Use of monodentate ligands in the asymmetric ketone hydrogenation

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Use of Monodentate Ligands in the Asymmetric Ketone Hydrogenation

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Chapter 1
Introduction

1.1 Chirality

Chirality is one of the most important topics in contemporary organic chemistry.[1-3] Chirality in molecules is best compared to one's own hands; they are exactly the same, but each other's mirror image and are in no way superimposable.

The same phenomenon can occur in (organic) molecules. If a molecule possesses an asymmetric center, for instance a carbon atom with four different substituents (see Figure 1), its mirror images are not superimposable and the molecule is called a chiral molecule (from the Greek word *χειρ* -cheir- which means hand)

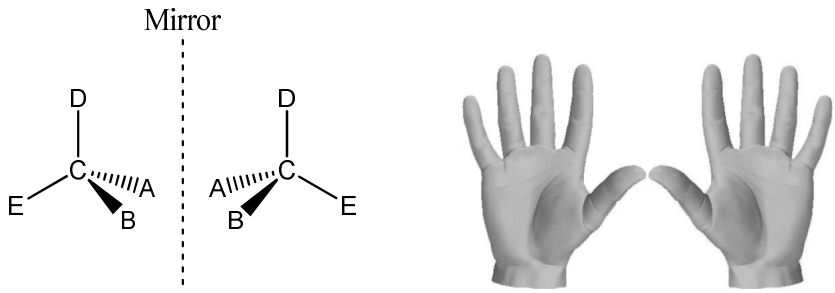


Figure 1: Example of a chiral "molecule" containing an asymmetric carbon atom with four different substituents, and of two (chiral) hands.

This results in an *R* (Rex = right) and an *S* (Sinister = left) form of the molecule. The *R* and the *S* molecules are called each other's enantiomers. The fact that molecules can have different spacial arrangements was first recognized by both LeBel[4] and Van 't Hoff[5] independently in 1874; the latter received the first Nobel prize in chemistry in 1901.

The main difference between two enantiomers is that they rotate the plane of a polarized light beam in opposite direction of each other. So one enantiomer rotates the light clockwise (+) whereas the other rotates it counterclockwise (-). Although the differences between two enantiomers are very limited, they are of great importance.

Many of nature's essential building blocks are chiral, enantiopure, molecules including amino acids, sugars and nucleosides. Because amino acids are chiral,

this means that also all proteins including enzymes are chiral. The most important consequence of the fact that enzymes are chiral (and enantiopure) is that they also can commonly bind to only one of the enantiomers of a substrate molecule, if this is also a chiral molecule. This property has serious consequences for the pharmaceutical industry.[6] Since it is often not known what kind of action the other enantiomer will display in the body, the pharmaceutical industry has to be very careful when selling a drug as a racemic mixture (i.e. both enantiomers are present in equal amounts in the mixture).
An example of two enantiomers that have different functions in nature are the two forms of ketamine (**1.1**) which are depicted in Figure 2. Where the *S* form is an anesthetic which is often used by veterinarians, the *R* form is a hallucinogenic compound.[7]

S-**1.1** *R*-**1.1**

Figure 2: *S* and *R* ketamine. Two enantiomers of the same compound with completely different functions.

Another example of enantiomers that have completely different functions is the molecule thalidomide, also known as Softenon®.[6] This compound was distributed as a mixture of enantiomers in the 1950s and provided to pregnant women to relieve nausea and insomnia complaints. But whereas the (*R*) enantiomer of the compound relieved the nausea and insomnia complaints it turned out that the (*S*) enantiomer blocked normal growth and development of their unborn children leading to a significant rise in births of malformed babies with women who used the drug.

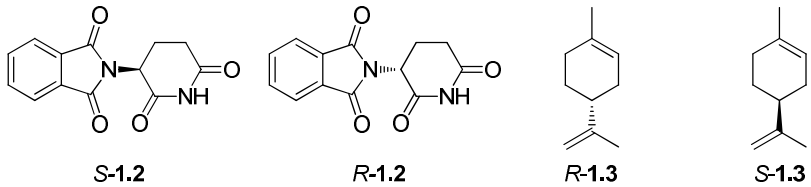


Figure 3: The two enantiomers of Thalidomide (**1.2**) and Limonene (**1.3**).

Not only in physiological processes related to drug action the differences between enantiomers can be seen but also, for example, the smell of two enantiomers can be completely different.[8] A nice example in this case is limonene (**1.3,** see Figure 3) of which the (*R*) form has a pine-like smell whereas the (*S*) from smells of orange peels.

