the biphasic catalyst system in water (Scheme 2.11).



Scheme 2.11 General biphasic catalytic system for hydroformulation reaction

The hydrophilic ligand containing the water-soluble catalyst converts the substrates (A-B = syngas, S = propene) to the products in which the catalyst (polar phases) can be separated from the product (nonpolar phases) by simple phase separation after the reaction. The leaching and loss rate of the catalysts are often below the limits of the detection, because of the insolubility and polarity of the ligand in the organic phase. Naturally, the aqueous biphasic systems require a minimum solubility of the reactant (S and A-B) in the organic phase. The incorporation of the biphasic system with the hydrogenation of C=O and C=C bonds have been published by Sinou [83], Southern [80] and by Herrmann and Kohlpainter [82], especially with chemical aspects up to 1993. The

nowadays investigated biphasic hydrogenation, using plenty of substrates mainly with the water-soluble TPPMS ligand coordinated to Rh or Ru complexes [84-86] could be a versatile key for the selective reductive operation in industry. Scheme 2.12 shows some very widely examined reactions.



Scheme 2.12 Two examples for deeply investigated reactions

Existing evidence for the extension of two-phase catalysis into the new area of a C_1-chemistry, for example Leitner et al. [87] described biphasic hydrogenation of CO_2 to formic acid. The biphasic hydrogenation of aromatic nitro compounds with Pd or Rh catalysts are investigated by Tafesh [88].

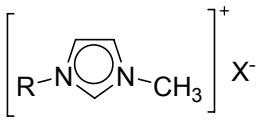
Activities on this field are the development of new solvent system such as N-methylpyrrolidon (NMP) or polyalkylene glycols. Alkali salts of mono-sulfonated triphenylphosphane (TPPMS) ligands combined with Rh are soluble in such a medium. The combination of the homogeneous catalysis with a catalyst recycling by a phase separation is the key advantage in this technique.

2.6.2 Immobilization by nonaqueous biphasic systems

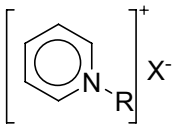
The low water solubility and the moisture sensibility of many organic compounds limit the application of aqueous catalysts. The nonaqueous biphasic system provides the catalyst only in the catalyst phase under the reaction conditions. Such kind of phases could be for example fluorous phases or ionic liquid phases. The choice of a nonaqueous phase for a defined reaction depends on the solvent properties of the product, if it is e.g. apolar, the catalyst phase should be polar and vice versa.

The *fluorous phase* is defined as the fluorocarbon-rich phase of a biphasic system consisting mostly perfluorinated alkanes, ethers or tertiary amines. Perfluorinated alkyl ethers or perfluorinated alkanes are also used as solvent. The mostly applied ligand for such an application is the normal homogeneous catalyst by modified with attached flourous ponytail to the core of the ligand. The most effective fluorocarbon ligands are linear or branched perfluoroalkyl chains with high carbon number. These ligands have been applied with success for cross-coupling, Diels-Alder, hydrosilylation and of course for hydrogenation reactions [89, 90]. In this case, again the phase separation is the key step of the recovery of the ligands paying attention on the solubility properties of these systems.

The other more detailed nonaqueous biphasic system uses *ionic liquids* (IL) as a second phase in addition to the product phase. These liquids are solvents that are entirely composed of ions. They have no vapor pressure and can be used as liquids over a wide range of temperature. They possess high ionic conductivity and a broad electrochemical window. Ionic liquids are currently under intensive investigation as alternative solvents for the biphasic catalysis. The term ionic liquid refers to 1-alkyl-3-methylimidazolium salts and pyridinium salts. The alkyl chain (R) corresponds to the structure C_nH_{2n+1}, while the counter anion (X^-) could be $AlCl_4$, $SnCl_3$, BF_4, PF_6, CF_3SO_3, SbF_6 or other molted salts e.g. ammonium or phosphonium. Examples for the structure of these liquids are shown in the Figure 2.7.



imidazolium ionic liquid

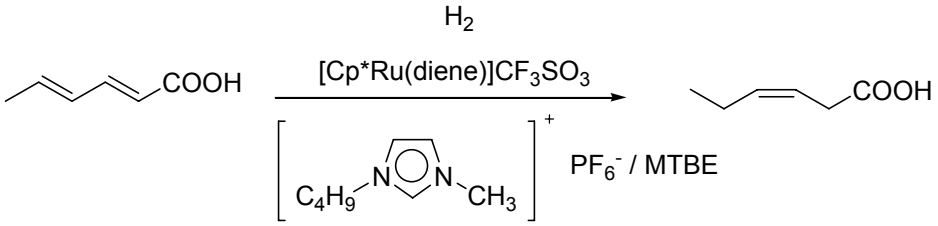


pyridinium ionic liquid

Figure 2.7 General structures of ionic liquids

In general, IL contains a bulky anion and a large cation with low symmetry. Therefore the lattice energy and the melting point of this solvent are low. The individual properties (polarities, melting points etc.) of the easily prepared IL are fine tunable by selection of the anion as well as the cation´s. The first research in the homogeneously catalyzed processes with IL was described in case of chloroaluminate melts for the Ni-catalyzed dimerization of propene by Guibard et al. in 1990 [91]. Because of the advantages of the excellent solubility of the organometallic compounds (numbers of traditional catalysts complexes) in IL, in some cases this liquid is used as a replacing media of the conventional organic solvent and as a supporting phase for the catalyst. In such cases the reuse or the recovery of the complexes are usually easy by simple phase separation or by extraction immediately after the reaction. These media also have an important influence on the reaction rate and selectivity, which depend on the anion that can be coordinating or noncoordinating as well as Lewis-acid, Lewis-basic or neutral. In this case, the cation does not play a significant role.

High selectivity and enhanced activity are reachable with IL in the hydrogenation reaction of alkenes in which the catalysts are equipped with the customary Ru, Rh, Pd or Pt metals. Examples are reported e.g. for enamide preparation with successfully immobilization and reuse of the catalyst several times without loss of catalytic activity [92], for Sonogashira coupling reactions performed in IL without copper salts and bulky phosphine ligands. The hydrogenation of *β*-aryl ketoesters using Ru/BINAP complex at room temperature IL has been published by Ngo at al. [93, 94] without metal contamination of the product and without leaching of the catalyst. In case of the hydrogenation of cyclohexadiene [95] and sorbic acid [96] the reactions show an extraordinary high product selectivity (Scheme 2.13).



Scheme 2.13 Hydrogenation of sorbic acid in IL

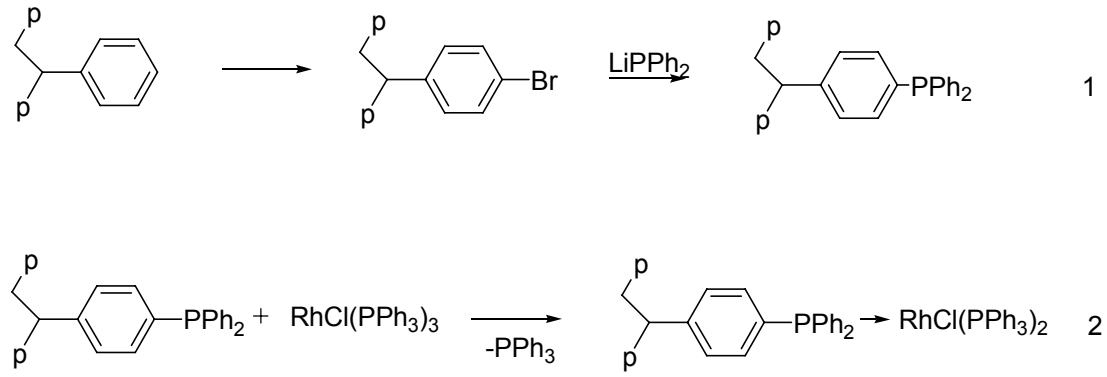
In conclusion, the ionic liquid as new class of a polar solvent provides a fine tunable medium for many biphasic homogeneous reactions by the appropriate selection of the anion, cation and the co-solvent. Consumption of the amount of the catalyst and the organic solvent can be reduced by utilization of the IL because of its nonvolatility property and the easy phase separation.

2.6.3 Immobilization and fixation to supported organic and inorganic polymers or matrices

An intensive research in this field started in the late 1960s when ligands named as ”supported” or “anchored” metal catalyst complexes were applied. These types of processes combine the advantages of the homogeneous catalysis (high selectivity and activity, good reproducibility) and the heterogeneous catalysis (easy separation and long lifetime of the catalysts). The first publications came from Acres et al. [97]. The anchoring of the complexes could be done by different methods: the first to be mentioned is the fixation or immobilization *via* covalent bonding to the organic and to the inorganic supports.

The most frequently used organic support is the polystyrene and styrene-divinylbenzene copolymers with several functional groups. The phosphinated polystyrene (eq. 1) seems to be the best auxiliary to design the structure of the anchored ligand [98] (Scheme 2.14). The often used routes to prepare polymer-anchored ligands (eq. 2) are the displacement of a ligand by coordinating to a soluble metal catalyst. The suitable complexing groups and polymers can be designed by simple organic synthesis. Instead of polystyrene

derivatives as a polymer, cellulose, polyacrylates, polyvinyls are also often applied in this technique for hydrogenation, hydrosilylation, oligomerization, dimerization reactions. For example, in the case of hydrogenation of olefins, the recycling of the catalyst is easily practicable because the complexes bounded to organic matrices have different affinity between the nonpolar olefins (product) and the polar organic matrixes. In principle, the chemoselectivity of immobilized metal (Rh, Ru, Pd) complexes is similar, whilst the activities are lower in comparison to the homogeneous systems. The steric properties (crosslinking, degree of flexibility) of the organic supports have a great importance in these systems because the catalytic reactions particularly take place on the surface of the polymers.

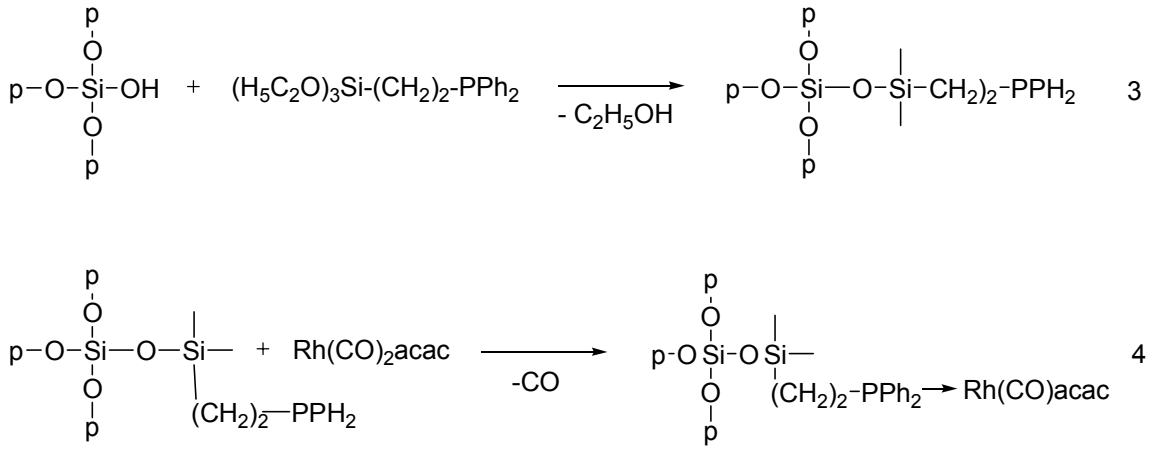


p = polymer or polymeric network

Scheme 2.14 Universal route for preparing and coordinating the functionalized ligand to the catalyst complex

The latest works and activities using soluble polymers to recover the catalyst have been published by Bergbreiter [99]. Xiao et al. [100] have published the hydrogenation of ketones with supported organic complexes applying a poly(ethylene glycol)-supported (PEG-2) chiral diamine as ligand, which is attached to the phenyl rings. Chen at al. [101] have prepared soluble bifunctional polymeric BINOL-BINAP and BINOL-BINAPO copolymers by condensation for enantioselective reactions and in the same year recyclable PEG and diguanidinium tethered BINAP have been described by Dellis et al. [102].

The use of inorganic support is less common than the previously mentioned organic polymers, although the better physical properties of the former can be more compensating for the better chemical properties of the latter [103]. These usually provide higher temperature, solvent and aging stability and rigid structure, which prevents the deactivation of the bounded catalysts. Disadvantages of these systems are the limited number of reactive surface groups (possibility of the further functionalization) and a lower limit of functional groups than in the organic supports. The commonly applied inorganic supports are silica, clay, glass, alumina, magnesia, ceramic. Among these auxiliaries, the silanol group modified silica is the most preferred support because of its pore size, pore volume, form and size of particles, surface area and number and nature of the surface groups. The mechanism of the catalytic system and the nature of such catalyst complexes remain unclear. Two alternative approaches have been applied to describe the attachment of the ligand to the supports (eqs. 3 and 4) (Scheme 2.15).



Scheme 2.15 eq. 3, ligand group is attached to the support, eq. 4, reaction between the phosphine-functionalized silica and the monomeric metal complex

Recent publications were presented in the hydrogenation of ketones using mainly silica-immobilized catalysts, e.g. Tu et al. [104, 105] have developed the chiral Ru-TsDPEN catalyst, which was successfully immobilized on amorphous silica gel and mesoporous

silicas of MCM-41 and SBA-15. Pugin et al. [106] published a silica gel supported chiral biaryl-diphosphine ligands (MeO-Biphep, Biphemp) for testing and recycling in asymmetric hydrogenation of methyl-acetamidocinnamate.

Other methods for the fixation of the ligand to the support are also accomplished, for example by ionic bond and by chemisorption or physisorption. Finally, the immobilization can take place by impregnation of the solid support with a liquid medium, which contains the dissolved homogeneous catalyst. The medium can be either of organic nature (SLPC = supported liquid-phase catalyst) or water nature (SAPC = supported aqueous-phase catalyst).

3 Results and Discussion

3.1 Aims and Scopes

The modern “green” chemistry requires minimizing of energy consumption and waste production. These two parameters have become a major concern for the chemical industry. The use of catalytic systems could be the answer, because they render rapid and selective chemical reactions.

As described in the last chapters, the ligand has a significant practical role in the catalytic transformations of different compounds. The appropriately selected ligand allows the reaction to perform with high conversion and selectivity giving a notable chance of profit for the manufacturer.

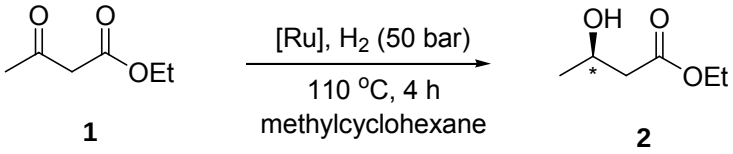
Our primary aim in the project was the recovery of the used ligand with at least 70 % after the reaction and the reuse of it in the next two runs. The Cl-MeO-Biphep ligand (**3**) is patented by Bayer AG (Lanxess FC) and applied for asymmetric transformations on an industrial scale. The standard reaction of the project was the reduction of *β*-ketoester to the corresponding alcohols (Scheme 1.1). In addition this ligand could be powerful in many other reactions to yield natural products, pharmaceuticals or special intermediates. The manufacturing costs of the product are determined by the used catalyst, solvent, and mainly by the applied ligand. That is why it will be useful to recycle the catalyst.

The initial work on this field was the control of the reaction conditions (temperature, H_2 pressure, reaction time, precursor and S/C ratio) with which appropriate conversion and highest *ee* could be reached. The following step was the test of different solvents to accomplish an advantageous reaction medium for the complete recovery of the complexes with e.g. SLPC systems or IL. Latest concept was the derivatization of the Cl-MeO-Biphep ligand in order to get an opportunity to obtain the derivative of the organic ligand in its pure solid form after the catalytic reaction. In this manner, the recycled ligand was reused in a new catalytic cycle to investigate the activity and selectivity in the hydrogenation reaction.

Another part of the project was the amination reaction (Scheme 1.2) using two Buchwald´s ligands mentioned earlier (section 2, compound **7** and **8**). Due to the similar

chemical properties compared to Cl-MeO-Biphep (**3**), the Dave-Phos (**7**) or X-Phos (**8**) can be recovered *via* derivatization of the ligand.

3.2 Asymmetric hydrogenation with different conditions and solvents using Cl-MeO-Biphep and BINAP ligands



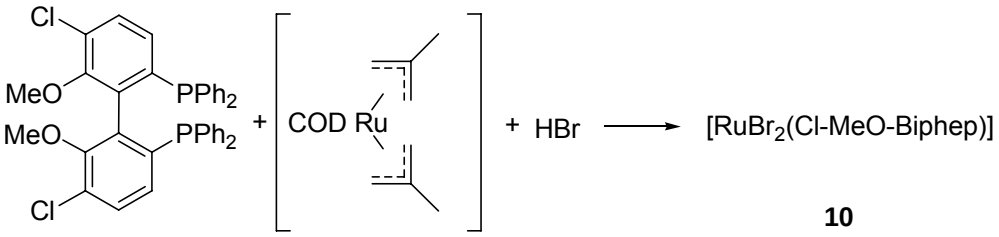
1 **2**

Scheme 3.1 Asymmetric hydrogenation of β-ketoester

To reach our aims, firstly the conditions of the hydrogenation reaction and the applied ligand itself were investigated in order to determine and to increase the activity of the system. In the following work, several types of recycling methods were tested to recover and/or reuse the organic ligand by building the catalyst complexes **10** and **12** with the corresponding precursor **9** before the standard hydrogenation reaction.

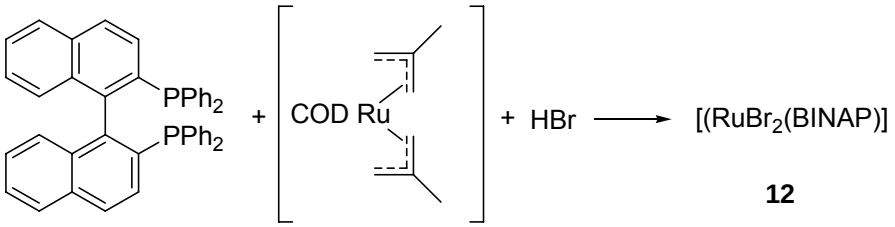
*3.2.1 Comparison of the two biaryl type phosphine ligands **3** and **11***

Firstly, asymmetric hydrogenation of **1** was carried out using Cl-MeO-Biphep (**3**) and BINAP ligand (**11**) with [bis-(2-methylallyl-cycloocta-1,5-diene) ruthenium(II)] complex (**9**) as precursor to gain experiences about the activity of the systems and to draw a comparison between ligand **3** and ligand **11**. In Scheme 3.2 a, and 3.2 b, the synthesis of complex **10** and **12** is depicted.



3 **9** **10**

Scheme 3.2a Synthesis of the new [$RuBr_2$(Cl-MeO-Biphep)] catalyst **10**



11 **9** **12**

Scheme 3.2b Synthesis of the known [$RuBr_2$(BINAP)] catalyst **12**

The hydrogen pressure and the reaction time were changed to obtain the highest conversion, which will be adopted as a standard condition for further investigations.

Table 3.1 Results of the hydrogenation of **1** applying different conditions and ligands

Entry	Ligand	Substrate	pH_2 [bar]	T [ºC]	t [h]	Conv.[a] [%]	Product
1	**3**	**1**	10	110	24	99	**2**
2	**11**	**1**	10	110	24	58	**2**
3	**3**	**1**	50	110	4	97.5	**2**

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). S/C=100. solvent: ethanol

In both cases (Table 3.1, Entry 1, 3), when ligand **3** was used, the conversion as well as the activity of the ligand was higher than with ligand **11**. As described in chapter 2, the BINAP (**11**) is the mostly applied phosphine ligand in asymmetric industrial processes.

The tested ligand **3** is also at least as active in case of hydrogenation of *β*-ketoesters (Table 3.1) as the extensively used and investigated BINAP **11**. Further investigations were focused exclusively on the ligand **3**. The results of the spectroscopic measurements showed slight modification and/or decomposition of **3** when the reaction time was reduced (4 hours). This could be monitored by ^{31}P-NMR spectra after the reactions.

*3.2.2 Use of different solvents for the reduction of **1***

Similar to the previous examples, the reactions are commonly conducted and deeply investigated in MeOH or EtOH in most of the cited literatures, due to the good solubility of the hydrogen in these solvents. Other media than cyclohexane were tested in order to solve the problem of the crystallization of the solvent in bigger scale industrial applications. Thus beside cyclohexane, methylcyclohexane was also tested as medium in the hydrogenation reaction under standard conditions to monitor the activity and selectivity of the complex **10** after more consecutive runs. Table 3.2 and Table 3.3 show the results of the hydrogenation in these solvents in consecutive runs.
In both cases (Table 3.2 and 3.3), the separation of the product **2** was performed *via* simple vacuum distillation and the residue consisting of complex **10** was used in the following run. In this manner, the same complex **10** was reused in 4 and 6 consecutive runs.

Table 3.2 Hydrogenation results using cyclohexane as solvent

Run	Ligand	Substrate	pH$_2$ [bar]	T [°C]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1	**3**(*R*)	**1**	50	110	4	99	-	**2**(*R*)
2	**3**(*R*)	**1**	50	110	4	99	53	**2**(*R*)
3	**3**(*R*)	**1**	50	110	4	99	51	**2**(*R*)
4	**3**(*R*)	**1**	50	110	4	99	40	**2**(*R*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). S/C=100. The same catalyst residue of **10** was used in every run.

Table 3.3 Hydrogenation results using methylcyclohexane as solvent

Run	Ligand	Substrate	pH_2 [bar]	T [ºC]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1	**3**(*R*)	**1**	50	110	4	99	64	**2**(*R*)
2	**3**(*R*)	**1**	50	110	4	99	69	**2**(*R*)
3	**3**(*R*)	**1**	50	110	4	99	56	**2**(*R*)
4	**3**(*R*)	**1**	50	110	4	99	24	**2**(*R*)
5	**3**(*R*)	**1**	50	110	4	-	12	**2**(*R*)
6	**3**(*R*)	**1**	50	110	4	99	15	**2**(*R*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). S/C=100. The same catalyst residue of **10** was used in every run.