1.2 Synthesis of chiral molecules

Because the two enantiomers of a chiral compound can have such different biological functions it is of crucial importance for (organic) chemists to develop methods for the enantioselective synthesis of chiral molecules.
As displayed in Figure 4 there are, presently, 3 main strategies for the preparation of an enantiomerically pure compound.[9]

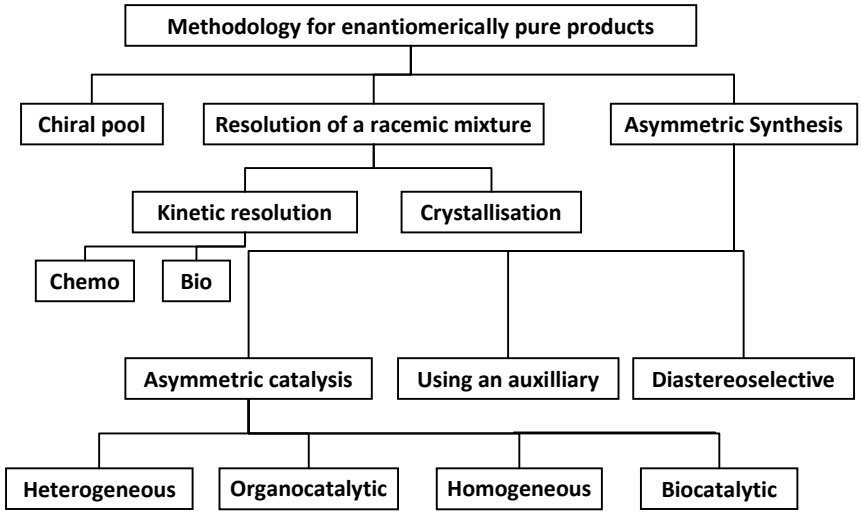


Figure 4: Synthesis options for chiral, non-racemic, compounds.

- The first is to use one of the compounds from nature's 'chiral pool'. This is a collection of compounds, the members of which are easily isolated from natural sources as a single enantiomer, such as amino acids, glucose and lactic acid. A drawback of this method is that mostly only one of the two enantiomers of the molecule is accessible this way since only one of the enantiomers is present in this chiral pool.

- The second is the separation of a racemic mixture, which is called resolution. This can be achieved in two ways; via kinetic resolution involving a chemical or biochemical chiral reagent or catalyst, in which one of the enantiomers will react away and the other remains in pure form. The other way is via selective crystallization using a chiral resolving agent. The problem with these methods is the fact that the maximum yield is 50%, since only halve of the mixture is of the correct chirality. This problem can be overcome by performing a so called dynamic kinetic resolution. In a dynamic kinetic resolution the non reactive enantiomer is racemized during the resolution making it possible for the reaction to go to full completion.

- The third method is asymmetric synthesis in which a prochiral compound is transformed into an, enantiomerically enriched, chiral one. This can be done in three different ways.
    - The first is based on the use of a chiral auxiliary. This is a chiral group that can be attached to a molecule thus creating two or more asymmetric centers. When there is more than one stereogenic center in a molecule, molecules are no longer enantiomers but they are called diastereomers. Diastereomers, in contrast to enantiomers, can be separated based on differences in physical properties. When the desired diastereomer is in hand, the auxiliary can be cleaved off again and the enantiomerically pure compound is obtained. A drawback of this method is the introduction of extra steps in the synthetic route compromising the overall yield.

    - The second way of making an enantiomerically pure compound via asymmetric synthesis is by using a diastereoselective synthesis. With this method a previously introduced stereogenic center is used to selectively create a second stereogenic center by for instance taking advantage of the difference in steric hindrance of the two diastereomeric transition states involved.

    - The last method for making an enantiomerically pure compound through synthesis is via asymmetric catalysis, in which a prochiral compound is transformed into an enantiomerically pure, or at least enriched, chiral compound with the help of a chiral catalyst. This catalyst can be a homogeneous, a heterogeneous, an organic or a biochemical one. In general the chiral catalyst has one or more interactions with the pro-chiral substrate. As a result of these interactions an environment is created in which one of the two chiral products is preferentially accessible. The strong point of this method is the fact that, usually, only a small amount of the catalyst is needed to make the reaction work in a selective manner. A drawback of this method is the fact that most catalysts are highly reaction specific and

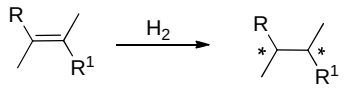
for every reaction type a screening of catalysts and conditions is needed to find the optimal performing combinations.

Despite its drawbacks asymmetric catalysis is becoming more and more important in the synthesis of chiral products in both academia as well as in industry.[9-12]

1.3 Homogeneous Asymmetric Hydrogenation

One of the most elegant and most studied reactions in asymmetric catalysis is asymmetric hydrogenation. Until the 1960s, attempts to get some enantioselectivity in a hydrogenation reaction relied on the use of chiral auxiliaries attached to the substrate or by using a heterogeneous catalyst attached to a chiral surface.[13] From the 1960s onwards, however, numerous methods for performing asymmetric hydrogenations on a wide range of substrates have been developed.[14] In the following a short historical overview is presented on the developments made in the asymmetric hydrogenation of C=C, C=N and C=O double bonds.