We were pleased to notice that all conversions remained nearly 100 %, which means that the activity of complex **10** is excellent under these conditions. During the whole process the catalyst **10** did not decompose. However, after the last run [$RuBr_2$-(Cl-MeO-Biphep)] complex **10** could be transformed and oxidized as the ^{31}P-NMR spectra indicate when cyclohexane or methylcyclohexane was used. The *ee* values (ranging from 40 % - 53 % and 15 % - 64 %, Table 3.2 and 3.3) show the same tendencies but slightly higher excesses were reached when methylcyclohexane was employed as a reaction medium. On the other hand, in all cases the *ee* drops after each run indicating impurities in the system.

The properties of methylcyclohexane when employing in bigger scales are also more eligible than cyclohexane´s due to the more complicated handling.

Propylene carbonate was also tried as a solvent for the transformation of reaction **1** because of the high boiling point (240 ºC) of the medium. It could give rise to accomplish the reuse of the complex **10** during more runs. In principal, the solvent phase can preserve the catalyst **10**, which can be utilized in several runs. The separation of the product could occur by distillation. Unfortunately, we did not have success with this process because the formation of hydride species [107] (δ (ppm) = 43.62, 59.06) and oxidization of the complex **10** (δ (ppm) = 26.73, 29.01) was observed after one hydrogenation reaction indicating by the lack of the catalyst peak (δ (ppm) = -14.91) in the ^{31}P-NMR spectra.

*3.2.3 Applying IL as a medium for the enantioselective hydrogenation of **1***

In this subsection the most encouraging recycling concept was the application of IL ($BMIM^+BTA^-$ = butyl-methyl-imidazolium-bis-triflylamide) as the solvent creating the immobilized catalyst of complex **10**. This liquid provides special media for recovering the organic ligand, through the separation in such a biphasic system could be conducted by simple distillation or extraction immediately after the transformation. The first and the second recovery test (Table 3.4 and Table 3.5) present the results, which show a great efficiency of the catalyst under these conditions.

Table 3.4 Hydrogenation using IL ($BMIM^+BTA^-$) as media (first recovery test)

Run	Ligand	Substrate	pH_2 [bar]	T [ºC]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1	**3**(*R*)	**1**	50	110	4	99	86.5	**2**(*R*)
2	**3**(*R*)	**1**	50	110	4	99	82.8	**2**(*R*)
3	**3**(*R*)	**1**	50	110	4	97	60.0	**2**(*R*)
4	**3**(*R*)	**1**	50	110	4	88	58.5	**2**(*R*)
5	**3**(*R*)	**1**	50	110	4	77	-	**2**(*R*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). S/C=100. The same catalyst residue of **10** was used in every run.

Table 3.5 Hydrogenation using IL ($BMIM^+BTA^-$) as media (second recovery test)

Run	Ligand	Substrate	pH_2 [bar]	T [ºC]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1	**3**(*R*)	**1**	50	110	4	99	93.5	**2**(*R*)
2	**3**(*R*)	**1**	50	110	4	99	82.7	**2**(*R*)
3	**3**(*R*)	**1**	50	110	4	99	69.2	**2**(*R*)
4	**3**(*R*)	**1**	50	110	4	87.5	52.2	**2**(*R*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). S/C=100. The same catalyst residue **10** was used in every run.

In the first case (Table 3.4), the separation of the product **2** was done by extraction with *n*-hexane, while in the second recovery test (Table 3.5) vacuum distillation was applied after each run. No significant differences between two ranges of results (conversion and

ee) were observed in spite of the thermal stress on the catalyst **12**, however the product **2** is obtained in higher purity when distillation was used (verified by ^{1}H-NMR).
The conversions in both cases reveal that in such a biphasic system the potential of the complex **10** shows high-level consistency without loss of catalytic activity during at least three subsequent runs. In both cases (Table 3.4, Table 3.5), the value of *ee* decreased slower after each run presenting less impurities in the system. The leaching of the catalyst may be avoided when distillation was used for the separation of product **2**.

In the last part, a mixture of IL ($BMIM^+BTA^-$) and the commonly applied EtOH was investigated to combine both advantages of them (good hydrogen solubility and excellent immobilization of the catalyst) in order to improve the performance of asymmetric reduction. Both, extraction and distillation are applicable for the separation of the product **2** from IL phase, but the latter mentioned process was more convenient. In case of extraction, slightly leaching (verified by ^{1}H-NMR) of the catalyst **10** from the IL phase may occur.

Table 3.6 Hydrogenation using IL ($BMIM^+BTA^-$)/EtOH (1:1) as reaction media

Run	Ligand	Substrate	pH_2 [bar]	T [°C]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1	**3**(*R*)	**1**	50	110	4	98.5	96.2	**2**(*R*)
2	**3**(*R*)	**1**	50	110	4	99	28.8	**2**(*R*)
3	**3**(*R*)	**1**	50	110	4	99	59.9	**2**(*R*)
4	**3**(*R*)	**1**	50	110	4	96.5	58.6	**2**(*R*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). S/C=100. The same catalyst residue **10** was used in every run.

Finally, the highest *ee* (Table 3.6, Run 1) compared to the investigated systems was achieved using IL/EtOH (1:1). Less impurity appeared due to the addition of IL when the reduction was carried out in common organic solvents. This fact was indicated also in the *ee* values.

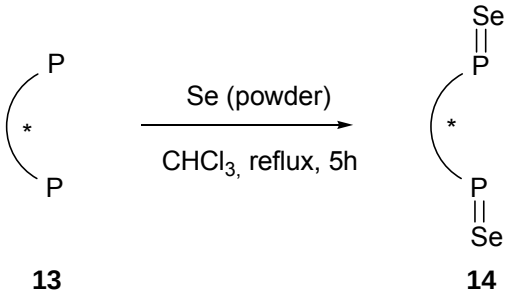
As a consequence, IL has a great advantage of recyclability and provides an excellent medium in which the compound **1** was hydrogenated both with high conversion and high *ee* (Tables 3.4, 3.5, 3.6). A disadvantageous property of IL system is, that the loaded catalyst especially the ligand is no more separable from this liquid. In some cases, the deactivated ruthenium may be separated from the ligand. This ligand in IL solution can be reused in catalytic transformation by adding fresh Ru-precursor.

Our aspect during the project was to accomplish an industrially-suited process in which the recycling of the ligand is profitable. The reduction in IL provides encouraging results and facilitates the recovery of the ligand. As a disadvantage, these liquids are usually purchased at a too high price (> 600 €/kg) for an industrial application.

To summarize, further asymmetric hydrogenations will be commonly conducted in methylcyclohexane at 50 bar hydrogen pressure and at 110 ºC for 4 hours.

*3.2.4 Investigation of σ-ability of Cl-MeO-Biphep (**3**)*

To estimate the σ-donor ability of the phosphorous center of the Cl-MeO-Biphep (**3**), phosphane-selenide (**14**) was prepared *in situ* from the corresponding diphosphanes with elemental selenium in chloroform under reflux [108] (Scheme 3.3). An increase in this coupling constant indicates a less basic phosphane. The *σ*-donor ability of a phosphane group can be calculated by measuring of the magnitude of $^{1}J_{P,Se}$ in the ^{77}Se isotopomer.



13 **14**

Scheme 3.3 Synthesis of diphosphane selenides

Table 3.7 ^{31}P-^{77}Se coupling constants of different ligands in compound **14** [108]

Entry	Diphosphane Ligand	$^{1}J_{P,Se}$ in 14 [Hz][a]
1	BINAP	738
2	**Cl-MeO-Biphep**	**764**
3	MeO-Biphep	742
4	Synphos	740
5	Segphos	738
6	PPh_3	732

[a] recorded in $CDCl_3$

The ^{31}P-^{77}Se coupling constant of Cl-MeO-Biphep (Table 3.7, Entry 2) is in good agreement with the literature [108], which means that this ligand has lower *σ*-donor ability than other chiral ligands e.g. MeO-Biphep, synphos or segphos. Due to this, ligand **3** is a poor *σ*-donor but a very good π-acceptor. This electrodeficiency on the phosphorous center is crucial in obtaining high levels of enantioselectivity. The measured $^{1}J_{P,Se}$ value could explaine the observed low affinity to oxygen of ligand **3** under mild conditions, which also verifies the low *σ*-donor ability of ligand **3**.

3.2.5 Scale up reaction for asymmetric hydrogenation in the research laboratory of Lanxess FC

The scale up of a well-working laboratory scale reaction can always cause problems. The chemical reaction is fixed at any given temperature, but this parameter may be influenced by mass and heat transfer. In addition, impurities of bulk materials, separation, unit operation problems or material handling problems may also cause side reactions, inhibition effects or decreasing of the yield.

During the cooperation with Lanxess FC, we had an opportunity to perform and verify the documented reaction conditions (Subsection 3.2) in 2 liter scale in Leverkusen. As we could observe the catalyst **10** remains active in two consecutive runs, while the *ee* decreases significantly after the first catalytic cycle.

Table 3.8 Hydrogenation results using methylcyclohexane as the solvent in 2 liter scale

Run	Ligand	Substrate	pH_2 [bar]	T [°C]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1	**3**(*R*)	**1**	50	110	4	98.5	86	**2**(*R*)
2	**3**(*R*)	**1**	50	110	4	94	47	**2**(*R*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). S/C=100. The same catalyst residue of **10** was used in both runs.

Herein, we show that our reaction conditions are appropriate for the enantioselective reactions (Table 3.8, Run 1) even in hundredfold scale. However, we observed a notable drop in the ee (Table 3.8, Run 2) due to system impurities in the case of the more difficult handling of complex **10** in larger scale and the possible lack of heat exchange.

3.2.6 Further improvement of asymmetric hydrogenation for the industrial applications with the view of costs

Some parameters can considerably influence the costs of an industrial reaction. The main cost-determining compounds are the precursor **9** and the ligand **3**. This work focuses on reducing the cost of the ligand *via* recycling, but the second main factor of such a transformation is the consumed amount of the valuable precursor (~200 € / g). To increase the profitability of the catalytic system in industrial application based on ligand **3** the ratio of substrate to catalyst, as well as the type of precursor **9** are varied. In this subsection two possibilities will be presented to increase the efficiency of the catalyst **10** *via* the precursor system. On the one hand, the S/C ratio could be adjusted to 1000 (Table 3.9 Entry 1, 2) with the preservation of the activity and selectivity of the catalyst. In this manner, the initial amount of precursor **9** will be decreased by achieving similar results. The recycling of the ligand **3** will be simpler if the system contains less amount of ruthenium. On the other hand, precursor **9** could be changed to the commonly used and cheaper ruthenium (III) chloride hydrate (Table 3.9, Entry 3a, 3b).

Table 3.9 Results of further investigations to reduce the cost of the industrial application

Entry	Ligand	Subst.	Precursor	S/C	pH_2 [bar]	T [°C]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Prod.
1[c]	**3**(***R***)	**1**	**9**	1000	50	110	4	98	-	**2**(***R***)
2[c]	**3**(***S***)	**1**	**9**	1000	50	110	4	94.5	54.3	**2**(***S***)
3a[c]	**3**(*S*)	**1**	$RuCl_3xH_2O$	100	50	110	4	99	57.9	**2**(*S*)
3b[c]	**3**(*S*)	**1**	$RuCl_3xH_2O$	100	50	110	4	99	65	**2**(*S*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). [c] These are single reactions without attempt for recycling.

As a conclusion, the adjustment of the S/C ratio to 1000 (Table 3.9, Entry 1, 2) and the use of a new precursor (Table 3.9, Entry 3a, 3b) did not have notable influence on the conversion. It remains on a high level. The *ee* drops significantly in the first reaction using less amount of precursor (Table 3.9, Entry 1, 2), indicating that $RuCl_3xH_2O$ auxiliary is at least as appropriate to create efficient and selective catalyst complex with ligand **3** than precursor **9**. The *ee* values are in good agreement with the hydrogenation results in methylcyclohexane (Table 3.3, Run 1). However, these two reactions do not show an authentic picture about the properties of the $RuCl_3xH_2O$ precursor. Beside the excellent conversions, better enanioselectivities may be achieved by more properly selected conditions ($p(H_2)$, T, t).

3.3 Derivatization of Cl-MeO-Biphep ligand (3)

In respect to recycling, the using of IL was not convenient for an industrial process. The further aim was to find a new concept for recovery of the ligand. The new scope of our development was the derivatization of the applied ligand, which was known for other chiral ligands years ago in the literature but was not used as a key step for the recycling of metal-suited catalyst complexes.

The derivatizations of ligand **3** to intermediates **3a - 3d** (Figure 3.1) were performed in order to yield beneficial intermediates to recycle the ligand **3** after the enantioselective hydrogenation of ethyl acetoacetate (**1**).

The idea of oxide **3a** was hit upon by examining the synthesis of the Cl-MeO-Biphep ligand (**3**), because the last step is the reduction of the oxide of **3** (Scheme 2.8 **E, F**). The sulfide **3b** and the borane complex **3c** of diphosphine ligand are mentioned in the literature [109-111]. Our purpose with the last derivative **3d** was to turn it into a water-soluble compound and to recycle it by phase separation. From the view of recycling, the complete transformation of Cl-MeO-Biphep ligand (**3**) into the corresponding derivatives **3a - 3d** without formation of byproducts is a major requirement.

Here, we report promising derivatization procedures for **3a** and **3b** in quantitative yields (Table 3.10). **3c** was prepared with maximum 79 % of conversion. Unfortunately, we did not have success to obtain the pure protonated form of **3d**. ^{31}P-NMR spectrum of **3d** shows mainly the significant peak of the Cl-MeO-Biphep ligand (**3**), thus the formation of **3d** did not take place even by changing the conditions of the preparation.

Structure of derivatives **3a** and **3b** were also confirmed by mass spectrometry (EI).

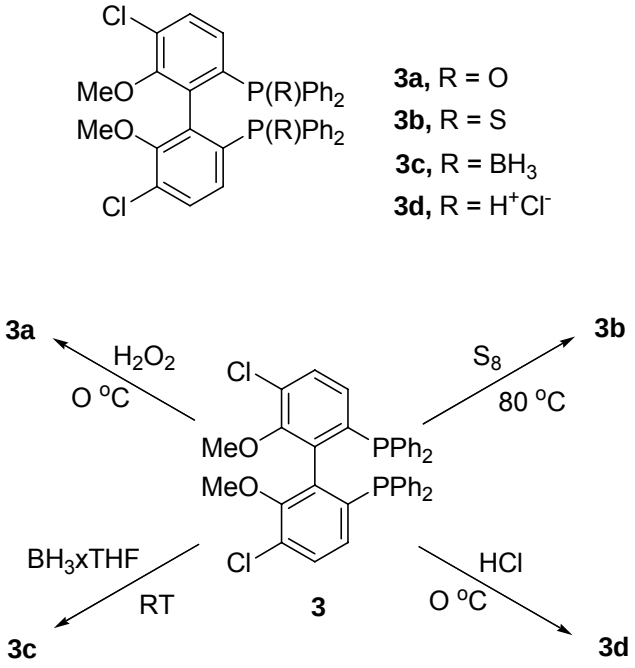


Figure 3.1 Derivatives of ligand **3**

Table 3.10 ^{31}P-NMR data for diphosphine derivatives of **3**

Entry	Ligand (reactant)	Diphosphane derivative	^{31}P-NMR[a] δ / ppm	$^{1}J_{P-C}$ [Hz]
1	**3**	**3a**	29.12	93
2	**3**	**3b**	43.81	85
3	**3**	**3c**	22.76	-
4	**3**	**3d**	-	-

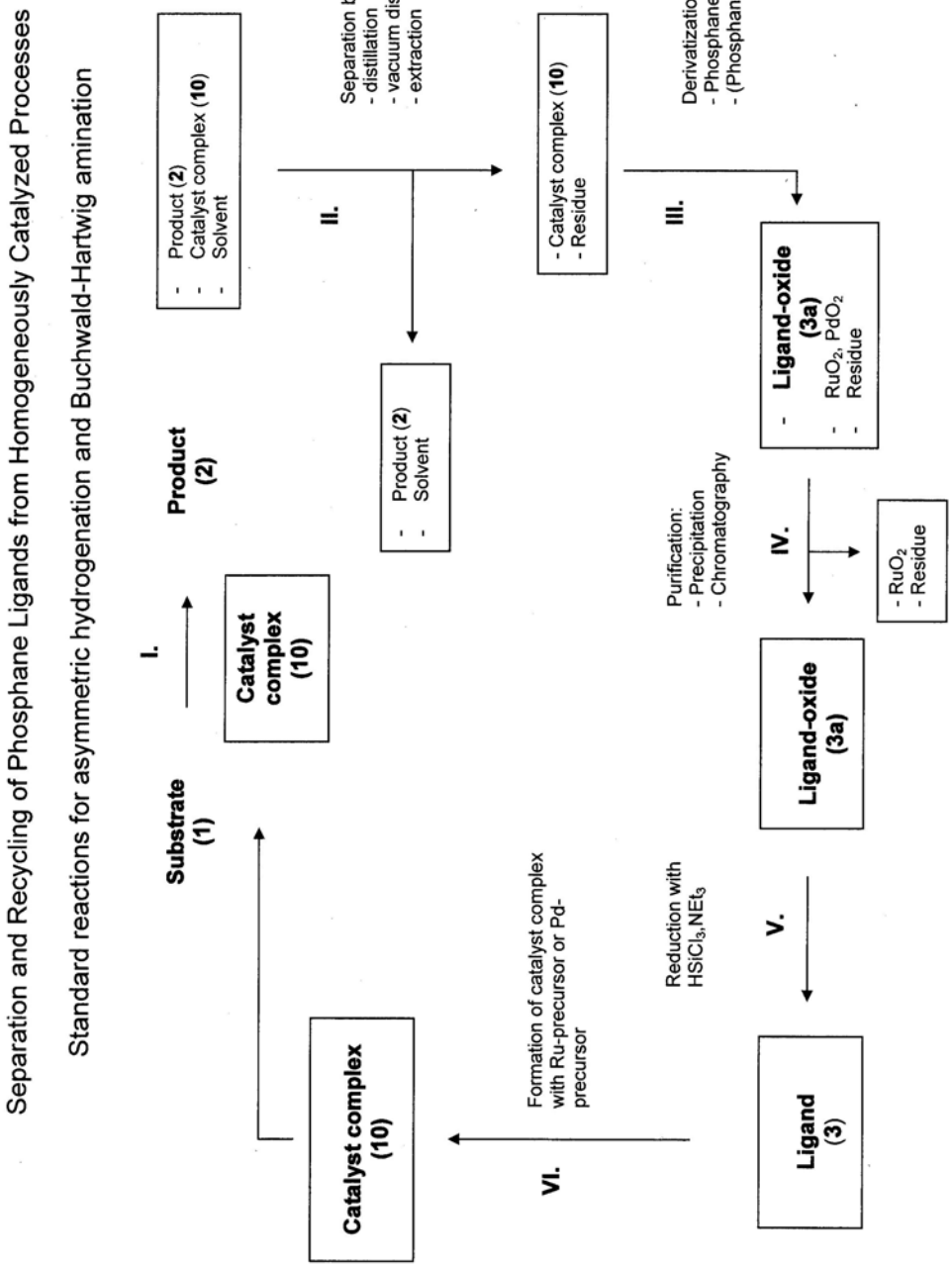
[a] recorded in $CDCl_3$

To summarize, oxide **3a** and sulfide **3b** formed (Table 3.10, Entry 1, 2) from **3** have been synthesized with excellent reliability and without formation of byproducts verified by two satellite peaks (derived from P-C couplings) near the main peak in the ^{31}P-NMR spectra of **3a** and **3b** and by 2D-NMR spectra. Thus, the possibility of their use in the recycling procedure was obvious.

Recycling reactions were also conducted with the sulfide derivative **3b,** but the isolation of this ligand derivative and the purification procedure were too difficult to apply routinely in the recycling. Moreover during the reduction of **3b** using $LiAlH_4$ as reducing agent, unfavorable H_2S gas is formed. Most encouraging results have been achieved with derivative **3a**, therefore the attempt for recycling will be performed and optimized solely *via* Cl-MeO-Biphep oxide derivative (**3a**) in the further investigations.

3.4 Optimization of the recycling procedure of Cl-MeO-Biphep ligand *via* oxide derivative 3a and its scale up

3.4.1 Designing a separation and recycling cycle to demonstrate the steps of the complete procedure



Scheme 3.4 Separation and recycling cycle for phosphine ligands from the catalytic process

This process cycle has been found to depict the complete recycling procedure. The consecutive steps of the Scheme 3.4 are performed first with *standard* (not reacted before) compound (e.g. ligand **3**, complex **10**) and afterwards with end-product **10** of the enantioselective hydrogenation to reveal the validity and the limitation of the proposed cycle (Scheme 3.4).

Firstly, oxidation and purification of the *in situ* formed complex **10** (Scheme 3.4, Step III-IV) were executed to monitor the proposed recycling cycle and to estimate the quality and yield of the recovered oxide **3a**. When steps III-IV (Table 3.11, Entry 1) were performed, ^{31}P-NMR indicated that the P-O bond of Cl-MeO-Biphep ligand oxide (**3a**) gave one single peak in the spectra (δ = 29.24 ppm). In this case, the conversion of oxidation of the complex **10** is nearly 100 %.
Next results were achieved by conducting steps I-IV in the Lanxess FC laboratory yielding 36.5 % of **3a** (Table 3.11, Entry 2). The recorded ^{31}P-NMR spectrum shows the significant peak of derivative **3a** at 29.27 ppm (Table 3.11, Entry 2) but this oxide contains a notable amount of product **2** according to ^{1}H-NMR spectrum because of the uncomplete distillation of **2** in vacuo.
Additional reactions were carried out in which the first half of the recycling procedure (Table 3.11, Entry 3, 4) has been tested resulting in 50.5 % of **3a** (^{31}P-NMR, δ = 29.04 ppm) after the step IV (Scheme 3.4). The same reaction was repeated by carrying out one enantioselective hydrogenation resulting in 59 % oxide **3a**. Outcomes and conditions of reactions are collected in the next table (Table 3.11).

In the last run (Table 3.11, Run 6) less substrate was applied (S/C=10) decreasing the significant contamination of the recovered ligand **3** by product **2**. We could verify very pure ligand oxide indicated by P-C coupling in the ^{31}P-NMR spectra at δ = 28.85 ppm (yield 63 %).