1.3.1 Asymmetric C=C hydrogenations



When in the 1960s the use of phosphorus ligands in transition metal catalyzed reactions was discovered and the Wilkinson-catalyst (Figure 5) was developed[15;16] it did not take long before the first chiral phosphorus ligands were employed in a homogeneous hydrogenation reaction. In 1968 it were the groups of Horner[17] and Knowles and Sabacky[18] who reported the first asymmetric hydrogenations using a P-chiral monodentate ligand.

The Knowles group was able to reach optical purities up to an excellent 90% in the rhodium catalyzed asymmetric hydrogenation of several α-acyl amino acrylic acids using CAMP (see Figure 5). The complex [Rh(COD)((R_p)-CAMP)$_2$]BF_4 was used in the asymmetric synthesis of the anti-Parkinson drug L-DOPA and was the first candidate for use in an industrial process. However, with the discovery of DIPAMP, by the group of Knowles, which was able to induce an ee up to 95%,[19] the CAMP ligand was replaced and the industrial process for making L-DOPA relied on the use of DIPAMP ever since.[20] In 1975 Kagan and co-workers[21;22] introduced chiral bisphosphorus ligands which no longer were P-chiral but had a stereogenic center in the backbone connecting the two phosphine groups.[23-25]

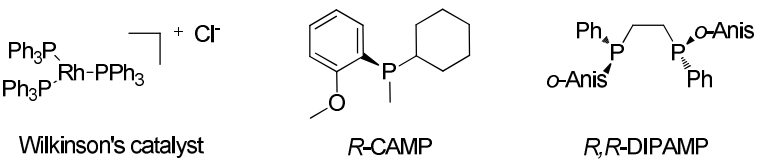


Figure 5: [Rh(I)(PPh_3)$_3$]Cl; Wilkinson's catalyst, the P-chiral phosphine ligand CAMP as used by Knowles and Sabacky and the DIPAMP ligand as developed by Horner.

Since those first reports, many groups have been involved in the search for new, faster and more selective catalysts for the hydrogenation of C=C double bonds and a lot of progress has been made since.[26]

Many different phosphorus ligands have been developed and used in highly enantioselective asymmetric C=C bond hydrogenation.[27] Until 2000, all successfully employed ligands were bidentates, but in that year three groups independently (re)discovered that also a monodentate ligand can lead to good conversions and excellent ee's (*vide infra*) (re)opening a whole new field in this type of research.

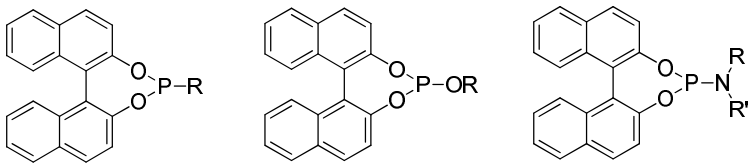
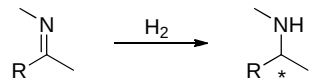


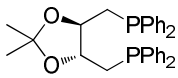
Figure 6: Monodentate ligands as used in asymmetric hydrogenations by the groups of Pringle[28], Reetz[29] and ours.[30]

These groups were the group of Pringle and Claver who used monodentate phosphonites,[28] the group of Reetz who used phosphites[29] and our own group introducing phosphoramidites.[30] All three groups reported the hydrogenation of dehydroamino acids in high yields and excellent ee's, using a rhodium catalyst which contained two of their monodentate ligands per metal center.

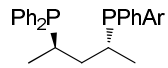
1.3.2 Asymmetric C=N Hydrogenation



Besides C=C double bonds, also other types of double bonds can be hydrogenated in an asymmetric fashion. In 1975 the first homogeneous Ru and Rh catalysts were discovered for the asymmetric hydrogenation of C=N double bonds. Botteghi *et al.*[31] and Kagan *et al.*[32] both used diop (see Figure 7) as chiral ligand in the hydrogenation of oximes and imines reaching up to 15 and 22% ee, respectively.



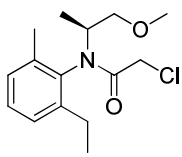
diop



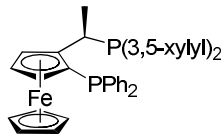
bdpp: **Ar = Ph**
$bdpp_{sulf}$: Ar = $C_6H_4SO_3Na$

Figure 7: The first ligands successfully used in the homogeneous asymmetric C=N hydrogenation.

The first hydrogenation reaching acceptable ee's (up to 72%) was performed by Vastag *et al.*[33] in 1984, using a bdpp-Rh complex in the hydrogenation of C=N-Alkyl type substrates. In 1989 a Rh catalyst was developed with which, in 1992, the first very high ee (92%) in this type of hydrogenation was obtained using mono-sulfonated bdpp ($bdpp_{sulf}$).[34-36] In 1999 Blaser and co-workers published the use of a ferrocenyl based bidentate ligand (**1.4**) in the iridium catalyzed asymmetric hydrogenation towards the product (*S*)-Metolachlor, which is used as a herbicide.[37] This process is currently one of the largest industrial enantiomeric catalytic processes exceeding 10^4 tons per year.



(*S*)-Metolachlor

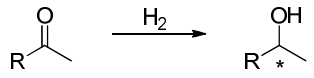


1.4

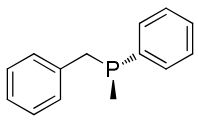
Figure 8: (*S*)-Metolachlor and the ferrocenyl type ligand (**1.4**) used in the iridium catalyzed asymmetric hydrogenation during its production.

In 2008 Mršić *et al.* showed for the first time the use of monodentate ligands in the asymmetric hydrogenation of C=N double bonds applying phosphoramidite ligands. They were able to reach full conversion and up to 89% ee in the asymmetric hydrogenation of quinolines.[38] Later our group reported ee's of up to 99% in the iridium catalyzed asymmetric hydrogenation of N-aryl imines using monodentate phosphoramidite ligands.[39]

1.3.3 Asymmetric C=O hydrogenation



The first asymmetric C=O hydrogenation was reported in 1972 by Bonvicini *et al.* who reported the Rh-catalyzed hydrogenation of acetophenone and 2-butanone. They obtained the resulting alcohols in 8.6% and 1.9% optical yield, respectively, using (*R*)-benzylmethylphenyl phosphine (see Figure 9) as their chiral ligand.[40] Since this first report a lot of work has been done and is still going on in this field.



(R)-benzylmethylphenyl phosphine

Figure 9: The chiral ligand as used by Bonvicini *et al.* in the first asymmetric hydrogenation of a ketone.[40]

The first rhodium catalyzed asymmetric hydrogenation which resulted in good ee's was reported in 1980 by Törös *et al.* Using diop as a ligand they were able to hydrogenate a number of acetophenones with an ee of up to 84%.[41]
Two key developments in this field came from the group of Noyori. In 1987 they reported the use of binap in the asymmetric hydrogenation of functionalized ketones using ruthenium complex **1.5**. They were able to hydrogenate a few β-ketoesters with excellent stereoselectivity.[42] This results was further extended a year later when they published excellent ee's in the asymmetric hydrogenation of a large number of functionalized ketones.[43]

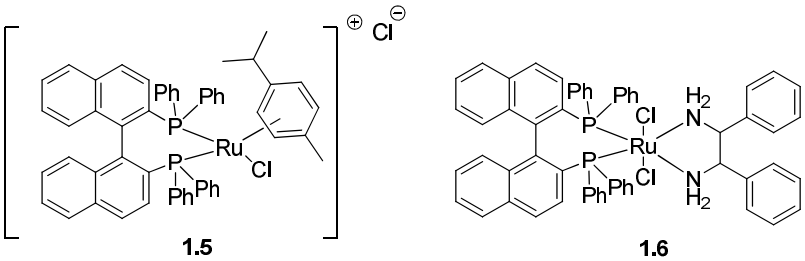


Figure 10: The two binap-based Noyori catalysts for functionalized (**1.5**) and non-functionalized ketones (**1.6**).

The second breakthrough came 8 years later, in 1995, when the same group reported a system which was able to hydrogenate, the till then very difficult substrate class of, unfunctionalized acetophenones. To the Ru-complex they reported in 1987 they added a chiral 1,2-diamine creating the highly active and selective catalyst **1.6**, after activation by a base.[44] A more complete overview of these important developments, including the mechanisms involved using these two types of complexes will be given in chapters 2 and 4 of this thesis.

Despite the fact that the initial reports on asymmetric ketone hydrogenation involved the use of a rhodium based catalyst, nowadays ruthenium is usually the metal of choice in the asymmetric hydrogenation of ketones. Besides these two metals, however, also other transition metals are able to function as catalysts in this type of transformation. In chapter 3 an overview will be given on the use of iridium in the asymmetric ketone hydrogenation. Here a small inventory is made on the lesser common metals used in these hydrogenations.

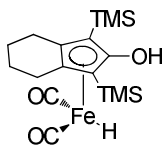
1.3.3.1 Cobalt

In 1985 it were Massonneau *et al.*[45] who reported the first asymmetric cobalt catalyzed hydrogenation of ketones. Using several di-cobalt complexes of the form $Co_2(CO)_6(PR_3)_2$, they were able to reduce acetophenone with a very low optical yield of 1.6% and 2-methyl cyclohexanone with an optical yield of up to 5%. Since then some cobalt complexes have been used with success in the transfer hydrogenation or hydrosilylation of ketones (*vide infra*) but until now none in the direct asymmetric hydrogenation of ketones.

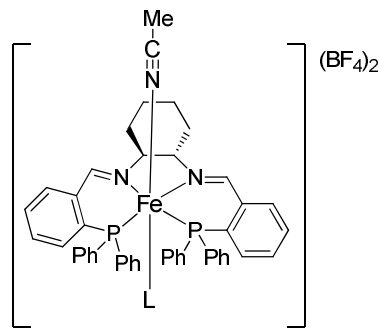
1.3.3.2 Iron

Iron, which takes its place in the periodic table just above ruthenium, is of great interest as a metal in catalysts because of its natural abundance and low price.[46] It took until 2007 before Casey and Guan reported the first efficient iron catalyst for the hydrogenation of ketones.[47] They were able to hydrogenate selectively several acetophenones as well as alkyl ketones and 1,2-diketone in good to excellent conversions using catalyst **1.7**, however since no chiral ligand was used also no ee's were found.