Table 3.11 First results of recycling procedure

Entry	Steps (Scheme 3.4)	Reactant	Sub.	Conv.[a] [%]	*ee*[b] [%]	Prod.	Recycled derivative [yield]	^{31}P-NMR[c] δ / ppm
1	III-IV	**10**[h]	-	-	-	-	**3a** (- %)	29.24
2[d]	I-IV	**3**(*R*)[i]+**10**[j]	**1**	98.5	86	**2**(*R*)	**3a** (36.5 %)	29.27
3[e]	I-IV	**3**(*S*)[i]+**10**[j]	**1**	98	82.7	**2**(*S*)	-	-
4[f]	I-IV	**3**(*S*)[i]+**10**[j]	**1**	98	67.1	**2**(*S*)	**3a** (50.5 %)	29.04
5[g]	I-IV	**3**(*S*)[i]+**10**[j]	**1**	58	77.9	**2**(*S*)	**3a** (59 %)	29.79
6[h]	I-IV	**3**(*S*)[i]+**10**[j]	**1**	98	51.2	**2**(*S*)	**3a** (63 %)	28.85

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). [c] recorded in $CDCl_3$, significant peak of the oxide derivative **3a**, [d] Reactions were conducted in the Lanxess FC laboratory. [e] first run of asymmetric hydrogenation, [f] second run of asymmetric hydrogenation, S/C=100. The same catalyst residue of **10** was used in both consecutive runs. Reaction conditions: $p[H_2]$ = 50 bar, T = 110 ºC, t = 4 hours, methylcyclohexane [g] Typical hydrogenation was taken place. S/C=100. [h] Typical hydrogenation reaction was carried out. S/C=10. [i] reactant for the step I (Scheme 3.4) [j] reactant for the step III (Scheme 3.4)

In summary, the oxide **3a** has been isolated in its pure form (Table 3.11, ^{31}P-NMR data) in the recycling steps and more than half of its initial amount could be recovered *via* this method. In all cases, there were no paramagnetic effects in the ^{31}P-NMR spectra because of the lack of Ru-derivative (RuO_2). However, the purity of the recovered **3a** is still not sufficient because product **2** contaminates significantly the oxide derivative **3a**. Further work was accomplished in order to optimize steps I-IV of the cycle (Scheme 3.4).

*3.4.2 Optimization of the reduction step using the standard oxide **3a***

A well-known reduction procedure [112] of Cl-MeO-Biphep ligand (**3**) (Scheme 3.4, Step V) exists already in the patented synthesis route of **3** applying $HSiCl_3$ as reducing agent (Scheme 2.8). This reduction was improved step by step to implement it with high reliability using standard, purchased ligand **3** working out the last reaction step in our proposed catalytic cycle (Scheme 3.4).

The complete step V. (Scheme 3.4) took place in three consecutive reactions using the same ligand **3** increasing the amount of reducing agent (0.3 ml, 1.3 ml, 2 ml) stepwise in each run. As a result, we could work out the condition of the complete reduction (followed by ^{1}H-NMR and ^{31}P-NMR) of purchased ligand **3** for the last synthesis step in the recycling procedure. These optimized conditions were employed in the further work.
The most convenient way to follow the increase of the rate of the reduced ligand oxide **3a** is to compare the ^{31}P-NMR spectra after each step. Moreover, the ^{1}H-NMR spectra may give additional information.

Table 3.12 Results of the reduction process with standard ligand **3**

Entry	Reactant[a]	Volume of the added reducer [mL]	Product(s)	^{31}P-NMR[b] δ / ppm (oxidized)	^{31}P-NMR[b] δ / ppm (reduced)	Conv. of the reduction [%]
1	**3a**	0.3	**3a+3**	28.63	-15.53	22
2	**3a**	1.3	**3a+3**	27.9	-15.17	51
3	**3a**	2	**3**	-	-15.07	99

[a] Always the very same reactant was used. [b] recorded in $CDCl_3$

In the ^{31}P-NMR spectra the peak of the reduced ligand is not always well-defined. Probably, beside the completely reduced ligand side products (showing AB system in the NMR spectra) can also be formed. Close to the significant peak of the ligand we can observe coupled peaks (P-C and P-P), respectively. We assume that at the beginning stage of the reaction the mono-oxide form of **3a** can also be generated.
Reduction of newly synthesized Cl-MeO-Biphep oxide (**3a**) was carried out under these conditions with complete transformation (99 %) and in a yield of 95 %. The next steps VI-I (Scheme 3.4) were performed by application of auxiliary **3** to control the activity and the selectivity of the reduced Cl-MeO-Biphep (**3a**) in the enantioselective hydrogenation of ethyl acetocetate (**1**). However, the reduced ligand **3** contains little amounts of other species (e.g. dimer or mono-oxide form of **3**), but they did not have appreciable impact on the activity of the catalyst **10**, as summarized in Table 3.13. The *ee* decreased slightly compared to the former results indicating impurities of ligand **3** in the system.

Table 3.13 Result of hydrogenation using reduced ligand **3**

Entry	Reaction steps (Scheme 3.4)	Ligand	Substrate	pH_2 [bar]	T [ºC]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1	V-VI-I	**3**(*S*)	**1**	50	110	4	99	71.1	**2**(*S*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). S/C=100.

3.4.3 Optimization of the recovery cycle

Thus, we have worked out a total reduction procedure of ligand **3a**. Therefore our next goal was to conduct the whole catalytic cycle using all steps of Scheme 3.4 and to perform the hydrogenation reaction again with the recycled ligand **3**.

The first aim was to determine the yield of the recovered ligand **3** and then a new hydrogenation was performed using it to check the activity of the recycled Cl-MeO-Biphep ligand (**3**) (Table 3.14). In this case, we could achieve excellent conversion (99%). Afterwards, a more detailed description [13] combined with our former experiences was employed to carry out the reduction step, which was routinely applicable and resulted in a more pure ligand of **3** after the recycling.

Table 3.14 Recycling results using steps of Scheme 3.4 and conducting a new hydrogenation with the recycled ligand **3**

Entry	Reaction steps (Scheme 3.4)	Reactant	^{31}P-NMR[a] δ / ppm of recovered **3**	Yield of recovered **3** [%]	Conversion[b] of the hydrogenation [%]
1[c]	II-I	**3**(*S*)	-15.17	49	99

[a] recorded in $CDCl_3$ [b] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [c] Recycled ligand **3** was used for the reaction. S/C=100.

As a result of all experiences, three complete recycling procedures were conducted to determine the quality and to improve the yield of the recovered ligand **3**. Initial amount of

the ligand **3** was adjusted to 0.5 g with which the cycle was investigated on a larger scale. The first problem of the scale-up reaction was caused by the non appropriate solvent, dibutylether, in step IV (Scheme 3.4), which has a high boiling point (142 ºC). Therefore, more than 40 % of pure oxide **3a** was lost by the evaporation of this solvent after the precipitation of RuO_2. The other problems were the handling of the bigger volumes and amounts of compounds and the avoiding the air-contact during each step of the cycle, except for step III and IV (Scheme 3.4).

To investigate the quality and quantity of the recovered ligand **3** after the complete recycling cycle, NMR, ICP-AES in order to determine the Ru conent and MS techniques were applied.

All ^{31}P-NMR spectra indicated mainly the peak of Cl-MeO-Biphep (**3**) (Table 3.15), as well as complete reduction of the oxide derivative **3a** without formation of byproducts. These results were also easy to assign with the help of ^{1}H-NMR spectra in which the oxidation of ligand **3** could be well demonstrated.

After all recycling procedures, the ruthenium content remained in the same order of magnitude verifying our good precipitation strategy for RuO_2. Nevertheless, in the last procedure (Table 3.15, Entry 3) the initial amount of Ru-precursor ($RuCl_3xH_2O$) was tenfold more than in procedure 1 or 2 (Table 3.15). Percent of remainder ruthenium amounts ranged from 0.8 % to 1.6 %.

In reaction 3 (Table 3.15, Entry 3), the S/C ratio was adjusted to 10 using ~ 5 g of ligand **3**. Therefore the contamination of the product had less influence than in the previous procedures, what is in good agreement with the NMR measurements. This fact indicates that the main problem of the full recycling cycle is the uncomplete separation of the product **2** by vacuum distillation (Scheme 3.4, step II). The highest yield (49 %) was achieved in reaction 2 (Table 3.15, Entry 2), when almost the half of the initial amount of ligand **3** was recovered in its pure solid form (^{31}P-NMR, δ = -15.16 ppm). In all cases, the structure of the recovered ligand **3** was confirmed by mass spectrometry (EI).

One of our initial goals was to recover more than 70 % of the applied ligand after the reaction. This should be accomplishable by further optimizations, which will be described in the next chapter.

Table 3.15 Results conducting the complete recycling cycle

Entry	Reaction steps (Scheme 3.4)	Lig.	Subst.	Prod.	Conv.[a] [%]	*ee*[b] [%]	Total Yield[c] [%]	[Ru][d] cont. [mg/kg]	^{31}P-NMR[e] δ / ppm
1[f]	I-V	**3**(*S*)	**1**	**2**(*S*)	99	87.1	33	1000	-15.15
2[g]	I-V	**3**(*S*)	**1**	**2**(*S*)	99	73.4	49	808	-15.16
3[h]	I-V	**3**(*S*)	**1**	**2**(*S*)	99	92.6	28.3	1865	-15.08

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). [c] yield of the recycled ligand (**3**), [d] Ru content of the recycled ligands **3** were measured by ICP-AES. [e] ^{31}P-NMR peak of the recovered ligand **3**, recorded in $CDCl_3$, [f] ~0.5 g ligand was used. S/C=100. [g] ~0.5 g ligand was used. S/C=100. [h] ~5 g ligand and $RuCl_3xH_2O$ as precursor were used. S/C=10.

To summarize, we have found a recycling cycle (Scheme 3.4) with good performance to recover the ligand in its solid form. The high quality of **3** was revealed using several techniques to test the validity of our proposed cycle. However, further work is necessary to increase the yield of the recycled ligand **3** giving rise to optimize this method as industrially-suited process.

3.4.4 Modeling of the recycling procedure as an industrial process

Our last investigation focused on the imitation of a real industrial process in which one recovery process of ligand **3** was taken place after 10 production steps (Scheme 1.1). We collected all residues of **10** from the hydrogenation reactions. By this way, we could assemble more detailed information about each consecutively conducted enantioselective hydrogenation. Data are summarized in Table 3.16.

Table 3.16 Results of 10 consecutive enantioselective hydrogenations

Run[a]	Reaction steps (Scheme 3.4)	$m_{init.\ compl.}$ [g] **10**	V_{sub} [ml] **1**	$m_{residue\ after\ the\ distillation\ step}$ (Scheme 3.4, II) [g] **10**	$V_{prod.}$ [ml] **2**	Conv.[b] [%]	*ee*[c] [%]
1	I-II	0.076	1	0.068	0.7	99	63.7
2	I-II	0.072	1	0.077	0.69	89.5	59.1
3	I-II	0.072	1	0.094	0.6	97.5	59
4	I-II	0.072	1	0.079	0.76	98	56.6
5	I-II	0.073	1	0.081	0.91	99	60
6	I-II	0.075	1	0.068	0.74	99	58.3
7	I-II	0.075	1	0.053	0.63	99	61
8	I-II	0.074	1	0.096	0.53	99	58.9
9	I-II	0.077	1	0.117	0.73	99	57.7
10	I-II	0.077	1	0.106	0.85	99	57.2
Total	-	**0.743**	**10**	**0.839**	**7.14**	**97.8**	**59.2**

[a] Typical hydrogenation was conducted. S/C=100. [b] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [c] Enantiomeric excesses were measured by chiral GC (Lipodex-E column).

In conclusion, 10 consecutive hydrogenations were carried out in which 71.4 vol. % of the total products **2** could be distilled. The average conversion was 97.8 % (very high level) and the total *ee* was 59.2 % (Table 3.16, last row, and Table 3.17, Entry 1).
As it can reveal, the combined residues of **10** were slightly contaminated by product **2** in spite of the precise vacuum distillation.

The complete recycling procedure (Scheme 3.4) was performed with the collected residues of **10**, which yielded 38 % recovered ligand **3** in its pure form (verified by ^{31}P-NMR). Furthermore, the recovered Cl-MeO-Biphep ligand (**3**) occurred as active catalyst (Table 3.17, Entry 2) compared to the purchased **3** (Table 3.17, Entry 1). ^{1}H-NMR spectrum shows little amount of impurities from the product **2**, but it has no influence in

respect to the further application of the ligand (Table 3.17, Entry 2). The *ee* value indicates a similar tendency in concern to the enantioselectivity.

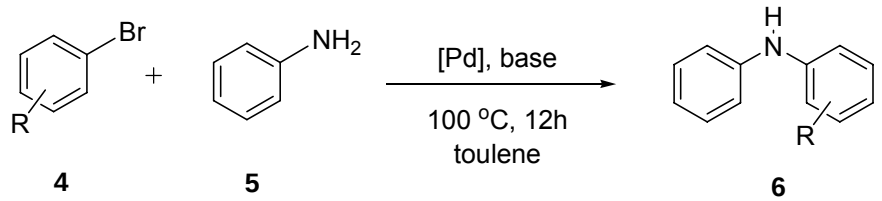
Table 3.17 Result of recovery process using the collected residue from the 10 hydrogenation reactions

Entry[a]	Reaction steps (Scheme 3.4)	Lig.	Subst.	Conv.[b] [%]	*ee*[c] [%]	Prod.	Total Yield[d] [%]	[Ru][e] cont. [mg/kg]	^{31}P-NMR[f] δ / ppm
1	I-V	**3**(*S*)	**1**	97.8	59.2	**2**(*S*)	38	446	-15.15
2[g]	I	**3**(*S*)	**1**	99	56.9	**2**(*S*)	-	-	-

[a] Conducting typical hydrogenation with S/C=100. [b] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [c] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). [d] yield of the recycled ligand **3**, [e] Ru content of recycled ligands **3** were measured by ICP-AES. [f] ^{31}P-NMR peak of the recovered ligand **3**, recorded in $CDCl_3$, [g] Hydrogenation reaction was carried out with the recycled ligand **3**.

Although, in this case the value of the ruthenium content was the lowest (446 mg/kg, remaining 0.4 % of the initial Ru content in the ligand) applying the complete recycling cycle. The yield of the ligand **3** was on an average level compared to the outcomes of Table 3.15 after the asymmetric hydrogenations.

3.5 Results of Buchwald-Hartwig amination and the recycling process applying Dave-Phos and X-Phos ligands



Scheme 1.2 General Buchwald-Hartwig amination reaction

At the beginning of this part of the project, we have already collected a lot of experiences about the recycling of Cl-MeO-Biphep ligand (**3**), for this reason the major attempt was to use the same recycling cycle (Scheme 3.4) for the two Buchwald ligands, too.

Our standard amination reaction is depicted in the Scheme 1.2. The nature and conditions of C-C coupling reactions differ from the enantioselective hydrogenation, but the applied ligands, named as Dave-Phos (**7**) and X-Phos (**8**) denote a number of similarities. These reactions work under mild conditions and do not require gas pressure. Therefore, formation of stable intermediates, which can hamper the recycling, is more seldom than in the asymmetric hydrogenation (confirmed by ^{31}P-NMR spectra). These transformations need special Pd-precursor and appropriately selected base as well as inert atmosphere to achieve complete transformation. Directly after the reaction, the separation of the product **6** causes the main problem to obtain pure ligand. Afterwards, the separation of the ligand **7** and **8** from Pd-precursor occurs by precipitation and continues *via* their derivatization. The Scheme 3.4 describes the general route for recycling, which was employed for the recovery of the Buchwald´s ligands either. Degree work has been presented from this part of the dissertation [113].

First of all, the C-C transformations were carried out with both ligands **7** and **8** to gain the first outcomes about the ligand activity. The factor enantioselectivity has no role in the Buchwald-Hartwig amination because of the lack of the chirality in the product **6** and the ligands as well. Thus, the efficiency of the reaction is demonstrated by measuring the conversion of the product **6**. The first reactions were conducted by properly adjusted conditions in a 250 mL scale, which were performed in the Lanxess FC laboratory (Table 3.18, Entry 1, 2). The same reactions were conducted in our laboratory in a 30 mL scale (Table 3.18, Entry 3). Other base NaO*t*Bu was selected in order to avoid the increase of accessory phosphorous content, which could have disturbed the especially versatile ^{31}P-NMR measurements after the amination. Under these conditions, complete conversions were achieved with Dave-Phos ligand (**7**) after 2 hours as detected by GC (Sil-Pona column).

As it can be seen in Table 3.18, the coupling reactions gave acceptable results, thus the additional investigations were to characterize the derivatives of ligands **7** and **8**,

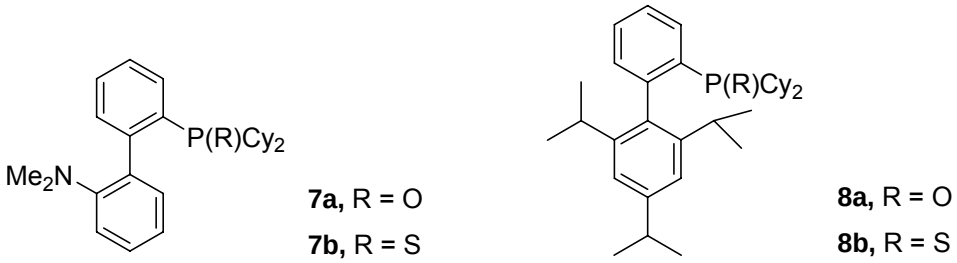
particularly their oxide and sulfide forms. Afterwards, steps of the cycle (Scheme 3.4) were performed to bring the oxidation and reduction of ligands **7**, **8** to perfection.

Table 3.18 Results of Buchwald-Hartwig aminations

Entry	Ligand	Substrate	Precursor	Base	T [ºC]	t [h]	Conv. [%]	Product	Scale (mL)
1	**7**	**4**+**5**	Pd_2dba_3	K_3PO_4	100	12	72[a]	**6**	250
2	**8**	**4**+**5**	Pd_2dba_3	K_3PO_4	100	12	78.5[a]	**6**	250
3	**7**	**4**+**5**	Pd_2dba_3	NaO*t*Bu	100	2	99[b]	**6**	30

[a] Conversions were determined by GC-MS in the Lanxess FC laboratory (Method: GC2_0341_01). [b] Conversions were measured by GC (Sil-Pona column, 50 m).

The methods mentioned in chapter 3.3 were applied to prepare and to characterize the derivatives of ligands Dave-Phos (**7**) and X-Phos (**8**). Because of the encouraging results of Cl-MeO-Biphep oxide (**3a**) and sulfide (**3b**) derivatives, we have synthesized solely these two forms of Dave-Phos (**7**) and X-Phos (**8**) ligands. Preparation of **7a**, **7b**, **8a**, **8b** (Figure 3.2) were taken place by the same procedures, which were used for the formation of Cl-MeO-Biphep derivatives **3a** and **3b**.



7a, R = O
7b, R = S

8a, R = O
8b, R = S

Figure 3.2 Derivatives of ligand **7** and **8**

Table 3.19 ^{31}P-NMR data for phosphane derivatives of **7** and **8**

Entry	Ligand (reactant)	^{31}P-NMR[a] δ / ppm (standard)	Phosphane Derivative	^{31}P-NMR[a] δ / ppm (reacted)	$^{1}J_{P-C}$ [Hz]
1	**7**	-9.47	**7a**	49.82	65.2
2	**7**	-9.47	**7b**	69.68	49.5
3	**8**	-11.96	**8a**	44.24	64.8
4	**8**	-11.96	**8b**	59.58	-

[a] recorded in $CDCl_3$

The derivatization of ligands **7** and **8** were carried out with complete conversions and in quantitative yields for all four cases. The recorded ^{31}P-NMR spectra showed the P-C coupling for three of the derivatives (**7a**, **7b**, **8a**) indicating very pure forms.
In addition, **7a**, **7b**, **8a**, **8b** were isolated in high yield, but our further studies focused especially on the oxides of Dave-Phos (**7a**) and X-Phos ligands (**8a**).

The complete reduction of two substances **7a**, **8a** was obvious requirement using as key step in the recycling process. Unfortunately, the complete reduction of standard **7a** and **8a** could not be realized in good conversion, because more than 15 % of X-Phos oxide (**8a**) and 17 % of Dave-Phos oxide (**7a**) were not reduced under the same conditions, which were applied for the complete transformation of Cl-MeO-Bihep oxide (**3a**). However, the purification of the completely reduced forms of **7a** and **8a** could be carried out by column chromatography, but this method is not very attractive for an industrially-suited application because of the relative high costs.
The following step was the work-up of the reaction mixture in which after the separation of the base (NaO*t*Bu) with water. a new problem arose, namely the isolation and purification of **7** and **8**.
The product **6** is solid (mp = 53 – 55 ºC), therefore the vacuum distillation (200 ºC, 14 mbar) was proven to be the best solution to separate diphenylamine (**6**) from the ligand **7** and **8**. By this method 71 - 77 % of **6** could be separated. A remarkable tendency observed when the scale up of amination reaction (Scheme 1.2) was performed. Even more **6** could be distilled from the reaction mixture up to 84 %, although complete

separation of **6** could not be achieved. Unfortunately, Dave-Phos ligand (**7**) has less thermal stability (lower melting point) under vacuum distillation (verified by NMR measurements), that is why the separation of that ligand (**7**) is not possible by this way.
The column chromatography can also overcome the separation problem of the product **6**, but it is not very profitable.
For the separation of ligand **7** and **8** another idea emerged, namely the protonation of the ligand after the C-C coupling. These ligands (**7**, **8**) should become water-soluble and easily separable by phase separation. This method was also tested, but we did not have notable results for application in the recycling, because of the formation of byproducts.

In summary, the vacuum distillation of **6** was applied exclusively and successfully for the amination with ligand **8** before the recycling method. The results of reduction of **8** provided also more encouraging outcomes than using the same method for ligand **7**.
As a last step, the recycling steps I-IV (Scheme 3.4) were implemented using X-Phos ligand (**8**) in order to evaluate the yields and the reliability of the proposed cycle after the Buchwald-Hartwig amination. In the next table (Table 3.20) some outcomes of the recycling procedure are collected.