The first asymmetric, iron based, hydrogenation catalyst was reported a year later by the group of Morris.[48] Using a chiral P-N-N-P ligand (see **1.8** in Figure 11) they were able to hydrogenate acetophenone in 40% conversion and up to 27% ee. The enantioselectivity is not yet very impressive but a good starting point for further optimization.



1.7



L = CH_3CN, CO, tBuNC

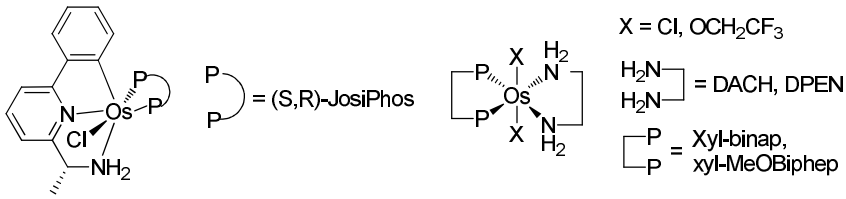
1.8

Figure 11: The first efficient iron catalyst (**1.7**) as published by Casey *et al.*[47] and the first iron catalyst (**1.8**) used for asymmetric hydrogenation of ketones as published by Sui-Seng *et al.*[48]

1.3.3.3 Osmium

Like iron also in the same group as ruthenium but then straight under it is the element osmium. Being in the same group as the best performing metal for carbonyl hydrogenations makes osmium a prime candidate for being used in this type of reactions. It has been stated it would be an even better candidate compared to iron and ruthenium, because it would bind stronger to the substrate

making the reaction proceed even faster compared to the other two metals.[49] A major drawback of using osmium however is the fact that all compounds or complexes containing it display very high levels of toxicity. Besides being very toxic it is also very expensive which prevents it from being a serious alternative for the much less toxic and cheaper ruthenium. Nevertheless it has been used as the metal in several ketone hydrogenation catalysts.
In 2008 Baratta *et al.*[50] reported the use of a osmium CNN pincer complex (**1.9**) which in combination with Josiphos (See Figure 12) was able to hydrogenate several acetophenones up to 98% ee with a remarkably low catalyst loading (0.005 mol% Os).



1.9 **1.10**

Figure 12: The osmium pincer Josiphos complex (**1.9**) and the $[OsX_2(diphosphine)(diamine)]$ complex (**1.10**) as used by Baratta *et al*[50;51] in the Os-catalyzed asymmetric hydrogenation of ketones.

The same group improved on their results two years later when they introduced a $[OsX_2(diphosphine)(diamine)]$ (X = Cl or OCH_2CF_3) (**1.10**) instead of the pincer complex **1.9**.[51] By using this complex, which very closely resembles the original ruthenium complex, they were able to hydrogenate a range of acetophenones with ee's varying between 87 and 99%.

1.3.3.4 Palladium

Despite its great performances as a metal in other transition metal catalyzed asymmetric transformations, such as Heck reactions, Suzuki reactions, allylic substitutions and olefinic hydrogenations, palladium has not often been used successfully in ketone hydrogenations.[52] It took until 2005 before the first report was made of a palladium catalyzed asymmetric hydrogenation of a ketone. It were Wang *et al.*[53] who published the use of a Pd/bisphosphine complex in

the hydrogenation of a few functionalized ketones. When using methyl-DuPhos as a ligand in 2,2,2-trifluorethanol they were able to reach up to 92% ee in the hydrogenation of α-phthalimide ketones (**1.11** in Figure 13). They recently improved their initial results by using C_{10}-TunePhos and are now able to obtain ee's up to 99%.[54]

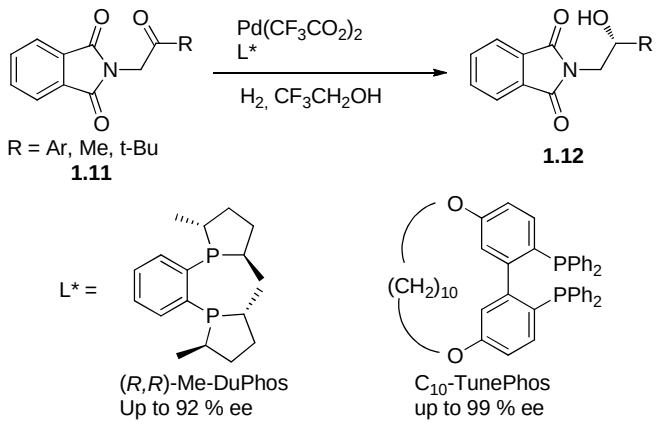


Figure 13: The palladium catalyzed asymmetric hydrogenation of ketones as reported by Wang *et al.*[53;54]

The second report using a palladium catalyst in a ketone hydrogenation was made by the group of Beletskaya in 2009.[55] They discussed the asymmetric hydrogenation of α-keto phosphonates **1.13** using a similar system as reported later by Wang *et al.*[54] They were able to obtain full conversion but only moderate ee's up to 55% when using MeO-BIPHEP as a chiral ligand.