Table 3.20 Results of the recycling procedure applying X-Phos ligand (**8**)

Entry	Reaction steps (Scheme 3.4)	Lig.	Subst.	Distilled Product [%]	Conv.[a] [%]	Yield of recovered ligand [%]	^{31}P-NMR[a] δ / ppm (**8a**)
1[c]	I-IV	**8**	**4**+**5**	**6** (70 %)	99	**8a** (70 %)	44.52
2[d]	I-IV	**8**	**4**+**5**	**6** (84 %)	99	**8a** (72 %)	45.19

[a] Conversions of the aminations were determined by GC (Sil-Pona column), [b] recorded in $CDCl_3$, [c] Amination was conducted in threefold scale with X-Phos ligand (**8**). [d] Amination was carried out in fivefold scale with X-Phos ligand (**8**) and purified by column chromatography.

To conclude, on the one hand the amination reaction with X-Phos ligand (**8**) resulted in a high yield (72 %) pure oxide of **8a** without formation of byproducts after the recycling steps I-IV (Scheme 3.4). Our proposed aim was achieved, i.e. the pure oxide (**8**) was

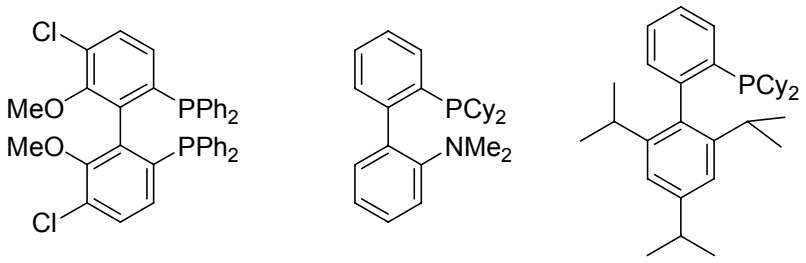
isolated what was confirmed by NMR techniques. Actually, further steps are needed to obtain the pure ligand **8** after the reduction. On the other hand, the recycling procedure did not succeed using Dave-Phos (**7**) because of its lower thermal stability and cumbersome reduction.

We suppose that the reduction procedure with X-Phos ligand (**8**) can be conducted in an effective way, however additional experiments i.e. improvement of all steps of Scheme 3.4 are required.

4 Summary and Outlook

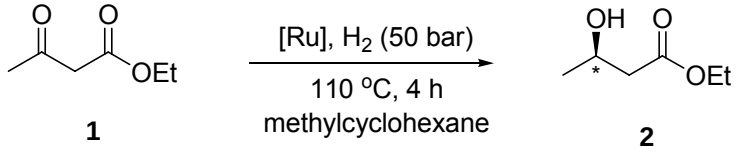
4.1 Summary

In this work, the main emphasis was placed on the reuse and recovery of the applied organic ligands **3**, **7**, **8** from homogeneously catalyzed processes.



3 7 8

As a standard test reaction, the enantioselective hydrogenation of ethyl acetoacetate (**1**) was applied to investigate Cl-MeO-Biphep ligand (**3**).



1 **2**

Scheme 4.1 Asymmetric hydrogenation of β-ketoester

The first concept was the reuse of the same catalyst residue in consecutive runs. This idea can be implemented simply in ionic liquid, which gives rise to apply the same complex in more consecutive cycles preserving the catalyst on high activity even after four or six runs in the enantioselective hydrogenation. Using IL as a medium for the enantioselective hydrogenation with the same catalyst (**10**) provides a very simple and

effective manner to reduce the costs of the processes *via* reusing the same complex (Table 4.1, Entry 3). Unfortunately, nowadays this reaction medium is purchased at a high price. Mixtures of IL and EtOH (1:1) (Table 4.1, Entry 4), cyclohexane and methylcyclohexane (Table 4.1, Entry 1, 2) were also tested as media for the standard reduction of *β*-ketoester applying the same catalyst residue [$RuBr_2$(Cl-MeO-Biphep)] (**10**) at least in four runs with high conversions, i.e. without loss of catalytic activity. In the Table 4.1 some outcomes of the first run are collected applying different solvents for the reuse of the complex **10** and presenting the improvement of the enantioselectivity.

As shown, the enantiomeric excesses increased significantly up to 96.2 % indicating less impurities in the system when IL or a mixture of IL/EtOH was provided the medium for the reaction. The formation of byproducts was also diminished applying this medium. These observations were verified by NMR measurements.

As a conclusion, the same catalyst **10** could be applied in more consecutive cycles presenting similar tendency in concern to the conversions and to the *ee* values. The application of the reaction in a bigger scale was also successful with constant conversion and *ee*, which indicates that this catalytic system could be useful in process development, too.

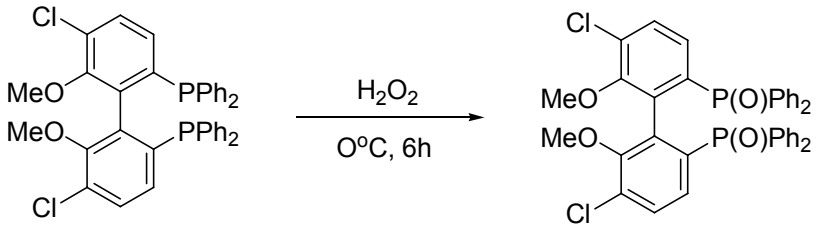
Table 4.1 Hydrogenation results in different media after the first run and changing main parameters

Entry	Ligand	solvent	Substrate	pH_2 [bar]	T [°C]	t [h]	Conv.[a] [%]	*ee*[b] [%]	Product
1[c]	**3**(*R*)	cyclohexane	**1**	50	110	4	99	53	**2**(*R*)
2[c]	**3**(*R*)	methylcyclohexane	**1**	50	110	4	99	64	**2**(*R*)
3[c]	**3**(*R*)	IL	**1**	50	110	4	99	93.5	**2**(*R*)
4[c]	**3**(*R*)	IL/EtOH	**1**	50	110	4	98.5	96.2	**2**(*R*)
5[d]	**3**(*R*)	methylcyclohexane	**1**	50	110	4	98.5	86	**2**(*R*)
6[e]	**3**(*R*)	methylcyclohexane	**1**	50	110	4	94.5	54.3	**2**(*R*)
7[f]	**3**(*R*)	methylcyclohexane	**1**	50	110	4	99	65	**2**(*R*)

[a] Conversions were determined by ^{1}H-NMR (200 MHz, $CDCl_3$). [b] Enantiomeric excesses were measured by chiral GC (Lipodex-E column). [c] Hydrogenation was carried out in a 20 mL scale. S/C=100. [d] Hydrogenation was carried out in a 2000 mL scale. S/C=100. [e] Hydrogenation was carried out with S/C=1000 in a 20 mL scale. [f] Hydrogenation was conducted with precursor $RuCl_3xH_2O$ in a 20 mL scale.

Other supplementary investigations have also been performed in order to reduce the cost of the complete process, namely the changing of the S/C ratio to 1000 using less amount of precursor (Table 4.1, Entry 6) or the use of simple $RuCl_3xH_2O$ auxiliary instead of [bis-(2-methylallyl-cycloocta-1,5-diene) ruthenium(II)] complex (**9**) (Table 4.1, Entry 7). The results were in good agreement and comparable with the outcomes of the first hydrogenation runs when the appropriate selected conditions were used.

Apart from these results, our major challenge was to figure out a recovery route consisting of easy, fast and reliable steps in a bigger scale with which the applied organic ligand can be recycled in pure solid form after the catalytic transformation. Derivatization to the oxide **3a** and sulfide **3b** of Cl-MeO-Biphep ligand (**3**) was investigated and synthesized in quantitative yield in order to prepare pure intermediates without formation of byproducts.



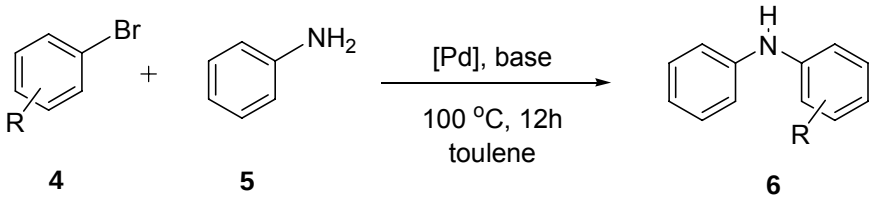
3 **3a**

Scheme 4.2 Preparation of ligand oxide **3a** (key step in the recycling cycle)

Among the characterized derivatives, oxide form **3a** of ligand **3** proven to be the best intermediate. Later on, **3a** was applied in the recycling procedure (Scheme 3.4) successfully. It was possible to recover up to 78.1 % of ligand oxide **3a** (Table 3.15, Entry 3) and up to 49 % of ligand **3** (Table 3.15, Entry 2) after the reduction step (Scheme 3.4, Step V). Naturally, further optimizations are needed to achieve nearly 70 % yield for the recovered pure ligand **3** and to develop this process as a profitable industrial application. The appropriate quality of the recycled Cl-MeO-Biphep (**3**) was confirmed by NMR, MS and ICP-AES teqhniques. The activity and selectivity of the recovered ligand **3** is in good agreement with the purchased Cl-MeO-Biphep ligand (**3**) (Table 3.17).

The model reactions of **10** consecutive hydrogenations were also carried out to collect outcomes about the total conversion (97.8 %) and enantiomeric excess (59.2 %).

The other investigated reaction is the Buchwald-Hartwig amination between bromobenzene (**4**) and aniline (**5**) was also tested using Dave-Phos (**7**) and X-Phos (**8**) ligands.



4 **5** **6**

Scheme 4.3 General Buchwald-Hartwig amination reaction

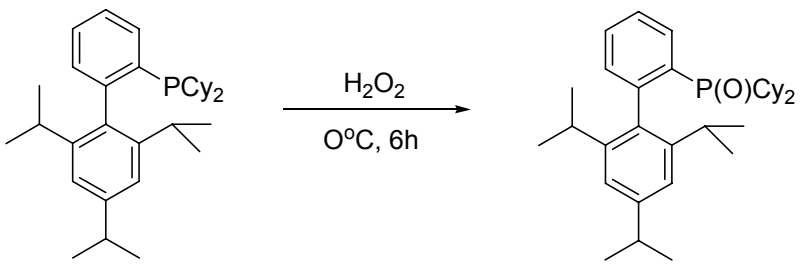
Optimization of the reaction was also carried out by changing the applied base by which 99 % conversion was reached in a 30 mL scale.

Table 4.2 Base vs. conversion in the amination reaction

Entry	Ligand	Base	Conv. of **6** [%]
1	**7**	K_3PO_4	72[a]
2	**8**	K_3PO_4	78.5[a]
3	**7**	NaO*t*Bu	99[b]

[a] Conversions were determined by GC-MS in the Lanxess FC laboratory (Method: GC2_0341_01).
[b] Conversions were measured by GC (Sil-Pona column, 50 m).

The developed recycling routes were extended and optimized for the two biaryl phosphine Buchwald-Hartwig ligands. The preparation of oxide forms **7a**, **8a** and sulfide forms **7b**, **8b** was completed in quantitative yields. All these derivatives were also completely characterized.



8 **8a**

Scheme 4.4 Preparation of ligand oxide **8a** (key step in the recycling cycle)

Unfortunately, Dave-Phos ligand (**7**) has lower thermal stability. Therefore, the separation of product **6** did not succeed by vacuum distillation without decomposition of the ligand **7**.

Up to 72 % of X-Phos oxide derivative (**8a**) was recovered in the recycling procedure, although further steps are required to estimate the quality and quantity of the recycled ligand **8**.

To conclude, the recovery procedure is applicable for the X-Phos ligand (**8**), too. Completing all steps of the recovery cycle (Scheme 3.4), same results may be achieved using ligand **8**, compared to Cl-MeO-Biphep (**3**).

Separation of both product **2** and **6** is a key step to recycle pure and even more active ligand for new catalytic reactions.

4.2 Outlook

The scaling up in various size plants can lead to variations in yielded products. The first authentic process optimization can be performed in a 500 kg scale, therefore the developed recycling procedure should be tested in 1 kg, 5 kg and 100 kg scale before. The yields of recycled ligand oxides (**3a**, **8a**) increased significantly ranging from 50.5 % to 78.1 %. These results can indicate that the performance of the developed process may be more efficient in larger scale.

The results of the hydrogenation reactions in cyclohexane and methylcyclohexane give rise to consider maybe there is only the need of a little part of the used catalyst complex **10**. In this case, there is a possibility to decrease the precursor/ligand mol ratio.

Replacement of [bis-(2-methylallyl-cycloocta-1,5-diene) ruthenium(II)] (**9**) by $RuCl_3xH_2O$ precursor could also be profitable in production scale.

Because of the formation of hydride complexes in the hydrogenation reaction, the influence of the hydrogen gas pressure should be optimized further.

The last step in the recycling cycle, namely the reduction should also be carried out and optimized for X-Phos ligand (**8**).

5 Experimental Part

5.1 General Technique

All reactions were carried out under argon atmosphere and all equipments e.g. flasks, Schlenk-tubes, polyethylene syringes, V2A-stainless steel needles were evacuated and flushed three times with inert gas before the utilization. All solvents were dried, distillated and stored under argon. During the reactions and workup, the addition and the removal of reactive agents and solvents were taken place under inert gas counter flow.
All chemicals and solvents were purchased from general fine chemicals manufacturers, (Aldrich, Merck, Fluka or Strem). The argon purity was signed with 4.8, as well as the hydrogen gas with 5.0. Both of them were employed without any further purification.
All catalytic hydrogenations were carried out in a 125 mL stainless steel autoclave, which was evacuated and flushed three times with argon gas. The temperature was regulated by oil bath and the autoclave was equipped with external stirrer and manometer.
The temperature was always regulated by water or oil bath.

NMR: The spectra were measured using BRUKER ARX 200, AMX 300, ARX 500. All spectra were recorded at room temperature. The chemical shift values of ^{1}H-NMR and ^{13}C-NMR spectra are given in ppm relative to $SiMe_4$. ^{31}P-NMR spectra were measured relative to external 85 % H_3PO_4 standard. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Broad resonances are indicated broad (br).

Mass Spectrometry: Fision MD 800. Relative intensity is related to basis peak.

IR Spectra: Nicolet FT-IR 510 p. The spectra were measured as KBr pellets or as thin films of neat compound. The absorptions are given in wave numbers (cm^{-1}). Origin 6.0 software was used to create the spectra.

ICP-AES: Spektroflame D, Ar plasma, 1150 W, (267.876 nm, 240.272 nm)

GC: The enantiomer excess (*ee*) of the standard asymmetric hydrogenation reaction (Scheme 1.1) was determined by Chrompack (Varian) CP9002.

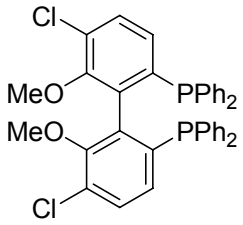
Column:	25 m Lipodex-E
Temperature:	Column 100 ºC isotherm
Injection temperature:	260 ºC
Detector temperature:	300 ºC (FID)
Hold Time:	20 min
Mobile phase:	Helium (0.6 bar)
R_t of ((*R*)-**2**)-enantiomer:	9.66 min
R_t of ((*S*)-**2**)-enantiomer:	10.51 min

The conversions of the Buchwald-Hartwig amination (Scheme 1.2) were followed after each 30 min by gas chromatography.

Column:	50 m Sil-Pona
Initial temperature:	80 ºC
End temperature:	250 ºC
Injection temperature:	250 ºC
Detector temperature:	300 ºC (FID)
Heat of rate:	8 ºC /min
Mobile phase:	Helium (0.6 bar)
R_t of bromobenzene (**4**):	17.85 min
R_t of aniline (**5**):	18.43 min
R_t of diphenylamine (**6**):	13.87 min

5.2 Characterisation and use of ligand 3 in asymmetric hydrogenation

5.2.1 Characterisation of (*R/S*)-5,5`-dichloro-6,6`-di-methoxy-2,2`-bis (diphenyl-phosphino)-1,1`-biphenyl) Cl-MeO-Biphep (3)



3

mp = 177 - 179 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.21 (s, 6H, OCH_3), 6.99 (d, *J* = 8.2 Hz, 2H, ArH), 7.22 – 7.28 (m, 10H, ArH), 7.29 – 7.35 (m, 10H, ArH), 7.37 – 7.39 (d, *J* = 8.2 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.1 (2C, OCH_3), 128.0 – 138.4 (34C, ArC), 154.4 (2C, ArC-OCH_3)
^{31}P-NMR (121 MHz, $CDCl_3$): δ = -14.92 (2P,PPh_2)

M/z (calculated) = 651.5
MS (EI / 200 ºC, 70 eV, R=1000): M/z (%) = 651.1 [M^+] (1), 573.2, 527.1, 465.2, 433.1, 386.1, 325.1, 264.1, 238.2, 183.0, 174.1, 108.0, 77.1, 31.1

IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3048, 2996, 2940, 1953, 1895, 1812, 1772, 1635, 1583, 1560, 1448, 1423, 1359, 1236, 1130, 1056, 1016, 869, 815, 742, 501, 433

5.2.2 Preparation of catalyst 10

(*R*)-Cl-MeO-Biphep (**3**) (22.8 mg, 0.033 mmol) and [(1,5-COD)Ru(2-methylallyl)$_2$] (**9**) (9.6 mg, 0.03 mmol) were placed in a 25-mL flask and degassed. Anhydrous acetone (3 mL) was added dropwise afterwards HBr (7.2 µL, 48 %) was slowly introduced to the

suspension and the mixture was stirred for about 30 min at room temperature whilst brown solution formed, which was evaporated under vacuum. The brown solid residue (9.5 mg, 0.01 mmol) was used without any purification as a catalyst for the hydrogenation reaction of the desired substrate.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.26 (s, 6H, OCH_3), 7.03 (d, *J* = 8.2 Hz, 2H, ArH), 7.22 – 7.28 (m, 10H, ArH), 7.32 – 7.36 (m, 10H, ArH), 7.41 (d, *J* = 8.2 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.2 (2C, OCH_3), 128.4 – 134.7 (34C, ArC), 154.5 (2C, ArC-OCH_3)
^{31}P-NMR (121 MHz, $CDCl_3$): δ = -14.91 (2P,PPh_2)

5.2.3 Preparation of catalyst 12

(*R*)-BINAP (**11**) (20.5 mg, 0.033 mmol) and [(1,5-COD)Ru(2-methylallyl)$_2$] (**9**) (9.6 mg, 0.03 mmol) were placed in a 25 mL flask and degassed. Anhydrous acetone (3 mL) was added dropwise. HBr (7.2 µL, 48 %) was slowly introduced to the suspension and the mixture was stirred for about 30 min at room temperature whilst a brown solution formed. The solvent was removed under reduced atmosphere. The brown solid residue (0.01 mmol, 8.8 mg) was used without any purification as a catalyst for the hydrogenation reaction of the desired substrate.

^{31}P-NMR (121 MHz, $CDCl_3$): δ= -11.32 (2P,PPh_2)

5.2.4 General procedure for enantioselective hydrogenation of *β*-ketoester

The corresponding catalyst complex **10** or **12** was applied for the hydrogenation of **1** in the selected solvent. The solution was placed in a 125 mL stainless steel autoclave, which was adjusted at hydrogen pressure and heated to 110 ºC for 24 or 4 hours. The substrate to catalyst ratio could be adjusted from 10 to 1000.

5.2.5 Recycling of 10 in cyclohexane (Table 3.2)

(*R*)-[(Cl-MeO-Biphep)-$RuBr_2$] (**10**) (36.5 mg, 0.04 mmol) was used without any purification as a catalyst for the hydrogenation reaction of the desired substrate (4 mmol) in cyclohexane (10 mL). The solution was placed in a 125 mL stainless steel autoclave, which was adjusted at 50 bar hydrogen pressure and heated to 110 ºC for 4 hours. The substrate to catalyst ratio was 100. The product **2** was distilled off under reduced atmosphere at 148 – 150 ºC.
Conversion = 99 %, *ee* = 53 %
The same catalyst residue **10** was reused in every runs. Fresh substrate **1** was added to to **10** and the hydrogenation was repeated four times under these conditions. Solvents were removed under reduced atmosphere after each run.

Spectrum of the used complex **10** after the last run:
^{31}P-NMR (121 MHz, $CDCl_3$): δ = 27.25 (2P,$P(O)Ph_2$), 29.41 (2P,$P(O)Ph_2$), 41.67 (hydride complex of **10**)

5.2.6 Recycling of 10 in methylcyclohexane (Table 3.3)

All reactions were performed similarly to the procedure “e” but methylcyclohexane (10mL) was used as solvent instead. S/C=100. After the hydrogenation the product **2** was distilled off in vacuo.
Conversion = 99 %, *ee* = 64 %
The same catalyst residue **10** was reused in every runs. Fresh substrate **1** was added to **10** and the hydrogenation was repeated six times under these conditions. Solvents were removed under reduced atmosphere after each run.

Spectrum of the used complex **10** after the last run:
^{31}P-NMR (121 MHz, $CDCl_3$): δ = 27.78 (2P,$P(O)Ph_2$), 30.01 (2P,$P(O)Ph_2$), 37.4, 58.35 (hydride complex of **10**)

5.2.7 Recycling of 10 in propylene carbonate

[(Cl-MeO-Biphep)-$RuBr_2$] (**10**) (36.5 mg, 0.04 mmol) was used without any purification as a catalyst for the hydrogenation reaction of the desired substrate **1** (4 mmol) in propylene carbonate (16 mL). The solution was placed in a 125 mL stainless steel autoclave, which was adjusted at 50 bar hydrogen pressure and heated to 110 ºC for 4 hours. The substrate to catalyst ratio was 100. The product **2** was separated by vacuum distillation but it was not confirmed by ^{1}H-NMR.

Spectrum of the used complex **10** after the reaction:
^{31}P-NMR (121 MHz, $CDCl_3$) δ = 26.73 (2P,P(O)Ph_2), 29.01 (2P,P(O)Ph_2), 43.62, 59.06, 65.96 (hydride complex of **10**)

5.2.8 Recycling of 10 in IL (BMIM$^+$BTA$^-$) medium (Table 3.4, 3.5)

(*R*)-[(Cl-MeO-Biphep)-$RuBr_2$] (**10**) (36.5 mg, 0.04 mmol) was used without any purification as a catalyst for the hydrogenation reaction of the desired substrate **1** (4mmol) in butyl-methyl-imidazolium-bis-triflylamide (8 mL). The solution was placed in a 125 mL stainless steel autoclave, which was adjusted at 50 bar hydrogen pressure and heated to 110 ºC for 4 hours. The substrate to catalyst ratio was 100. The product **2** was isolated either by extraction with n-hexane (30 mL) (first recovery test) or vacuum distillation at 145 – 147 ºC (second recovery test) after every run.
Conversion = 99 %, *ee* = 93.5 %
The same catalyst **10** and IL were reused in every runs. Fresh substrate **1** was added to the resulting IL and the hydrogenation was repeated five and four times under these conditions.

Spectrum of the used complex **10** after the last run:
^{31}P-NMR (121 MHz, $CDCl_3$): δ = -15.18 (2P,PPh_2), 56.93, 57.63 (hydride complex of **10**)

5.2.9 Recycling of 10 in IL ($BMIM^+BTA^-$)/EtOH (1:1) medium (Table 3.6)

[(Cl-MeO-Biphep)-$RuBr_2$] (**10**) (36.5 mg, 0.04 mmol) was used without any purification as a catalyst for the hydrogenation reaction of the desired substrate **1** (4 mmol) in ionic liquid (4 mL) and ethanol (4 mL). The solution was placed in a 125 mL stainless steel autoclave, which was adjusted at 50 bar hydrogen pressure and heated to 110 ºC for 4 hours. S/C=100.

The separation of **2** was performed either by extraction or by distillation.

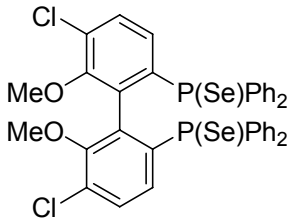
Conversion = 98.5 %, *ee* = 96.2 %

a, The IL/EtOH phase was extracted with n-hexane (30 mL) and after the phase separation the solvents were evaporated.

b, Ethanol and product **2** were separated at 145 – 147 ºC by vacuum distillation and the solvent was removed afterwards under reduced atmosphere.

Fresh ethanol and substrate **1** were added to the resulting IL, the hydrogenation was repeated four times under these conditions.

5.2.10 Preparation of diphosphane selenide derivative (14)



14

The (*R*)-[(Cl-MeO-Biphep)-$RuBr_2$] (**10**) ligand (119 mg, 0.12 mmol) was added to an excess of selenium (239 mg, 3.03 mmol) and suspended in toluene (7 mL), which was refluxed during 12 hours at 80 ºC. After that, the solution was cooled down and filtered by syringe filter and ca. 0.4 mL was placed in a NMR tube. It was analysed in 0.1 mL C_6H_6 by ^{31}P-NMR.

^{31}P-NMR (121 MHz, C_6H_6): δ = 32.25 (2P,P(Se)Ph_2), $^1J_{P\text{-}Se}$ = 381.5 Hz), 35.39 (2P, P(Se)Ph_2), 38.53 (2P,PPh_2, $^1J_{P\text{-}Se}$ = 381.5 Hz)

5.2.11 Scale up reaction for enantioselective hydrogenation of 1 (Table 3.8)

[(Cl-MeO-Biphep)-RuBr_2] (**10**) (8.76 g, 9.6 mmol) was used as a catalyst for the hydrogenation of the desired substrate (**1**) (125 mL, 0.96 mol) in methylcyclohexane (1800 mL). The solution was placed in a stainless steel autoclave, which was adjusted to 50 bar hydrogen pressure and heated to 110 ºC for 12 hours. S/C=100. After the reaction the product **2** was distilled off at 145 – 147 ºC in vacuo.
Conversion = 98.5 %, *ee* = 86 %
The same catalyst **10** was applied in both consecutive runs. Fresh substrate **1** was added to the catalyst residue **10** and the hydrogenation was repeated once again under these conditions.

Spectra of the used complex **10** after the first run:
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.18 (s, 6H, OCH_3), 6.92 (d, *J* = 8.2 Hz, 2H, ArH), 7.15 – 7.20 (m, 10H, ArH), 7.22 – 7.31 (m, 10H, ArH), 7.33 (d, *J* = 8.2 Hz, 2H, ArH)
^{31}P-NMR (121 MHz, $CDCl_3$): δ = - 15.02 (2P,PPh_2), 28.86 (2P,P(O)Ph_2)

5.2.12 Supplementary hydrogenation reaction adjusting the S/C ratio to 1000 (Table 3.9, Entry 1, 2)

2.2 mg (0.007 mmol) precursor **9** and 5.5 mg (0.008 mmol) Cl-MeO-Biphep (**3**) were stirred in 6 mL acetone with one drop HBr (48 %) to prepare 7.3 mg (0.008 mmol) [(Cl-MeO-Biphep)-RuBr_2] catalyst (**10**).
After the evaporation of solvent, the complex **10** was reacted with 1 mL (8 mmol) ethyl acetoacetate (**1**) as substrate using 50 bar hydrogen pressure at 110 ºC for 4 hours in methycyclohexane in a 125 mL stainless steel autoclave. The product **2** was distilled off at 145 – 147 ºC in vacuo.

Conversion = 94.5 %, *ee* = 54.3 %

Spectrum of the used complex **10** after the reaction:
^{31}P-NMR (121 MHz, $CDCl_3$): δ = - 15.46 (2P, PPh_2)

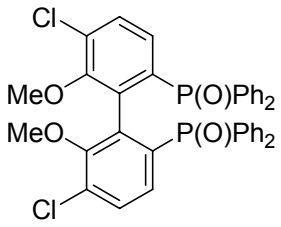
5.2.13 Supplementary hydrogenation changing the precursor to $RuCl_3xH_2O$ (Table 3.9, Entry 3, 4)

7.3 mg (0.08 mmol) [(Cl-MeO-Biphep)-$RuBr_2$] catalyst (**10**) was prepared from 15 mg (0.08 mmol) $RuCl_3xH_2O$ precursor, 50 mg (0.076 mmol) **3** and 14,2 µL HBr (48 %) in acetone (6 mL). This mixture was stirred for 1 hour and after the solvent was evaporated.
The prepared **10** was added to 1 mL (8 mmol) ethyl acetoacetate (**1**) as substrate using 50 bar hydrogen pressure at 110 ºC for 4 hours in methycyclohexane in a 125 mL stainless steel autoclave. The product **2** was distilled off at 145 – 147 ºC in vacuo.
Conversion = 99 %, *ee* = 65 %

Spectrum of the used complex **10** after the reaction:
^{31}P-NMR (121 MHz, $CDCl_3$): δ = 29.32 (2P, $P(O)Ph_2$), 30.87 (2P, $P(O)Ph_2$)

5.3 Derivatization of ligand 3

5.3.1 Cl-MeO-Biphep oxide derivative 3a [114] (Table 3.10)



3a

Cl-MeO-Biphep (**3**) (0.36 g, 0.55 mmol) and 10 mL of CH_2Cl_2 were placed in a 100 mL round-bottomed flask. To the cooled solution 4 mL of H_2O_2 (35 %) was added at 0 ºC. The mixture was stirred for 2 hours at 0 ºC and then for 4 hours at room temperature. Afterwards 10 mL water was added. Aqueous phases were extracted with 3x3 mL of CH_2Cl_2. The organic phases were washed with 10 mL aqueous sodium hydrogen sulfite ($NaHSO_3$) dried over $MgSO_4$ and the solvent was distilled off. White solid **3a** could be isolated in its pure solid form as indicated by P-C coupling (quantitative yield, 0.378 g, 99 %).

mp = 220 – 223 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.46 (s, 6H, OCH_3), 7.01 (q, *J* = 8.3 Hz, 2H, ArH), 7.24 – 7.28 (m, 4H, ArH) 7.34 – 7.39 (m, 4H, ArH), 7.41 – 7.44 (m, 4H, ArH), 7.48 – 7.53 (m, 2H, ArH), 7.62 – 7.67 (q, *J* = 7.9 Hz, 8H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.5 (2C, OCH_3), 128.0 – 137.0 (34C, ArC), 154.6 (1C, ArC-OCH_3), 154.7 (1C, ArC-OCH_3)

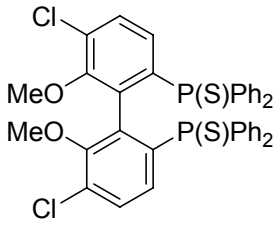
^{31}P-NMR (200 MHz, $CDCl_3$): δ = 28.86 (P-C coupling), 29.12 (2P,$P(O)Ph_2$), 29.32 (P-C coupling)

M/z (calculated) = 683.5

MS (EI / 200 ºC, R=1000): M/z (%) = 683.2 [M^+] (3), 651.4, 604.9, 558.9, 480.9, 448.9, 341.0, 310.0, 277.0, 201.0, 154.0, 77.0, 46.9

IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3016, 2955, 2345, 1992, 1842, 1756, 1563, 1434, 1365, 1257, 1203, 1114, 1016, 885, 815, 723, 694, 520, 433

5.3.2 Cl-MeO-Biphep sulfide derivative 3b [108] (Table 3.10)



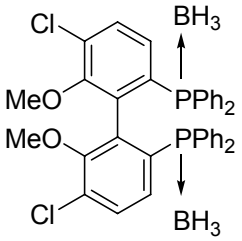
3b

Cl-MeO-Biphep (**3**) (0.5 g, 0.77 mmol) and elemental sulphur (0.39 g, 1.53 mmol) were stirred in 10 mL toluene at 80 ºC for 12 hours. The mixture was cooled down and then filtered and dried over $MgSO_4$. Afterwards it was evaporated to obtain a pale brown solid **3b** in quantitative yield (0.55 g, 99 %). ^{31}P-NMR spectrum shows total conversion.
mp = 231 – 233 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.16 (s, 6H, OCH_3), 6.93 – 7.11 (m, 4H, ArH), 7.18 – 7.26 (m, 6H, ArH), 7.32 – 7.35 (m, 6H, ArH), 7.62 – 7.72 (m, 4H, ArH), 7.78 – 7.82 (m, 4H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 59.5 (2C, OCH_3), 127.8 – 135.7 (34C, ArC), 154.0 (1C, ArC-OCH_3), 154.1 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = 43.60 (P-C coupling), 43.81 (2P,P(S)Ph_2), 44.02 (P-C coupling)

M/z (calculated) = 714.1
MS (EI / 200 ºC, R=1000): M/z (%) = 714.2 [M^+] (100), 529.2, 497.1, 465.2, 451.1, 373.1, 357.1, 297.0, 183.1, 139.0, 57.1

5.3.3 Cl-MeO-Biphep borane complex 3c (Table 3.10)

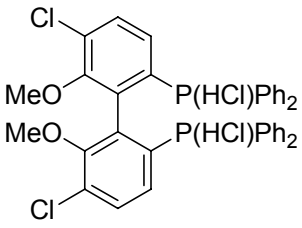


3c

Cl-MeO-Biphep (**3**) (0.4 g, 0.61 mmol) and 6 mL of BH_3xTHF (1 M solution in THF) were stirred at room temperature for 6 hours. The mixture was hydrolyzed by adding a solution of 10 mL H_2O dropwise and extracted with CH_2Cl_2 (3x3 mL). The solution was dried over $MgSO_4$ and evaporated to give a white solid mono borane complex **3c** (0.294 g, 71 %) as a simple product.
Conversion = 79 %

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.01 (s, 6H, OCH_3), 7.06 (t, *J* = 8.4 Hz, 2H, ArH), 7.10 – 7.21 (m, 4H, ArH), 7.22 – 7.31 (m, 8H, ArH), 7.33 – 7.45 (m, 6H, ArH), 7.45 – 7.53 (t, *J* = 7 Hz, 2H, ArH), 7.60 – 7.68 (t, *J* = 7 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 59.2 (2C, OCH_3), 128.0 – 135.5 (34C, ArC), 154.6 (1C, ArC-OCH_3), 154.7 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = -15.23 (2P,PPh_2), -15.05 (2P,PPh_2), 22.76 (2P,P(BH_3)Ph_2)

5.3.4 Cl-MeO-Biphep hydrochloric acid salt adduct 3d (Table 3.10)



3d

Cl-MeO-Biphep (**3**) (0.3 g, 0.46 mmol) and 2 mL of HCl (37 %) were stirred in 5 mL of methanol at 0 ºC and then for 4 hours at room temperature. 6 mL mixture of MeOH / H_2O (1:1) were added and then extracted with methanol (3x3 mL). The organic solvent was dried over $MgSO_4$ and evaporated. The product **3d** could be obtained as a pale yellow solid (0.201 g, 60 %) but not confirmed by NMR measurements.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.22 (s, 6H, OCH_3), 7.0 (d, *J* = 8.7 Hz, 2H, ArH), 7.19 – 7.24 (m, 10H, ArH), 7.27 – 7.28 (m, 10H, ArH), 7.32 – 7.39 (d, *J* = 7.4 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.1 (2C, OCH_3), 128.0 – 138.3 (34C, ArC), 154.6 (1C, ArC-OCH_3), 154.7 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = -15.19 (2P,PPh_2)

5.4 Optimization of the recycling cycle for ligand 3

5.4.1 Steps III-IV of the recycling cycle (Table 3.11, Entry 1)

47 mg, (0.072 mmol) Cl-MeO-Biphep ligand (**3**) and 22 mg (0.07 mmol) were stirred with dropwise added 14,2 µL HBr (48 %) in acetone (6 mL) to prepare (76 mg, 0.083 mmol) [(Cl-MeO-Biphep)-$RuBr_2$] catalyst (**10**) after the evaporation of the solvent. The complex **10** was oxidized by 1 mL of H_2O_2 (35 %) in 2 mL dichloromethane. The black liquid was stirred overnight at room temperature. 15 mL water was added and after the phase separation the organic phase was evaporated.
Afterwards 4 mL of dibutylether was given to the residue to precipitate the Ru-derivative (RuO_2) from the ligand oxide **3a** and this mixture was stirred at 140 °C overnight. The solution was cooled down and filtered. The filtrated solid was washed with 3x3 mL of dibutylether and the organic phases were dried over $MgSO_4$ and evaporated under reduced atmosphere resulting the oxide as a white solid **3a** (68.9 mg, 0.1 mmol).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.45 (s, 6H, OCH_3), 7.01 (q, *J* = 8.4 Hz, 2H, ArH), 7.23 – 7.26 (m, 4H, ArH), 7.33 – 7.35 (m, 4H, ArH), 7.40 – 7.43 (m, 4H, ArH), 7.48 – 7.51 (m, 2H ArH), 7.53 – 7.56 (m, 2H, ArH), 7.57 – 7.65 (m, 6H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.5 (2C, OCH_3), 128.0 – 137.0 (34C, ArC), 154.6 (1C, ArC-OCH_3), 154.7 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = 29.24 (2P,P(O)Ph_2)

5.4.2 Steps I-IV of the recycling cycle performed in the Lanxess FC laboratory (Table 3.11, Entry 2)

[(Cl-MeO-Biphep)-$RuBr_2$] (**10**) (8.76 g, 9.6 mmol) was used as a catalyst for the hydrogenation of the desired substrate (**1**) (125 mL, 0.96 mol) in methylcyclohexane (1800 mL). The solution was placed in a stainless steel autoclave, which was adjusted to 50 bar hydrogen pressure and warmed to 110 ºC for 12 hours. S/C=100. Conversion of hydrogenation is 98.5 %.
After the first run 2.0 g (2.19 mmol) [(Cl-MeO-Biphep)-$RuBr_2$] (**10**) from the reaction residue was dissolved in 120 mL CH_2Cl_2 and then 5 mL H_2O_2 were introduced slowly to the mixture and stirred overnight. Afterwards 250 mL water was given to perform the phase separation. The organic layer containing solid (RuO_2) was filtered and removed to obtain brown oily residue, which was extracted with 150 mL *n*-hexane. The solvent was dried over $MgSO_4$ and removed under reduced atmosphere. The desired oxide was obtained as a white solid **3a** (0.547 g, 36.5 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.43 (s, 6H, OCH_3), 6.98 (q, *J* = 8.3 Hz, 2H, ArH), 7.16 – 7.21 (m, 4H, ArH), 7.23 – 7.32 (m, 4H, ArH), 7.38 – 7.50 (m, 4H, ArH), 7.53 – 7.58 (m, 2H, ArH), 7.61 – 7.67 (m, 2H, ArH), 7.69 – 7.76 (m, 6H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.6 (2C, OCH_3), 128.0 – 134.5 (34C, ArC), 154.8 (2C, ArC-OCH_3)
^{31}P-NMR (400 MHz, $CDCl_3$): δ = 29.27 (2P,P(O)Ph_2),

5.4.3 Steps I-IV of the recycling cycle (Table 3.11, Entry 3, 4)

58 mg (0.089 mmol) Cl-MeO-Biphep ligand (**3**) and precursor 29 mg (0.09 mmol) precursor **9** were stirred with dropwise added 14,2 µL HBr (48 %) in acetone (6 mL) to prepare [(Cl-MeO-Biphep)-$RuBr_2$] complex (**10**) after the evaporation of solvent. The complex **10** was reacted with 1.0 mL (8 mmol) ethyl acetoacetate (**1**) as substrate in 10 mL of methylcyclohexane in a 125 mL stainless steel autoclave. Two consecutive runs were carried out by applying same catalyst complex using 50 bar of hydrogen pressure at 110 °C for 4 hours.

After the second run the reaction residue was treated with 1 mL H_2O_2 (35 %) in 5 mL of dichloromethane for 1 hour at room temperature resulting dark brown solution. Then 25 mL water and additional 5 mL CH_2Cl_2 were added for phase separation. The organic layer was evaporated and dibutylether (3 mL) was added to precipitate the Ru-derivative (RuO_2) from the ligand oxide **3a**. The liquid was stirred and heated for 2 hours at 140 °C then it was cooled down slowly. After the filtration, the solid was washed with 10 mL of dibutylether and the filtrate was dried over $MgSO_4$ and evaporated by in vacuo to obtain (30.8 mg, 50.5 %) oxide form **3a** of the ligand.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.46 (s, 6H, OCH_3), 7.01 (q, *J* = 8.4 Hz, 2H, ArH), 7.25 – 7.29 (m, 4H, ArH), 7.34 – 7.38 (m, 4H, ArH), 7.41 – 7.45 (m, 4H, ArH), 7.46 – 7.54 (m, 2H, ArH), 7.61 – 7.66 (m, 8H, ArH)

^{13}C-NMR(125 MHz, $CDCl_3$): δ = 60.5 (2C, OCH_3), 128.0 – 132.6 (34C, ArC)

^{31}P-NMR (200 MHz, $CDCl_3$): δ = 29.04 (2P,$P(O)Ph_2$)

5.4.5 Steps I-IV of the recycling cycle (Table 3.11, Entry 5)

50 mg (0.077 mmol) Cl-MeO-Biphep (**3**) 22 mg (0.068 mmol) precursor **9** were stirred with dropwise added 14,2 µL HBr (48 %) in acetone (6 mL) to prepare complex **10** after the evaporation of solvent. The complex **10** was reacted with 1.0 mL (8 mmol) ethyl acetoacetate (**1**) as substrate in 15 mL methylcyclohexane in a 125 mL stainless steel autoclave. One hydrogenation reaction was taken place by applying the catalyst

complex using 50 bar of hydrogen pressure at 110 °C for 4 hours. Conversion of hydrogenation: 58 %.

The reaction residue was treated with 2 mL H_2O_2 (35 %) in 9 mL dichloromethane for 1 hour at room temperature resulting dark brown solution. Then 25 mL water and additional 5 mL CH_2Cl_2 were added to the phase separation. The organic layer was evaporated and dibutylether (4 mL) was added to precipitate the Ru-derivative (RuO_2) from the ligand oxide **3a**. The liquid was stirred and heated for 2 hours at 140 °C then it was cooled down slowly. After the filtration, the solid was washed with 10 mL of dibutylether and the filtrate was dried over $MgSO_4$ and evaporated by vacuum pump to obtain (31 mg, 59 %) oxide form **3a** of the ligand.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.39 (s, 6H, OCH_3), 6.99 (q, *J* = 8.4 Hz, 2H, ArH), 7.26 – 6.32 (m, 4H, ArH), 7.37 – 7.43 (m, 4H, ArH), 7.45 – 7.49 (m, 4H, ArH), 7.51 – 7.55 (m, 2H, ArH), 7.57 – 7.63 (m, 8H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.5 (2C, OCH_3), 128.0 – 132.6 (34C, ArC), 169.3 (2C, ArC-OCH_3)

^{31}P-NMR (200 MHz, $CDCl_3$): δ = 27.68 (2P, $P(O)Ph_2$), 29.79 (2P, $P(O)Ph_2$)

5.4.6 Steps I-IV of the recycling cycle (Table 3.11, Entry 6)

0.542 g (0.83 mmol) Cl-MeO-Biphep (**3**) 0.223 g (0.7 mmol) precursor **9** were stirred with dropwise added 0.15 mL HBr (48 %) in acetone (30 mL) to prepare complex **10** after the evaporation of solvent. The complex **10** was reacted with 1.0 mL (8 mmol) ethyl acetoacetate (**1**) as substrate in 60 mL of methylcyclohexane in a 125 mL stainless steel autoclave. One hydrogenation reaction was taken place by applying the catalyst complex using 50 bar of hydrogen pressure at 110 °C for 4 hours. S/C=10. Conversion of hydrogenation: 98 %.