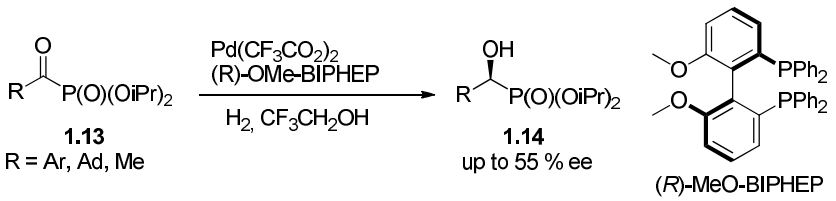


Figure 14: The palladium catalyzed asymmetric hydrogenation as reported by the group of Beletskaya.[55]

1.3.3.5 Copper

In 2007 the group of Shimizu published the first enantioselective method in which copper was used in the catalytic complex. When the chiral BDPP ligand was added to the precursor [$Cu(NO_3)(P(3,5\text{-xylyl})_3)_2$], in the presence of NaO*t*Bu and 3-6 equivalents of $P(3,5\text{-xylyl})_3$, they were able to reach full conversions and up to 91% ee in the hydrogenation of several acetophenones.[56]

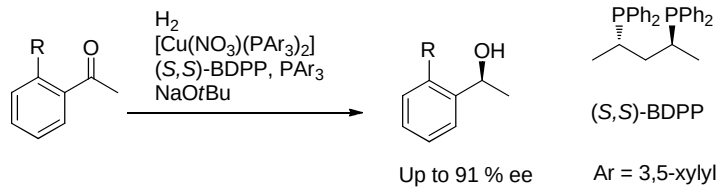


Figure 15: The copper catalyzed hydrogenation of acetophenones as published by Shimizu *et al.*[56]

1.4 Other ways of reducing ketones asymmetrically

Besides the asymmetric hydrogenation of ketones using dihydrogen, over the years also other methods have been successfully developed for transforming a ketone into an alcohol in an asymmetric fashion. Here an overview will be given on the asymmetric transfer hydrogenation, borohydride reduction, hydrosilylation and enzymatic reduction.

1.4.1 Transfer hydrogenations

One of the most important alternatives for direct hydrogenation using hydrogen gas is transfer hydrogenation.[57-59] In transfer hydrogenations two hydrogen atoms, from an external hydrogen donor, are transferred onto the substrate. This process is catalyzed by a (transition) metal catalyst. The two main hydrogen sources used in transfer hydrogenation (Figure 16) reaction are secondary alcohols, such as *iso*-propanol (IPA), and formic acid and its salts. Often a formic acid / triethylamine mixture (TEAF) is used. IPA has the benefit of being

environmentally friendly, easy to handle and cheap. However, there are a few drawbacks to this method. Since the reaction is reversible, the outcome of the reaction is determined by the oxidation potential of the ketone alcohol couple. A way to drive the reaction to full conversion is performing it under slightly reduced pressure in order to evaporate the acetone while it is being formed.

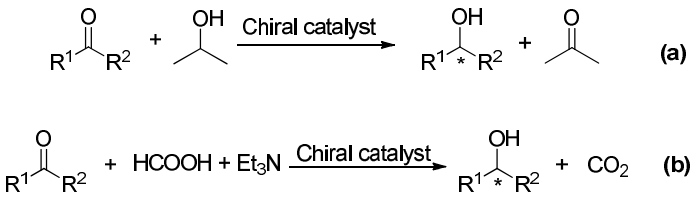
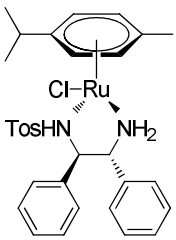


Figure 16: a) IPA; b) TEAF; the two most popular hydrogen donors in transfer hydrogenation reactions.

The azeotropic mixture of 5 : 2 formic acid and Et_3N is most frequently used when TEAF is the reducing agent in a transfer hydrogenation. It is easily formed by distilling a HCOOH / Et_3N mixture just prior to use. Because during the transfer hydrogenation reaction CO_2 is formed the equilibrium is shifted to the side of the desired product. A drawback of using TEAF is that some of the catalysts are not able to cope with the acidic conditions and decompose rapidly or lose their catalytic activity completely. Secondly it has been shown by the group of Xiao that the optimum pH for transfer hydrogenations lies above the obtained pH if the azeotropic TEAF mixture is used.[60] The low pH of the mixture also makes that the catalysts which have to be activated by base are usually not applicable when using TEAF.