The reaction residue was treated with 8 mL H_2O_2 (35 %) in 15 mL dichloromethane for 1 hour at room temperature resulting dark brown solution. Then 25 mL water and additional 5 mL CH_2Cl_2 were added to the phase separation. The organic layer was evaporated and dibutylether (20 mL) was added to precipitate the Ru-derivative (RuO_2)

from the ligand oxide **3a**. The liquid was stirred and heated for 2 hours at 140 °C then it was cooled down slowly. After the filtration, the solid was washed with 10 mL dibutylether and the filtrate was dried over $MgSO_4$ and evaporated in vacuo to obtain (0.355 g, 63 %) oxide form **3a** of the ligand.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.39 (s, 6H, OCH_3), 6.99 (q, *J* = 8.4 Hz, 2H, ArH), 7.17 – 7.26 (m, 4H, ArH), 7.30 – 7.34 (m, 4H, ArH), 7.37 – 7.42 (m, 4H, ArH), 7.44 – 7.49 (m, 2H, ArH), 7.58 – 7.65 (m, 8H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.4 (2C, OCH_3), 128.4 – 137.0 (34C, ArC), 154.6 (1C, ArC-OCH_3), 154.7 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = 28.85 (2P,P(O)Ph_2)

5.4.7 Reduction procedure of 3a [112] (Table 3.12)

0.1 g (0.146 mmol) Cl-MeO-Biphep oxide (**3a**) was solved in 10 ml xylene and 3 ml NEt_3. This mixture was heated to 60 °C under reflux then a mixture of 2 ml trichlorosilane and 5 ml xylene was added slowly to the suspension. It was heated and stirred overnight at 110 °C. Afterwards the reaction mixture was cooled to room temperature and solved in 15 mL CH_2Cl_2. Then the solution was cooled to 0 °C and NaOH (10 w/w %) was added dropwise until pH=10 was reached. The suspension was filtered under argon atmosphere over 5 g Al_2O_3 (90 active, acidic). The organic phase was collected in a second flask and the water phase was extracted with 20 mL CH_2Cl_2. The collected dichloromethane phases were washed two times with 10 mL water under argon atmosphere. The organic layer was dried over $MgSO_4$ and reduced to a volume of 5 mL in vacuo since crystallization of the ligand **3** started. Organic solvent was removed under reduced atmosphere, thus **3** was obtained as a white powder (68 mg, 71 %).
This reaction was performed in three consecutive runs using total amount of 2 ml reducing agent and 0.1 g standard Cl-MeO-Biphep oxide derivative (**3a**).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.22 (s, 6H, OCH_3), 6.99 (d, *J* = 8.2 Hz, 2H, ArH), 7.21 – 7.25 (m, 10H, ArH), 7.25 – 7.33 (m, 10H, ArH), 7.37 (d, *J* = 8.2 Hz, 2H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 59.6 (2C, OCH_3), 128.0 – 133.0 (34C, ArC), 167.7 (2C, ArC-OCH_3)

^{31}P-NMR (200 MHz, $CDCl_3$): δ = - 15.07 (2P,Ph_2)

5.4.8 Hydrogenation with reduced ligand 3 (Table 3.13)

The reduction procedure was performed with 0.118 g, (0.173 mmol) extra pure Cl-MeO-Biphep oxide derivative **3a**, which was dissolved in a mixture of 5 mL xylene and 3 mL NEt_3. This solution was heated to 60 °C under reflux then a mixture of 4 mL (in two portions) trichlorosilane and 9 ml xylene was added slowly to the suspension. It was heated and stirred overnight at 110 °C. Afterward the mixture was cooled to room temperature and solved in 15 mL CH_2Cl_2. Then the solution was cooled to 0 °C and NaOH (10 w/w %) was dropped until pH=10 was reached. The suspension was filtered under argon atmosphere over 5 g Al_2O_3 (90 active, acidic). The organic phase was collected in a second flask and the water phase was extracted with 20 mL CH_2Cl_2. The collected dichloromethane phases were washed two times with 20 mL water under argon atmosphere. The organic layer was dried over $MgSO_4$ and reduced for a volume of 5 mL in vacuo when the crystallization of the ligand **3** started. The solvent was removed under reduced atmosphere. Ligand **3** was obtained as a white powder (0.11 g, 95 %) and used continually in the next hydrogenation reaction.
Afterwards typical hydrogenation reaction was conducted in which the catalyst complex (**10**) was prepared from (51 mg, 0.079 mmol) recovered Cl-MeO-Biphep ligand (**3**), (23 mg, 0.072 mmol) Ru(II)-bis-(2-methylallyl)cycloocta-1,5-diene-complex (**9**) and 14,2 µL HBr (48 %) in 6 mL acetone. The solvent was evaporated. Afterwards ethyl acetoacetate (**1**) (1.0 mL, 8 mmol) and the prepared catalyst complex **10** were placed with 15 mL of methylcyclohexane in a 125 mL stainless steel autoclave using 50 bar of hydrogen pressure at 110 °C for 4 hours. Conversion = 99 %, *ee* = 71.1 %

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.18 (s, 6H, OCH_3), 6.94 (d, *J* = 8.2 Hz, 2H, ArH), 7.16 – 7.20 (m, 10H, ArH), 7.26 – 7.28 (m, 10H, ArH), 7.32 – 7.37 (d, *J* = 8.2 Hz, 2H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 59.5 (2C, OCH_3), 127.8 – 138.3 (34C, ArC), 154.4 (1C, ArC-OCH_3), 154.4 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = - 15.13 (2P,PPh_2)

5.4.9 Optimization of steps of the recycling cycle (Table 3.14)

47 mg, (0.072 mmol) Cl-MeO-Biphep ligand (**3**) and 22 mg (0.07 mmol) precursor **9** were stirred in 6 mL acetone and than 0.15 mL HBr (48 %) was added dropwise. The solvent was evaporated completely. The prepared (76 mg, 0.083 mmol) [(Cl-MeO-Biphep)-$RuBr_2$] catalyst (**10**) was oxidized by 1 mL of H_2O_2 (35 %) in 2 mL dichloromethane at 0ºC. The black liquid was stirred overnight at room temperature. 15 mL water was added and after the phase separation the organic phase was evaporated.
Afterwards 4 mL dibutylether was given to the residue to precipitate the Ru-derivative (RuO_2) from the ligand oxide **3a** and this mixture was stirred at 140 °C overnight. The solution was cooled down and filtered. The filtrated solid was washed with 3 x 3 mL dibutylether and the organic phases were evaporated under reduced atmosphere resulting the oxide as a white solid **3a** (68.9 mg, 0.1 mmol).
This phosphine oxide **3a** was dissolved without any further purification in a mixture of 8mL xylene and 1.5 mL NEt_3. This solution was heated to 60 °C under reflux then a mixture of 1.5 mL trichlorosilane and 0.8 ml xylene was added slowly (in two portions) to the suspension. It was heated and stirred overnight at 110 °C. Afterwards the mixture was cooled to room temperature and solved in 15 mL CH_2Cl_2. Then the solution was cooled to 0 °C and 2 ml NaOH (30 w/w %) was added dropwise to a pH of 10 was reached. The suspension was filtered under argon atmosphere over 5 g Al_2O_3 (90 active, acidic). The organic phase was collected in a second flask and the water phase was extracted with 18 mL CH_2Cl_2. The collected dichloromethane phases were extracted with 22 mL brine under argon atmosphere. After the phase separation the organic layer was dried over $MgSO_4$, filtered and the solvent was completely distilled off. The product **3** was crystallized from chloroform at 0 °C and obtained as a white powder (23 mg, 49 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.18 (s, 6H, OCH_3), 6.94 (d, *J* = 8.2 Hz, 2H, ArH), 7.16 – 7.23 (m, 10H, ArH), 7.27 – 7.28 (m, 10H, ArH), 7.31 – 7.34 (d, *J* = 8.2 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.1 (2C, OCH_3), 126.0 – 138.4 (34C, ArC), 154.4 (1C, ArC-OCH_3), 154.5 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = -15.17 (2P,PPh_2)

The recovered **3** was tested further in a typical hydrogenation reaction. 23 mg (0.035 mmol) Cl-MeO-Biphep (**3**), 11 mg (0.035 mmol) precursor **9** and 6 mL acetone were stirred and than 0.75 µL HBr (48 %) was added. The solvent was evaporated completely. The prepared **10** was reacted with 0.5 mL (4 mmol) ethyl acetoacetate (**1**) as substrate in 10 mL methylcyclohexane in a 125 mL stainless steel autoclave. Hydrogenation reaction was taken place by using 50 bar of hydrogen pressure at 110 °C for 4 hours. Conversion of hydrogenation: 99 %. After the reaction the product **2** was distilled off in vacuo at 148 – 150 °C.
Conversion = 99 %

5.4.10 Optimization of each step of the whole recycling (Table 3.15, Entry 1)

The catalyst complex **10** was prepared from 0.531 g (0.82 mmol) Cl-MeO-Biphep (**3**), 0.251 g (0.79 mmol) precursor **9** and 0.15 mL HBr (48 %) in 20 mL acetone. The solvent was evaporated and the complex **10** was reacted with 10.4 mL (80 mmol) ethyl acetoacetate (**1**) in 40 mL methylcyclohexane in a 125 mL stainless steel autoclave. Hydrogenation reaction was conducted by using 50 bar of hydrogen pressure at 110 °C for 4 hours. After the reaction the product **2** was distilled off in vacuo at 148 – 150 °C. Conversion = 99 %. *ee* = 87.1 %

The oxidation step was carried out with 8 mL H_2O_2 (35 %) in 25 mL dichloromethane at 0 ºC overnight. Then 50 mL dichloromethane and 140 mL water were added for the phase separation. The organic layer was evaporated to obtain 1.638 g solid residue.
Afterwards 30 mL DBE was added to this powder to separate the Ru-derivative (RuO_2) from the ligand oxide **3a** and this mixture was stirred at 140 °C overnight. The solution

was cooled down and the solid was filtered off. The residue was washed with 3x10 mL diethylether and the organic layers were collected and evaporated under reduced atmosphere resulting in the oxide **3a** as a white solid (0.56 g, 0.82 mmol).
This solid was dissolved in 30 mL xylene and 16 mL (0.12 mol) NEt_3 and reduced by a mixture of 19 mL (0.19 mol) $HSiCl_3$ and 10 mL xylene. It was heated and stirred overnight at 110 °C. Afterwards the mixture was cooled to room temperature and 15 mL CH_2Cl_2 was added. Then the solution was cooled to 0 °C and 8 ml NaOH (30 w/w %) was dropped until pH=10 was reached. The suspension was filtered under argon atmosphere over 5 g Al_2O_3 (90 active, acidic) and washed with 80 mL dichloromethane. The organic phases were collected in a second flask and the phase separation was carried out with 50 mL water and 10 mL brine. After phase separation, the organic layer was dried over $MgSO_4$, filtered and the solvent was completely distilled off. The product **3** was crystallized from 8 mL chloroform at 0 °C and obtained as a white powder (0.174 g, 33 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.20 (s, 6H, OCH_3), 6.97 (d, *J* = 8.2 Hz, 2H, ArH), 7.18 – 7.22 (m, 10H, ArH), 7.26 – 7.30 (m, 10H, ArH), 7.34 – 7.36 (d, *J* = 8.2 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.1 (2C, OCH_3), 128.0 – 138.4 (34C, ArC), 154.3 (1C, ArC-OCH_3), 154.4 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = - 15.15 (2P,PPh_2)

M/z (calculated) = 651.5
MS (CI / 120 ºC, R=1000): M/z (%) = 651.2 [M^+] (2), 524.2, 462.2, 417.2, 391.3, 319.3, 263.1, 201.1, 153.1, 57.1, 43.1

Ru content of catalyst complex before the hydrogenation (calculated) = 124.2 g Ru/kg
ICP-AES = 1000 mg/kg (Ru content after the recycling)

5.4.11 Optimization of each step of the whole recycling (Table 3.15, Entry 2)

The catalyst complex **10** was prepared from 0.533 g (0.82 mmol) Cl-MeO-Biphep (**3**), 0.248 g (0.78 mmol) precursor **9** and 0.15 mL HBr (48 %) in 20 mL acetone. The mixture was stirred for 1hour after that the solvent was evaporated and the complex **10** was reacted with 10.4 mL (80 mmol) ethyl acetoacetate (**1**) as substrate in 40 mL methylcyclohexane in a 125 mL stainless steel autoclave. Hydrogenation reaction was conducted by using 50 bar of hydrogen pressure at 110 °C for 4 hours. After the reaction the product **2** was distilled off in vacuo at 148 – 150 °C.
Conversion = 99 %. *ee* = 73.4 %

The oxidation step was carried out with 10 mL H_2O_2 (35 %) in 20 mL dichloromethane at 0 ºC overnight. Then 100 mL dichloromethane and 100 mL water were added to allow phase separation. The organic layer was evaporated to obtain 0.957 g residue.
Afterwards 40 mL MTBE was added to this solid to separate the Ru-derivative (RuO_2) from the ligand oxide **3a** and this mixture was stirred at 140 °C for 4 hours. The solution was cooled down and the solid was filtered off. The residue was washed with 2x10 mL MTBE and the organic phases were collected and evaporated under reduced atmosphere resulting in the oxide **3a** as a white solid (0.719 g).
This solid was dissolved in 30 mL xylene and 16 mL (0.12 mol) NEt_3 and reduced by a mixture of 19 mL (0.19 mol) $HSiCl_3$ and 10 mL xylene. It was heated and stirred overnight at 110 °C. Afterwards the mixture was cooled to room temperature and 15 mL CH_2Cl_2 was added. Then the solution was cooled to 0 °C and 15 ml NaOH (30 w/w %) was dropped until pH=10 was reached. The suspension was filtered under argon atmosphere over 5 g SiO_2 (60, neutral) and washed with 150 mL dichloromethane. The organic phases were collected in a second flask and the phase separation was carried out with 100 mL water and 8 mL brine. After phase separation, the organic layer was dried over $MgSO_4$ and filtered. The sovent was completely distilled off and the product **3** was crystallized from 8 mL chloroform at 0 °C and obtained as a white powder (0.261 g, 49 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.19 (s, 6H, OCH_3), 6.97 (d, *J* = 8.2 Hz, 2H, ArH), 7.18 – 7.25 (m, 10H, ArH), 7.26 – 7.33 (m, 10H, ArH), 7.34 – 7.38 (d, *J* = 8.2 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.1 (2C, OCH_3), 128.1 – 138.4 (34C, ArC), 154.4 (1C, ArC-OCH_3), 154.5 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = - 15.16 (2P,PPh_2)

M/z (calculated) = 651.5
MS (EI / 200 ºC, 70 eV, R=1000): M/z (%) = 651.3 [M^+] (1), 577.3, 541.3, 503.2, 479.2, 429.2, 355.1, 327.1, 279.2, 224.2, 195.2, 149.1, 105.1, 69.1, 43.0

Ru content of catalyst complex before the hydrogenation (calculated) = 122.5 g Ru/kg
ICP-AES = 808 mg/kg (Ru content after the recycling)

5.4.12 Optimization of each step of the whole recycling (Table 3.15, Entry 3)

The catalyst complex **10** was prepared from 5.212 g (8 mmol) Cl-MeO-Biphep (**3**), 1.66 g (8 mmol) $RuCl_3xH_2O$ precursor and 1.5 mL HBr (48 %) in 40 mL acetone. The mixture was stirred for 1 hour. The solvent was evaporated and the complex **10** was reacted with 10.4 mL (80 mmol) ethyl acetoacetate (**1**) as substrate in 40 mL methylcyclohexane in a 125 mL stainless steel autoclave. Hydrogenation reaction was taken place by using 50 bar of hydrogen pressure at 110 °C for 4 hours. After the reaction the product **2** was distilled off in vacuo at 148 – 150 °C.
Conversion = 99 %. *ee* = 92.6 %

The oxidation step was carried out with 18 mL H_2O_2 (35 %) in 50 mL dichloromethane at 0 ºC overnight in a 1000 mL round-bottomed flask. Then 300 mL dichloromethane and 100 mL water were added to allow phase separation. The organic layers were evaporated to obtain dark brown powder residue.
Afterwards 200 mL MTBE was added to this powder to separate the Ru-derivative (RuO_2) from the ligand oxide **3a** and this mixture was stirred at 140 °C for 4 hours. The solution was cooled down and the solid was filtered off. 200 mL MTBE was used for

washing the flask. The residue was washed with 2x10 mL MTBE and the organic layers were collected and evaporated under reduced atmosphere resulting in the oxide **3a** as a white solid (4.27 g, 78.1 %).

This solid was solved in 110 mL xylene and 100 mL (0.72 mol) NEt_3 and reduced by a mixture of 120 mL (1.2 mol) $HSiCl_3$ and 100 mL xylene in two portions in a 1000 mL round-bottomed flask. It was heated and stirred overnight at 110 °C. Afterwards the mixture was cooled to room temperature and 100 mL CH_2Cl_2 was added. Then the solution was cooled to 0 °C and 40 ml NaOH (30 w/w %) was added dropwise to pH=10 was reached. The suspension was filtered *via* Büchner funnel, which was filled with 10 g SiO_2 (60, neutral). The residue was washed with 650 mL dichloromethane. The organic phases were collected in a second flask and reduced for its half volume. Afterwards phase separation was carried out with 400 mL water and 60 mL brine. The organic layer was dried over $MgSO_4$, filtered and the solvent was completely distilled off. The product **3** was crystallized from 15 mL chloroform at 0 °C and obtained as a white powder (1.476 g, 28.3 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.25 (s, 6H, OCH_3), 7.01 – 7.03 (m, 2H, ArH), 7.23 – 7.30 (m, 10H, ArH), 7.31 – 7.37 (m, 10H, ArH), 7.38 – 7.41 (d, *J* = 8.3 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.2 (2C, OCH_3), 127.9 – 138.4 (34C, ArC), 154.5 (1C, ArC-OCH_3), 154.6 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = - 15.08 (2P,PPh_2)

M/z (calculated) = 651.5
MS (EI / 200 ºC, 70 eV, R=1000): M/z (%) = 651.1 [M^+] (1), 636.9, 619.1, 573.2, 527.1, 481.1, 465.1, 431.1, 373.0, 325.1, 294.1, 244.1, 183.0, 149.0, 108.0, 91.1, 57.1, 43.0

Ru content of catalyst complex before the hydrogenation (calculated) = 116.7 g Ru/kg
ICP-AES = 1865 mg/kg (Ru content after the recycling)

5.4.13 Modeling of the recycling procedure as an industrial process (Table 3.16 and Table 3.17, Entry 1)

The catalyst complex for 10 hydrogenation reactions was prepared with 0.527 g (0.8 mmol) Cl-MeO-Biphep (**3**) and 0.227 g (0.7 mmol) precursor **9** in 20 mL anhydrous acetone. 0.15 mL HBr (48 %) was added dropwise and stirred for 1 hour afterwards the solvent was evaporated.

Prepared [(Cl-MeO-Biphep)-$RuBr_2$] (**10**) (0.08 mmol) was used without any purification as a catalyst for each hydrogenation reaction with 1 mL (8 mmol) substrate **1** in methylcyclohexane (15 mL). The solution was placed in a 125 mL stainless steel autoclave, which was adjusted at 50 bar hydrogen pressure and warmed to 110 ºC for 4 hours. The substrate to catalyst ratio was 100. The solvent was evaporated and the product **2** was separated by vacuum distillation at 148 - 150 ºC from the residue, which contains ligand **3** and precursor **9**. The same hydrogenation was carried out 10 times using always new catalyst complex **10**. The product **2** was separated by vacuum distillation at 148 – 150 ºC after each hydrogenation.

Conversion = 97.8 %. *ee* = 59.2 %

All residue were collected together after 10 hydrogenation reactions and 0.839 g residue was oxidized by 8 mL H_2O_2 (35 %) in 20 mL dichloromethane at 0 ºC overnight in a 200 mL round-bottomed flask. Then 45 mL dichloromethane and 120 mL water were added to allow phase separation. The organic layers were evaporated to obtain dark brown powder residue.

Afterwards 40 mL DBE was added to this powder to separate the Ru-derivative (RuO_2) from the ligand oxide **3a** and this mixture was stirred at 140 °C for 4 hours. The solution was cooled down and the solid was filtered off. 13 mL DBE was used for washing the flask. The residue was washed with 2x3 mL DBE and the organic layers were collected and evaporated under reduced atmosphere resulting the oxide as a white solid **3a** (0.576 g).

This solid was solved in 40 mL xylene and 16 mL (0.12 mol) NEt_3 and reduced by a mixture of 19 mL (0.19 mol) $HSiCl_3$ and 10 mL xylene. It was heated and stirred overnight at 110 °C. Afterwards the mixture was cooled to room temperature and extra

10 mL CH_2Cl_2 was added. Then the solution was cooled to 0 °C and 8 ml NaOH (30 w/w %) was added dropwise until pH=10 was reached. The suspension was filtered under argon atmosphere over 5 g Al_2O_3 (90 active, acidic) and washed with 130 mL dichloromethane. The organic phases were collected in a second flask and the phase separation was carried out with 50 mL water and 20 mL brine. After the phase separation the organic layer was dried over $MgSO_4$, filtered and the solvent was completely distilled off. The product **3** was crystallized from 10 mL chloroform at 0 °C and obtained as a white powder (0.202 g, 38 %). The average conversion of 10 hydrogenations is 97.8 % and average *ee* of the hydrogenation is 59.2 %.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.23 (s, 6H, OCH_3), 6.97 – 7.03 (d, *J* = 8.2 Hz, 2H, ArH), 7.21 – 7.28 (m, 10H, ArH), 7.29 – 7.35 (m, 10H, ArH), 7.36 – 7.43 (d, *J* = 8.2 Hz, 2H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 60.1 (2C, OCH_3), 128.0 – 138.4 (34C, ArC), 154.4 (1C, ArC-OCH_3), 154.5 (1C, ArC-OCH_3)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = -15.15 (2P,PPh_2)

M/z (calculated) = 651.5
MS (CI / 120 ºC, 70 eV, R=1000): M/z (%) = 651.2 [M^+] (2), 623.4, 591.4, 525.2, 467.2, 403.2, 391.3, 263.1, 201.1, 115.1, 57.1, 43.1

Ru content of catalyst complex before the hydrogenation (calculated) = 114.4 g Ru/kg
ICP-AES = 446 mg/kg (Ru content after the recycling)

5.4.14 Hydrogenation reaction using recovered ligand 3 (Table 3.17, Entry 2)

58 mg (0.08 mmol) recovered **3**, 29 mg (0.08 mmol) were stirred in 6 mL acetone and then 14.2 µL HBr (48 %) was added dropwise. The mixture was stirred for 1 hour after that the solvent was evaporated to obtain catalyst complex **10**. Typical hydrogenation was conducted with this catalyst complex **10** for the hydrogenation of 1mL **1** (8 mmol) in methylcyclohexane (10 mL). The solution was placed in a 125 mL stainless steel

autoclave, which was adjusted at the appropriate bar hydrogen pressure and warmed up to 110 ºC for 24 or 4 hours. S/C=100. The product **2** was separated by vacum distillation at 148 – 150 ºC.
Conversion = 99 %. *ee* = 56.9 %

5.5 Amination reaction using Dave-Phos (7) and X-Phos (8) ligand

5.5.1 General amination reaction with Dave-Phos ligand (7) performed in Lanxess FC laboratory (Table 3.18, Entry 1)

The amination reaction was conducted under argon in a 250 mL scale (10 wt%). 24.5 mL (0.27 mol) of aniline and 28.2 mL (0.27 mol) bromobenzene were added in a 500 mL round-bottomed flask to 250 mL toluene. Afterwards 85.4 g (0.4 mol) K_3PO_4 as a base and a mixture of 3.7 g (4.02 mmol) Pd_2dba_3 and 3.1 g (8.05 mmol) Dave-Phos (**7**) in 50 mL toluene were placed to the solution.
The reaction was conducted at 100 °C overnight and after that 200 mL water was added to perform phase separation at room temperature.
Conversion = 72 % (determined by GC-MS)

5.5.2 General amination reaction with X-Phos ligand (8) performed in Lanxess FC laboratory (Table 3.18, Entry 2)

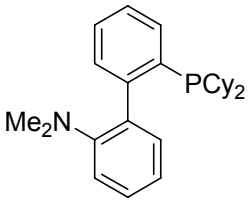
The amination reaction was conducted under argon in a 250 mL scale. 24.5 mL (0.27 mol) of aniline and 28.2 mL (0.27 mol) bromobenzene were added in a 500 mL round-bottomed flask to 250 mL toluene. Afterwards 85.4 g (0.4 mol) K_3PO_4 as a base and a mixture of 3.7 g (4.02 mmol) Pd_2dba_3 and 3.8 g (8.05 mmol) X-Phos (**8**) in 50 mL toluene were placed to the solution.