Transfer hydrogenations proceed in general with a transition metal catalyst present in the solution. When the reaction is aluminium catalyzed and IPA is used as the hydrogen donor the reaction is also known as the Meerwein-Ponndorf-Verley reduction whereas the backward reaction, the oxidation of the alcohol, is known as the Oppenauer oxidation.
To date the best and most general catalyst for the asymmetric transfer hydrogenation of ketones is the one developed by the group of Noyori.[61] The catalytic complex consists of a half-sandwich Ru-arene to which the mono-

tosylated DPEN is complexed, as can be seen in structure **1.15**. Most catalysts for transfer hydrogenation are based on Rh or Ru but there are some Ir,[62] Sm[63] and Fe[46] catalysts known that show good performance. However, their performances cannot compare to those obtained with Rh or Ru based catalysts.



1.15

Figure 17: The best performing transfer hydrogenation catalyst **1.15** to date as developed by the group of Noyori.[61]

The benchmark substrates for asymmetric transfer hydrogenation are the acetophenone type ketones. A number of ligands have been reported that perform very well to excellent in the transfer hydrogenation of acetophenones.[57;64] For the asymmetric transfer hydrogenation, mainly amino alcohol type ligands are used, but also monotosylated or monomethylated diamines perform very well is this reaction. Phosphine ligands generally perform less well as ligands in the asymmetric transfer hydrogenation, but there are a few that still give good to excellent selectivities.[65]

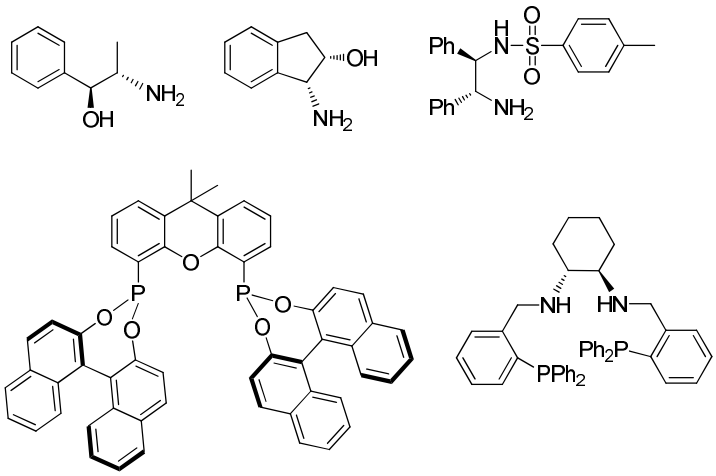


Figure 18: Some representative, well performing, ligands in the asymmetric transfer hydrogenation.

Besides the benchmark substrate acetophenone, other substrate classes have also been tested; some of them are depicted in Figure 19. Most substitutions in the phenyl ring or at the α-position of acetophenones can be tolerated in the transfer hydrogenations leading to excellent ee's.[66;67]
The only really difficult substrate, the t-butyl phenyl ketone, still is reduced with a good selectivity resulting in 85% ee. In the case of the methyl alkyl ketones, which are commonly reduced with low ee's (36-63%), it is actually the t-butyl substrate which gives the best result reaching up to 99% ee.

What can also be concluded from the results shown in Figure 19 is the fact that β-ketoester are reduced less selective and they need a phenyl group in order to give good to excellent ee's.[68]
An additional advantage of transfer hydrogenation are the good results obtained when water is used as a solvent. The groups of Xiao,[64] Guo,[69] Wang[70] and others[71] dedicated their research successfully to developing this greener way of reducing ketones. Various, catalysts, mainly based on Rh, Ir and Ru, have been developed over the years which give excellent results in the asymmetric transfer hydrogenation of acetophenones.[72]

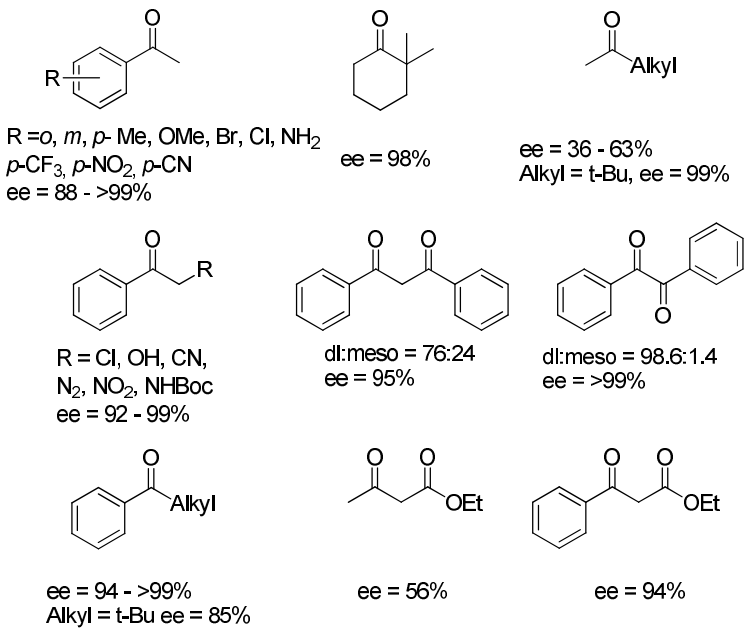


Figure 19: Various substrates which were tested in asymmetric transfer hydrogenation.