The reaction was conducted at 100 °C overnight and after that 200 mL water was added to perform phase separation at room temperature.
Conversion = 78.5 % (determined by GC-MS)

5.5.3 Improvement of general amination reaction using Dave-Phos ligand (7) (Table 3.18, Entry 3)

The amination reaction was conducted under argon in a 25 mL scale. 0.9 mL (9.87 mmol) aniline and 1 mL (9.5 mmol) bromobenzene were added in a 500 mL round-bottomed flask to 30 mL toluene. Afterwards 2.85 g (29.7 mmol) NaO*t*Bu as a base and a mixture of 0.15 g (0.16 mmol) $Pd_2(dba)_3$ and 0.13 g (0.33 mmol) Dave-Phos (**7**) in 5 mL toluene were placed to the solution. The reaction was taken place at 100 °C overnight.
After the reaction 20 mL water was added to perform phase separation at room temperature.
Conversion = 99 % (determined by GC-MS)

5.5.4 Characterization of (2-dicyclohexylphosphino-2´-(N,N-dimethylamino)-biphenyl) (Dave-Phos) 7



7

mp = 117 – 119 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.79 – 0.99 (m, 2H, CH_2), 1.01 – 1.21 (m, 4H, CH_2), 1.22 – 1.45 (m, 4H, CH_2), 1.53 – 1.68 (m, 7H, CH, CH_2), 1.74 – 1.76 (m, 2H, CH_2), 1.82 – 1.84 (m, 2H, CH_2), 2.03 – 2.10 (m, 1H, CH), 2.49 (s, 6H, $N(CH_3)_2$), 6.99 – 7.03 (m, 2H,

ArH), 7.06 – 7.09 (m, 1H, ArH), 7.31 – 7.36 (t, *J* = 7.7 Hz, 3H, ArH), 7.42 (t, *J* = 7.5 Hz, 1H, ArH), 7.58 (d, *J* = 7.4 Hz, 1H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 26.5 – 30.9 (10C), 33.4 – 36.8 (2C), 43.3 (2C), 117.3 (ArC), 120.7 (ArC), 125.9 (ArC), 128.1 (ArC), 130.5 (ArC), 132.4 (ArC), 132.8 (ArC), 135.3 (ArC), 135.8 (ArC), 135.9 (ArC), 149.6 (ArC), 151.5 (ArC)

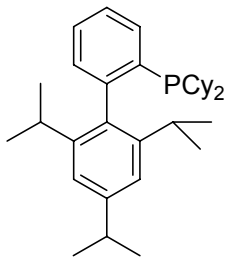
^{31}P-NMR (500 MHz, $CDCl_3$): δ = - 9.47 (P,PCy_2)

M/z (calculated) = 393.5

MS (EI / 200 ºC, R=1000): M/z (%) = 393.2 [M^+] (4), 349.1, 311.0, 310.2, 267.1, 212.3, 194.1, 183.3, 152.0, 55.1

IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3049, 2923, 2850, 2769, 2651, 1920, 1592, 1494, 1442, 1317, 1269, 1239, 1195, 1157, 1106, 1051, 1003, 946, 885, 850, 746, 671, 619, 572, 543, 522, 499, 464.

5.5.5 Characterization of (2-dicyclohexylphosphino-2´,4´,6´-triisopropyl-biphenyl) (X-Phos) 8



8

mp = 178 – 180 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.7 Hz, 6H, CH_2), 1.07 – 1.30 (m, 16H, CH_3), 1.33 – 1.39 (m, 6H, CH_2), 1.61 – 1.64 (m, 2H, CH_2), 1.69 – 1.71 (m, 4H, CH_2), 1.75 – 1.77 (m, 4H, CH_2), 1.89 (s, 2H, CH), 2.41 – 2.49 (m, 2H, $CH(CH_3)_2$), 2.96 (m, 1H,

$CH(CH_3)_2$), 7.04 (s, 2H, ArH), 7.17 – 7.23 (m, 1H, ArH), 7.32 – 7.41 (m, 2H, ArH), 7.63 (t, *J* = 7 Hz, 1H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 22.9 (2C), 24.0 (2C), 25.8 (2C), 26.5 – 27.6 (10C), 30.6 (2C), 34.1 (1C), 34.6 (1C), 34.7 (1C), 120.3 (2C, ArC), 126.1 (ArC), 127.6 (ArC), 131.6 (ArC), 132.3 (ArC), 136.5 (ArC), 136.6 (ArC), 146.0 (ArC), 147.6 (ArC), 147.7 (ArC), 147.9 (ArC)

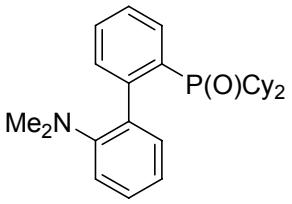
^{31}P-NMR (500 MHz, $CDCl_3$): δ = - 11.96 (P,PCy_2)

M/z (calculated) = 476.7

MS (EI / 200 ºC, R=1000): m/z (%) = 476.5 [M^+] (6), 433.2, 419.0, 351.2, 278.9, 269.2, 225.1, 183.0, 178.0, 83.1, 55.1

IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3042, 2959, 2940, 2923, 2845, 1606, 1570, 1448, 1359, 1317, 1267, 1168, 1106, 1054, 997, 945, 889, 875, 779, 767, 650, 596, 517, 462

5.5.6 Dave-Phos oxide derivative 7a (Table 3.19, Entry 1)



7a

Dave-Phos ligand (**7**) (0.35 g, 0.89 mmol) and 10 mL CH_2Cl_2 were placed in a 100 mL round-bottomed flask. To the cooled solution 3 mL H_2O_2 (35 %) was added at 0 ºC. The mixture was stirred at 0 ºC than room temperature overnight. Afterwards 10 mL water was added. Aqueous phase was extracted with 3x3 mL CH_2Cl_2. The organics phases were dried over $MgSO_4$ and evaporated to gain a pale yellow solid **7a** (quantitative yield).

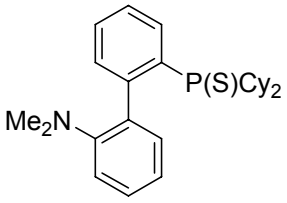
mp = 141 – 143 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.88 – 1.05 (m, 2H, CH_2), 1.09 – 1.27 (m, 5H, CH_2), 1.28 – 1.46 (m, 4H, CH_2), 1.47 – 1.63 (m, 5H, CH_2), 1.69 – 1.79 (m, 4H, CH_2), 1.87 – 2.06 (m, 2H, CH), 2.55 (s, 6H, $N(CH_3)_2$), 6.97 – 7.07 (m, 3H, ArH), 7.32 – 7.39 (m, 2H, ArH), 7.46 (t, *J* = 7.6 Hz, 1H, ArH), 7.53 (t, *J* = 7.4 Hz, 1H, ArH), 7.97 (t, *J* = 7.3 Hz, 1H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 25.6 – 26.7 (10C), 36.4 – 37.7 (2C), 44.0 (2C), 117.5 (ArC), 121.1 (ArC), 126.6 (ArC) 128.7 (ArC), 130.7 (ArC), 132.0 (ArC), 132.8 (ArC), 133.7 (ArC), 134.6 (ArC), 144.6 (ArC), 144.8 (ArC), 151.3 (ArC)
^{31}P-NMR (500 MHz, $CDCl_3$): δ = 49.65 (P-C coupling), 49.82 (P,$P(O)Cy_2$), 49.97 (P-C coupling)

M/z (calculated) = 409.5
MS (EI / 200 ºC, R=1000): m/z (%) = 409.2 [M^+] (47), 394.2, 365.2, 326.2, 283.1, 244.1, 228.1, 215.1, 194.1, 180.1, 152.1, 83.1, 55.1

IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 3053, 2925, 2850, 2775, 2661, 2370, 1593, 1494, 1442, 1315, 1277, 1165, 1105, 1055, 1003, 848, 746, 669, 619, 572, 503, 447

5.5.7 Dave-Phos sulfide derivative 7b (Table 3.19, Entry 2)



7b

0.4 g (1 mmol) Dave-Phos ligand (**7**) and elemental sulphur (0.32 g, 1.23 mmol) were stirred in 10 mL toluene at 95 ºC for 12 hours. The mixture was cooled down and then filtered and dried over $MgSO_4$. Afterwards it was evaporated to obtain a pale yellow solid **7b** in quantitative yield (0.43 g, 99 %). ^{31}P-NMR spectrum shows total conversion.
mp = 155 – 157 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.84 – 1.02 (m, 2H, CH_2), 1.06 – 1.13 (m, 2H, CH_2), 1.18 – 1.27 (m, 4H, CH_2), 1.28 – 1.34 (m, 1H, CH), 1.42 – 1.58 (m, 5H, CH, CH_2), 1.59 – 1.69 (m, 4H, CH_2), 1.70 – 1.73 (m, 2H, CH), 1.77 – 1.80 (m, 2H, CH_2), 2.60 (s, 6H, $N(CH_3)_2$), 6.99 – 7.12 (m, 3H, ArH), 7.25 – 7.35 (m, 2H, ArH), 7.36 – 7.45 (m, 1H, ArH), 7.49 (m, 1H, ArH), 8.65 (q, *J* = 7.4 Hz, 1H, ArH)

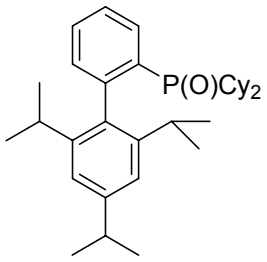
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 25.3 – 28.1 (10C), 37.0 – 38.1 (2C), 44.1 (2C), 117.4 (ArC), 121.3 (ArC), 126.7 (ArC), 126.8 (ArC), 129.0 (ArC), 130.5 (ArC), 130.6 (ArC), 132.8 (ArC), 133.1 (ArC), 133.2 (ArC), 137.0 (ArC), 137.1 (ArC)

^{31}P-NMR (200 MHz, $CDCl_3$): δ = 69.74 (P-C coupling), 69.86 (P,$P(S)Cy_2$), 69.98 (P-C coupling)

M/z (calculated) = 425.6

MS (EI / 200 ºC, R=1000): m/z (%) = 425.2 [M^+] (45), 381.1, 349.2, 310.2, 299.1, 260.1, 216.0, 194.1, 183.0, 83.1, 55.0

5.5.8 X-Phos oxide derivative 8a (Table 3.19, Entry 3)



8a

X-Phos ligand (**8**) (0.34 g, 0.72 mmol) and 10 mL CH_2Cl_2 were placed in a 100 mL round-bottomed flask. To the cooled solution 3 mL H_2O_2 (35 %) was added at 0 ºC. The mixture was stirred at 0 ºC than room temperature overnight. Afterwards 10 mL water was added. Aqueous phase was extracted with 3x3 mL CH_2Cl_2. The organics phases were dried over $MgSO_4$ and evaporated to gain a white powder **8a** (0.35 g, 99 %).

mp = 213 - 215 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.7 Hz, 6H, CH_2), 1.05 – 1.24 (m, 6H, CH_2), 1.26 – 1.33 (m, 12H, CH_3), 1.34 – 1.46 (m, 4H, CH_2), 1.64 – 1.68 (m, 2H, CH_2), 1.75 – 1.79 (m, 8H, CH_2), 1.84 – 1.95 (m, 2H, CH_2), 2.45 (m, 2H, $CH(CH_3)_2$), 2.95 (m, 1H, $CH(CH_3)_2$), 7.0 (s, 2H, ArH), 7.15 – 7.20 (m, 1H, ArH), 7.39 – 7.51 (m, 2H, ArH), 7.69 (t, *J* = 7.5 Hz, 1H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 22.8 (2C), 24.1 (2C), 25.8 (2C), 26.0 – 26.8 (10C), 30.8 (2C), 34.1 (1C), 37.5 (1C), 37.9 (1C), 120.2 (2C, ArC), 125.9 (ArC), 126.0 (ArC), 129.7 (ArC), 131.8 (ArC), 133.5 (ArC), 133.6 (ArC), 145.2 (ArC), 147.7 (ArC), 147.7 (ArC), 147.9 (ArC)

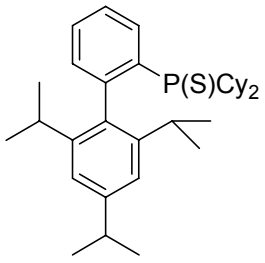
^{31}P-NMR (500 MHz, $CDCl_3$): δ = 44.07 (P-C coupling), 44.24 (P,$P(O)Cy_2$), 44.39 (P-C coupling)

M/z (calculated) = 492.7

MS (EI / 200 ºC, R=1000): m/z (%) = 492.2 [M^+] (23), 449.2, 367.1, 349.1, 334.1, 278.1, 263.1, 233.1, 214.1, 181.0, 133.0, 83.1, 55.0

IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2939, 1751, 1608, 1450, 1357, 1317, 1261, 1191, 1124, 1072, 947, 890, 871, 823, 769, 739, 669, 544, 495

5.5.9 X-Phos sulfide derivative 8b (Table 3.19, Entry 4)



8b

0.43 g (0.9 mmol) X-Phos ligand (**8**) and elemental sulphur (0.36 g, 1.38 mmol) were stirred in 10 mL toluene at 95 ºC for 12 hours. The mixture was cooled down and then filtered and dried over $MgSO_4$. Afterwards it was evaporated to obtain a pale yellow solid **8b** in quantitative yield (0.46 g, 99 %). ^{31}P-NMR spectrum shows total conversion.

mp = 224 – 226 ºC

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.7 Hz, 6H, CH_2), 1.06 – 1.22 (m, 6H, CH_2), 1.24 – 1.30 (m, 6H, CH_3), 1.31 – 1.35 (m, 6H, CH_2), 1.37 – 1.51 (m, 4H, CH_2), 1.53 – 1.64 (m, 4H, CH_2), 1.74 – 1.79 (m, 4H, CH_2), 1.84 – 1.86 (m, 2H, CH_2), 1.98 – 2.08 (m, 2H, CH_2), 2.41 (m, 2H, $CH(CH_3)_2$), 2.95 (m, 1H, $CH(CH_3)_2$), 7.0 (s, 2H, ArH), 7.15 – 7.21 (m, 1H, ArH), 7.39 – 7.49 (m, 2H, ArH), 7.99 – 8.04 (m, 1H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.5 (2C), 24.2 (2C), 25.8 (2C), 26.6 – 27.2 (10C), 30.8 (2C), 34.2 (1C), 34.6 (1C), 39.8 (1C), 120.3 (2C, ArC), 125.3 (ArC), 126.2 (ArC), 131.6 (ArC), 132.8 (ArC), 132.9 (ArC), 135.5 (ArC), 137.9 (ArC), 145.4 (ArC), 146.0 (ArC), 148.4 (ArC)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = 59.58 (P,P(S)Cy_2)

M/z (calculated) = 508.8
MS (EI / 200 ºC, R=1000): M/z (%) = 508.2 [M^+] (14), 465.1, 383.1, 255.7, 191.8, 159.8, 127.8, 95.9, 63.9

5.5.10 Reduction procedure of standard Dave-Phos oxide derivative 7a

305 mg (0.75 mmol) Dave-Phos oxide (**7a**) was solved in 5 ml xylene and 3 ml (0.02 mol) NEt_3. This was heated to 60 °C under reflux then a mixture of 5 ml (0.05 mol) trichlorosilane and 5 ml xylene was added slowly to the suspension. It was heated and stirred overnight at 110 °C. Afterward reaction mixture was cooled to room temperature and solved in 15 mL CH_2Cl_2. Then the solution was cooled to 0 °C and NaOH (10 w/w %) was added dropwise until pH=10 was reached. The suspension was filtered under argon atmosphere over 5 g Al_2O_3 (90 active, acidic). The organic phase was collected in a second flask and the water phase was extracted with 20 mL CH_2Cl_2. The collected dichloromethane phases were washed 2x10 mL water under argon atmosphere. The organic layer was reduced to a volume of 10 mL in vacuo. Organic layer was dried over $MgSO_4$ and completely removed under reduced atmosphere, thus **7** was obtained as a pale yellow powder (245 mg, 83 %). Conversion of reduction: 83 %.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.88 – 0.95 (m, 2H, CH_2), 1.12 – 1.16 (m, 4H, CH_2), 1.27 – 1.32 (m, 4H, CH_2), 1.50 – 1.67 (m, 7H, CH, CH_2), 1.72 – 1.78 (m, 2H, CH_2), 1.81 – 1.83 (m, 2H, CH_2), 2.03 – 2.10 (m, 1H, CH), 2.48 (s, 6H, $N(CH_3)_2$), 6.94 – 7.11 (m, 3H, ArH), 7.28 – 7.37 (m, 3H, ArH), 7.40 – 7.44 (m, 1H, ArH), 7.75 – 7.62 (m, 1H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 25.9 – 30.8 (10C), 33.3 – 36.7 (2C), 43.2 (2C), 117.3 (ArC), 120.7 (ArC), 125.8 (ArC), 128.1 (ArC), 130.5 (ArC), 130.8 (ArC), 132.4 (ArC), 132.8 (ArC), 135.8 (ArC), 135.9 (ArC), 149.5 (ArC), 151.5 (ArC)
^{31}P-NMR (200 MHz, $CDCl_3$): δ = -9.59 (P,PCy_2), 47.78 ($P(O)Cy_2$)

5.5.11 Reduction procedure of standard X-Phos oxide derivative 8a

112 mg (0.23 mmol) X-Phos oxide (**8a**) was solved in 5 ml xylene and 3 ml NEt_3. This resulting was heated to 60 °C under reflux then a mixture of 4 ml (0.04 mol) trichlorosilane and 4 ml xylene was added slowly to the suspension. It was heated and stirred overnight at 110 °C. Afterward reaction mixture was cooled to room temperature and solved in 8 mL CH_2Cl_2. Then the solution was cooled to 0 °C and NaOH (10 w/w %) was added dropwise until pH=10 was reached. The suspension was filtered under argon atmosphere over 5 g Al_2O_3 (90 active, acidic). The organic phase was collected in a second flask and the water phase was extracted with 10 mL CH_2Cl_2. The collected dichloromethane layers were washed two times with 10 mL water under argon atmosphere. The organic layer was reduced to a volume of 5 mL in vacuum. Organic phase was dried over $MgSO_4$ and removed under reduced atmosphere, thus **8** was obtained as a white powder (92 mg, 84 %). Conversion of reduction: 85 %.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.00 – 1.07 (d, *J* = 6.7 Hz, 6H, CH_2), 1.24 – 1.29 (m, 6H, CH_3), 1.30 – 1.42 (m, 16H, CH_2, CH_3), 1.59 – 1.66 (m, 2H, CH_2), 1.71 – 1.85 (m, 8H, CH_2), 1.87 – 1.91 (m, 2H, CH), 2.48 (m, 2H, $CH(CH_3)_2$), 2.98 (m, 1H, $CH(CH_3)_2$), 7.06 (s, 2H, ArH), 7.17 – 7.26 (m, 1H, ArH), 7.36 – 7.39 (m, 2H, ArH), 7.65 (t, *J* = 7 Hz, 1H, ArH)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 22.9 (2C), 24.1 (2C), 25.9 (2C), 26.0–26.8 (10C), 30.9 (2C), 34.1 (1C), 37.5 (1C), 38.0 (1C), 120.2 (ArC), 125.8 (ArC), 129.8 (ArC), 130.9

(ArC), 131.7 (ArC), 132.4 (ArC), 134.7 (ArC), 136.5 (ArC), 136.6 (ArC), 145.8 (ArC), 146.0 (ArC), 147.7 (ArC)

^{31}P-NMR (200 MHz, $CDCl_3$): δ = - 12.11 (PCy_2), 44.58 ($P(O)Cy_2$)

5.5.12 Examined separation procedures of product (6) after the amination

Vacuum distillation of the product **6** at 200 ºC (14 mbar), the temperature of the cooler was adjusted to 60 ºC.

Column chromatography over silica gel with 1:1 CH_2Cl_2 / EtOAc, ($R_{f(6)}$ = 0.9, $R_{f(\mathbf{7a},\ \mathbf{8a})}$ = 0.3) as eluent provided the ligand oxide derivative **7a**, **8a**.

Separation of the ligand **7** and **8** by protonation: the reaction was run overnight and after that 200 mL water was added to make phase separation. The catalyst complex was filtered. After the phase separation, the organics phase was treated with 5 mL HCl (37 %) to protonate the ligand. The solution was neutralized with a mixture of 1.8 g NaOH in 5 mL water. The ligand was in the water phase after the protonation.
Water was removed and the residue was solved in 30 mL dichloromethane (inorganic salt remained in the flask) and oxidized with 5 mL H_2O_2 (35 %). Water was added to perform phase separation and the organic layer was dried over $MgSO_4$ and completely removed. Yellow solid was obtained using both ligand (**7**, **8**) but not confirmed by NMR measurements as pure ligand oxide derivatives of **7a** or **8a**.

5.5.13 Recycling method using X-Phos ligand (Table 3.20, Entry 1)

The amination reaction was conducted in threefold bigger scale under argon with 2.45 mL (26.8 mmol) aniline and 2.82 mL (26.8 mmol) bromobenzene were added in a 200 mL round-bottomed flask to 75 mL toluene. Afterwards 3.9 g (40.5 mmol) NaO*t*Bu as a base and a mixture of 0.37 g (0.40 mmol) $Pd_2(dba)_3$ and 0.375 g (0.82 mmol) X-Phos (**8**)

in 15 mL toluene were placed to the solution. The reaction was taken place at 100 °C overnight.

Spectra of product **6**:

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.83 (s, 1H, NH), 7.25 (t, *J* = 7.3 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 4H), 7.56 (t, *J* = 7.4 Hz, 4H)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 118.2 (4C), 121.3 (2C), 129.7 (4C), 143.5 (2C)

After the reaction, at room temperature 3x20 mL water was added to perform phase separation. The organic phase was evaporated and distilled under reduced atmosphere (200 °C, 14 mbar). 3.208 g (70 %) product **6** was separated from the ligand **8**. Afterwards the residue containing this ligand was solved in 15 mL CH_2Cl_2 and oxidized by 7.5 mL H_2O_2 (35 %) at 0 °C overnight. Then 25 mL water and additional 5 mL CH_2Cl_2 were added to the phase separation. The organic layer was evaporated and dibutylether (10 mL) was added to precipitate the Pd-derivative (PdO_2) from the ligand oxide **8a**. The liquid was stirred and heated for 2 hours at 140 °C then it was cooled down slowly. After the filtration, the solid was washed with 10 mL dibutylether and the filtrate was dried over $MgSO_4$ and completely distilled off in vacuo. 265 mg (70 %) **8a** was obtained as white solid.

mp = 209 – 211 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.7 Hz, 6H, CH_2), 1.04 – 1.23 (m, 6H, CH_2), 1.23 – 1.34 (m, 12H, CH_3), 1.36 – 1.56 (m, 4H, CH_2), 1.58 – 1.70 (m, 2H, CH_2), 1.74 – 1.76 (m, 8H, CH_2), 1.84 – 1.97 (m, 2H, CH_2), 2.47 (m, 2H, $CH(CH_3)_2$), 2.93 (m, 1H, $CH(CH_3)_2$), 7.01 (s, 2H, ArH), 7.15 – 7.24 (m, 1H, ArH), 7.37 – 7.51 (m, 2H, ArH), 7.71 (t, *J* = 7.5 Hz, 1H, ArH)

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 22.8 (2C), 23.9 (2C), 25.5 (2C), 26.0 – 26.8 (10C), 30.6 (2C), 34.1 (1C), 37.4 (1C), 37.9 (1C), 120.2 (2C, ArC), 126.0 (ArC), 126.5 (ArC), 129.8 (ArC), 131.8 (ArC), 134.1 (ArC), 135.9 (ArC), 141.9 (ArC), 145.2 (ArC), 147.6 (ArC), 148.0 (ArC)

^{31}P-NMR (200 MHz, $CDCl_3$): δ = 44.52 ($P(O)Cy_2$)

5.5.14 Recycling method using X-Phos ligand (Table 3.20, Entry 2)

The amination reaction was conducted in threefold bigger scale under argon with 4.1 mL (44.7 mmol) aniline and 4.7 mL (44.5 mmol) bromobenzene were added in a 200 mL round-bottomed flask to 80 mL toluene. Afterwards 6.45 g (67.5 mmol) NaO*t*Bu as a base and a mixture of 0.62 g (0.66 mmol) $Pd_2(dba)_3$ and 0.625 g (1.3 mmol) X-Phos (**8**) in 15 mL toluene were placed to the solution. The reaction was taken place at 100 °C overnight.

Spectra of product **6**:
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.81 (s, 1H, NH), 7.08 (t, *J* = 7.3 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 4H), 7.41 (t, *J* = 7.4 Hz, 4H)
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 118.1 (4C), 121.2 (2C), 129.5 (4C), 143.2 (2C)

After the reaction, at room temperature 3x30 mL water was added to perform phase separation. The organic phase was evaporated and distilled under reduced atmosphere (200 °C, 14 mbar). 6.34 g (84 %) product **6** was separated from the ligand **8**. Afterwards the residue containing this ligand was solved in 15 mL CH_2Cl_2 and oxidized by 12 mL H_2O_2 (35 %) at 0 °C overnight. Then 40 mL water and additional 5 mL CH_2Cl_2 were added to the phase separation. The organic layer was evaporated and dibutylether (10 mL) was added to precipitate the Pd-derivative (PdO_2) from the ligand oxide **8a**. The liquid was stirred and heated for 2 hours at 140 °C then it was cooled down slowly. After the filtration, the solid was washed with 2x10 mL dibutylether and the filtrate was dried over $MgSO_4$ and completely distilled off in vacuo. 465 mg (72 %) **8a** was obtained as white solid.
mp = 208 – 210 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.7 Hz, 6H, CH_2), 1.08 – 1.18 (m, 6H, CH_2), 1.24 – 1.35 (m, 12H, CH_3), 1.36 – 1.43 (m, 4H, CH_2), 1.61 – 1.66 (m, 2H, CH_2), 1.74 – 1.79 (m, 8H, CH_2), 1.86 – 1.94 (m, 2H, CH_2), 2.45 (m, 2H, $CH(CH_3)_2$), 2.93 (m, 1H, $CH(CH_3)_2$), 7.01 (s, 2H, ArH), 7.17 – 7.24 (m, 1H, ArH), 7.36 – 7.51 (m, 2H, ArH), 7.70 (t, *J* = 7.5 Hz, 1H, ArH)

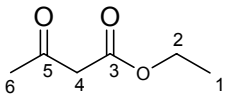
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 22.7 (2C), 24.1 (2C), 25.9 (2C), 26.0 – 26.8 (10C), 30.8 (2C), 34.1 (1C), 37.4 (1C), 38.0 (1C), 120.2 (2C, ArC), 126.0 (ArC), 126.1 (ArC), 129.8 (ArC), 131.8 (ArC), 133.5 (ArC), 133.6 (ArC), 136.0 (ArC), 145.2 (ArC), 145.7 (ArC), 147.7 (ArC)

^{31}P-NMR (200 MHz, $CDCl_3$): δ = 45.19 ($P(O)Cy_2$)

6 Spectra

Asymmetric Hydrogenation

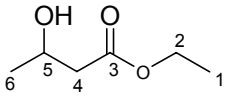
Spectra of substrate 1



^{1}H-NMR spectrum of **1** (200 MHz, $CDCl_3$):

δ = 1.29 (t, *J* = 7.1 Hz, 3H, $C^{1}H_3$), 2.27 (s, 3H, $C^{6}H_3$), 3.45 (s, 2H, $C^{4}H_2$), 4.20 (q, *J* = 7.1 Hz, 2H, $C^{2}H_2$)

Spectra of product 2

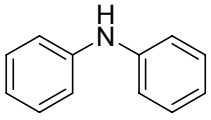


^{1}H-NMR spectrum of **2** (200 MHz, $CDCl_3$):

δ = 1.23 – 1.32 (m, 6H, $C^{1,6}H_3$), 2.44 – 2.48 (m, 2H, $C^{4}H_2$), 3.10 (s, 1H, OH), 4.13 – 4.24 (m, 3H, $C^{2}H_2$, $C^{5}H$)

Buchwald-Hartwig amination

Spectra of product 6

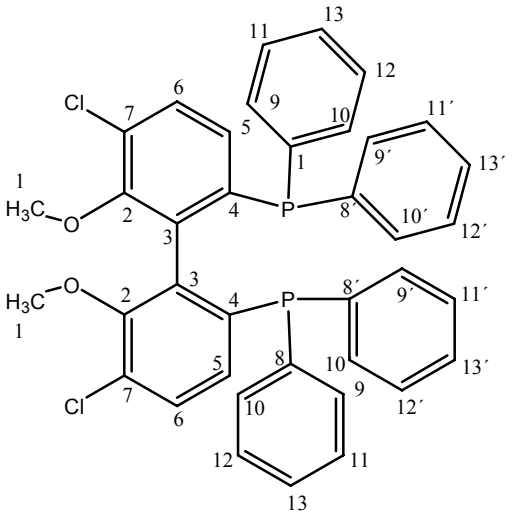


^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.48 (s, 1H, NH), 7.08 (t, *J* = 8 Hz, 2H), 7.18 (d, *J* = 9.5 Hz, 4H), 7.45 (t, *J* = 6.9 Hz, 4H)

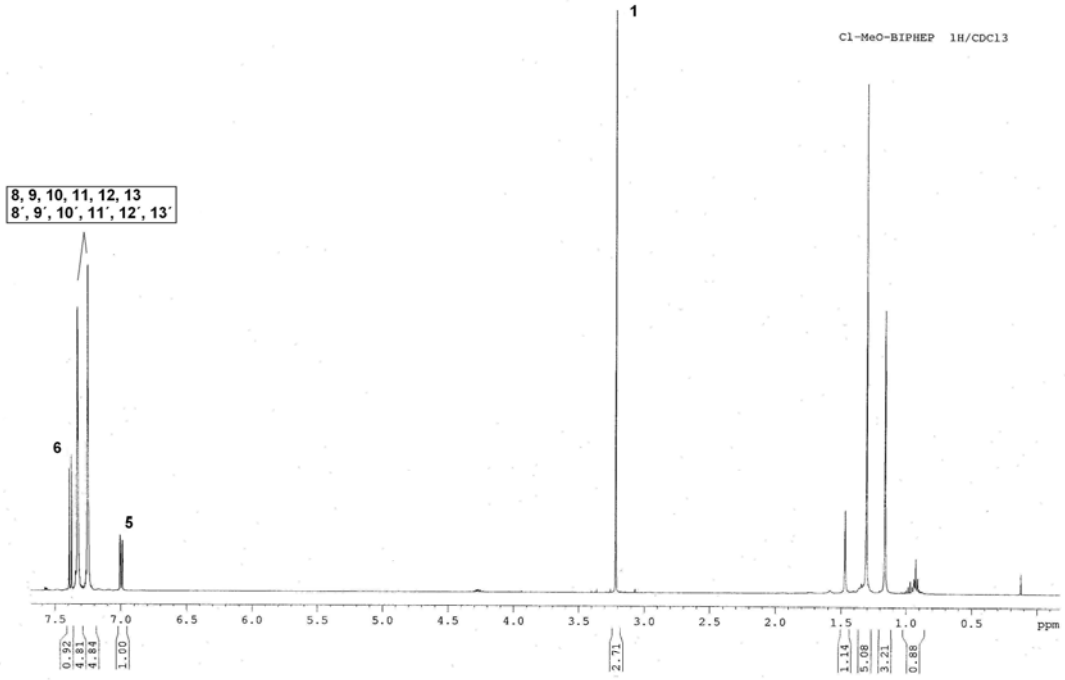
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 117.9 (4C), 121.3 (2C), 129.5 (4C), 143.2 (2C)

Spectra of Cl-MeO-Biphep ligand (**3**) and its phosphine oxide **3a**

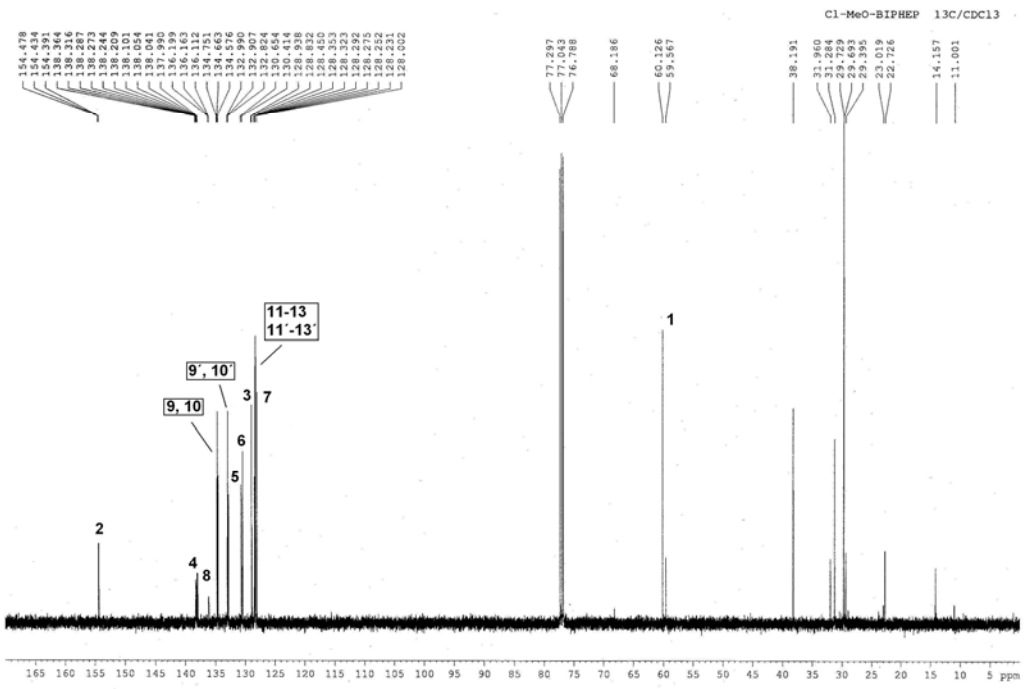
Spectra of **3** were assigned by 2D-NMR techniques (COSY, HMBC, HMQC) [115].



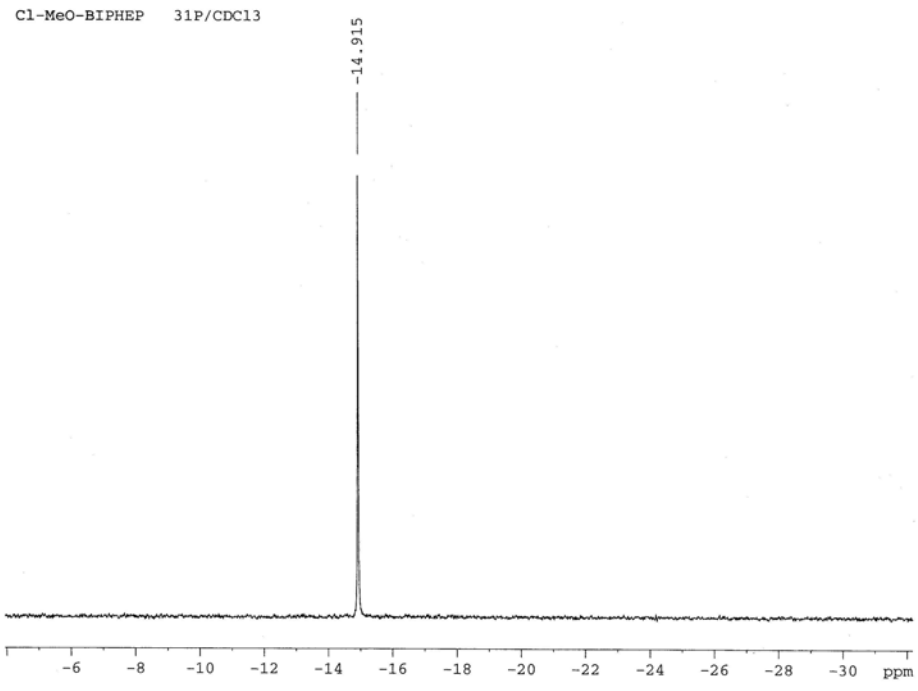
Cl-MeO-Biphep ligand (**3**)



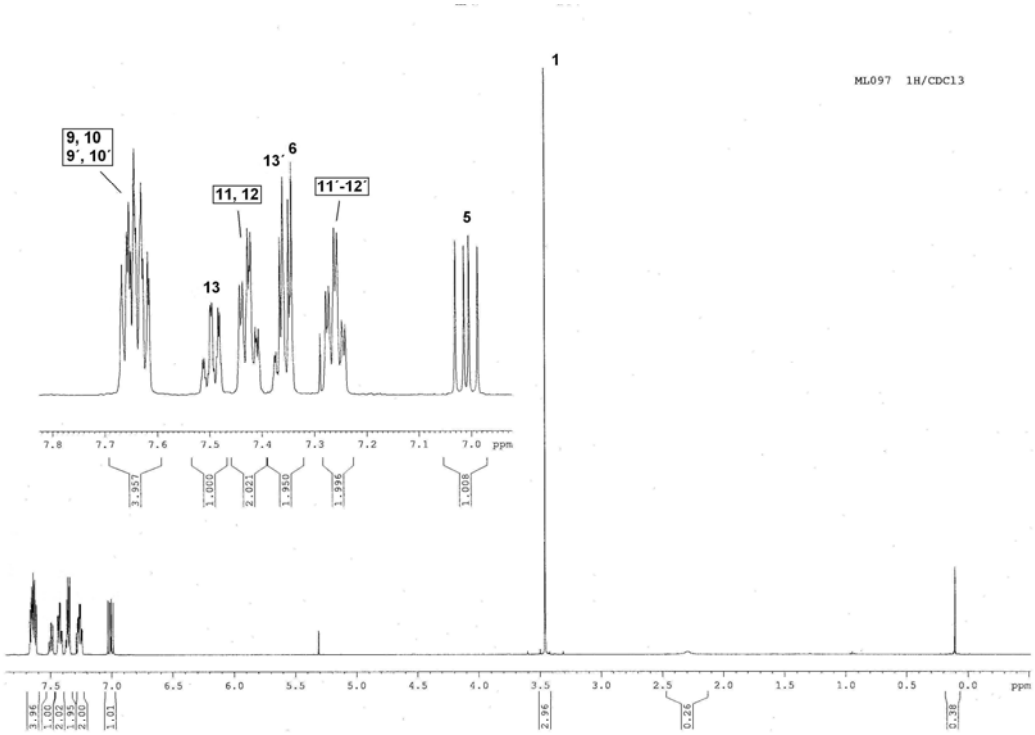
^{1}H-NMR spectrum of Cl-MeO-Biphep ligand (**3**)



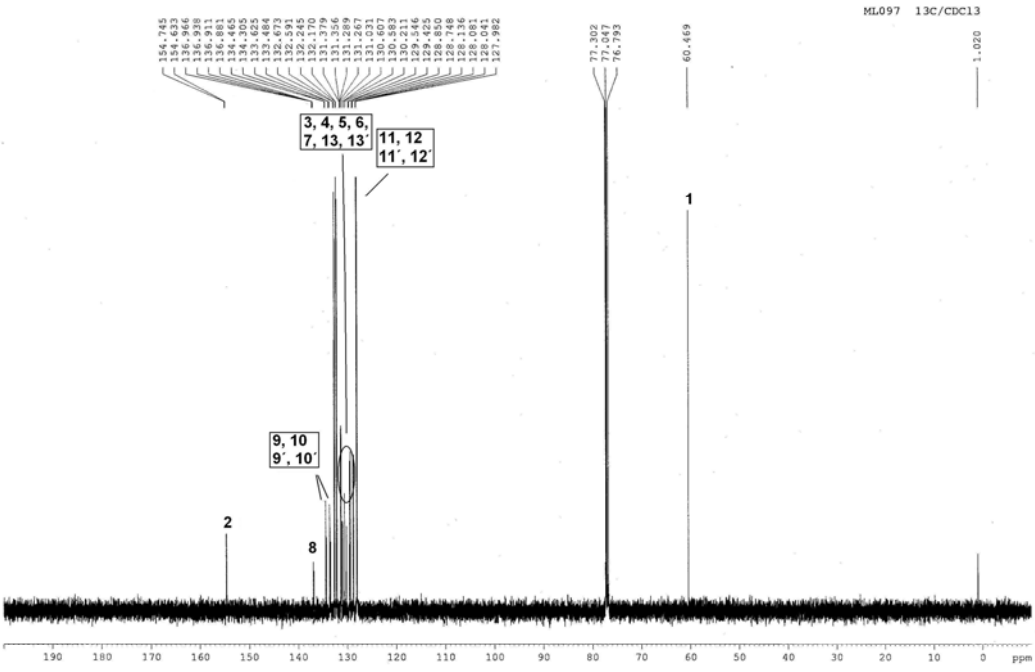
^{13}C-NMR spectrum of Cl-MeO-Biphep ligand (**3**)



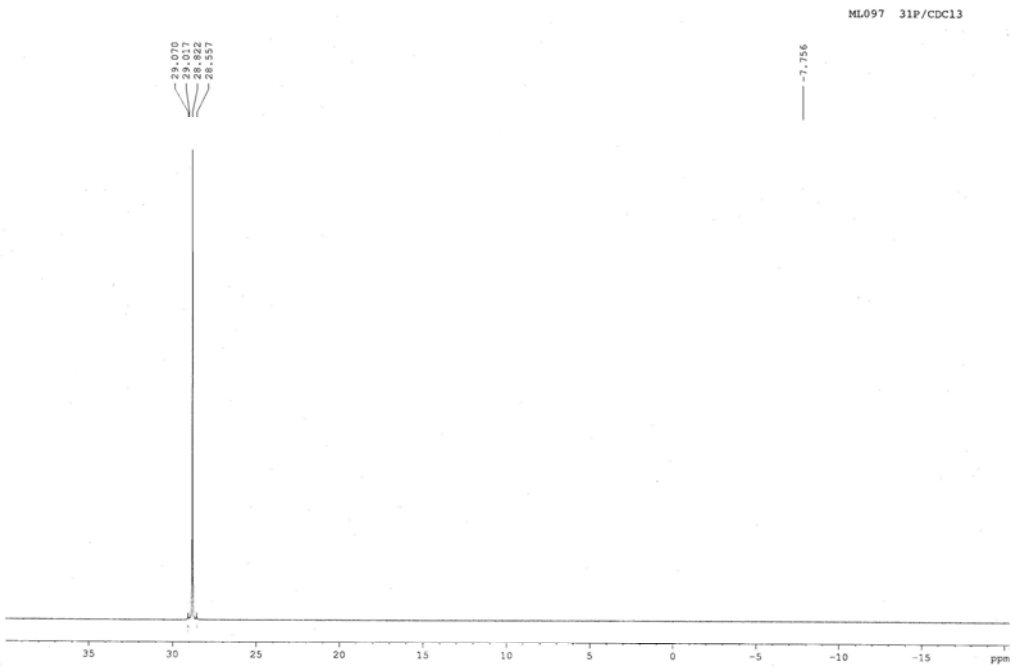
^{31}P-NMR spectrum of Cl-MeO-Biphep ligand (**3**)



^{1}H-NMR spetrum of Cl-MeO-Biphep ligand-oxide (**3a**)



^{13}C-NMR spectrum of Cl-MeO-Biphep ligand-oxide (**3a**)



^{31}P-NMR spectrum of Cl-MeO-Biphep ligand-oxide (**3a**)

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