1.4.2 Borohydride reduction

The classical way of reducing ketones is via a hydride reduction using $NaBH_4$ or $LiAlH_4$ in which the hydrides attack the carbon of the carbonyl function. The boron or aluminiumalkoxide complex subsequently hydrolyses upon aqueous or acidic work up creating the alcohol product. However, simple as this transformation is, it produces a lot of environmentally unfriendly waste, since the metalhydrides have to be used stoichiometrically. Moreover, the metal hydride salts are not always easy to handle and can produce very reactive reaction mixtures. Despite these drawbacks, a number of groups have successfully put effort in developing asymmetric boranes to use in an asymmetric version of the borohydride reductions.[73] Since in these cases still a stoichiometric amount of the chiral hydride reagent was needed other groups tried to develop a chiral borane which could be used in a catalytic fashion, thus circumventing the need for stoichiometric amounts of chiral reagents.[74]

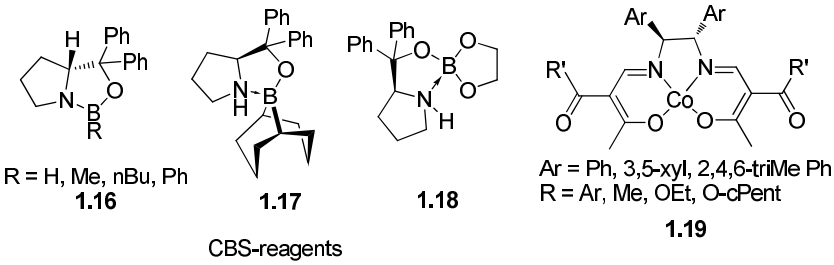


Figure 20: A few CBS-type boranes (**1.16**, **1.17**, **1.18**) that perform excellent in the boron based catalytic asymmetric reduction of ketones and an example of a cobalt complex (**1.19**) used in the borohydride reduction of ketones.

The first to succeed in developing such a system were Corey, Bakshi and Shibata, after whom the reagent was named (CBS-reagent, (**1.16**) Figure 20).[75;76]

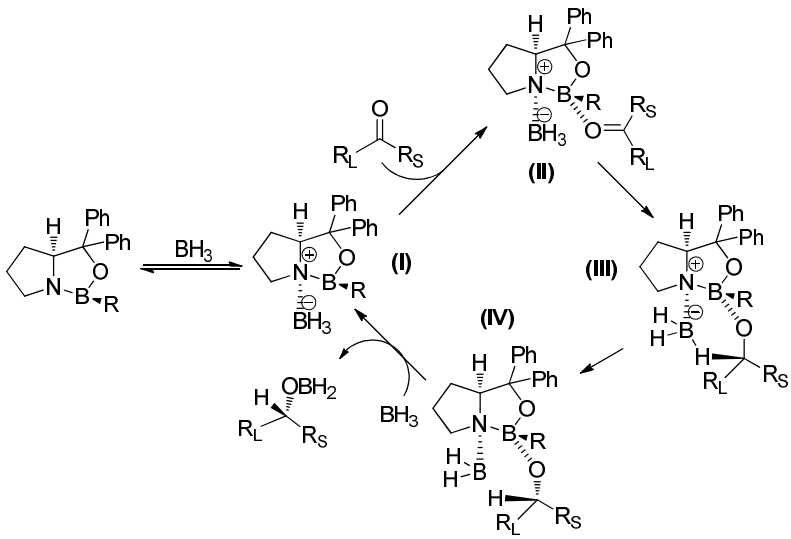


Figure 21: Mechanism for the boron hydride based catalytic asymmetric reduction of ketones using the CBS-reagent

The mechanism[77] of the CBS reduction, which is depicted in Figure 21 is well understood and starts with a molecule of BH_3 coordinating to the Lewis-basic nitrogen of the CBS-reagent (**I**), after which the ketone can coordinate to the boron atom of the CBS catalyst (**II**). A hydride subsequently transfers from the

BH_3-group to the ketone (**III**-**IV**) after which the product is released from the reagent as its alkoxyborane and another BH_3-molecule complexes again to the CBS-reagent (**I**). Upon aqueous or acidic work up the alcohol is formed.
Besides the use of boranes as catalysts, Yamada *et al.* developed cobalt complexes which can act as a catalyst in the borohydride reduction of ketones.[78] Some of these complexes are made using a tetradentate β-ketoiminato ligand (**1.19**, Figure 20) synthesized from a 1,3-diketone or a β-ketoester together with a chiral 1,2-diamine. When a cobalt complex is used as catalyst, regular $NaBH_4$ can be used as a reductant leading to ee's up to 97% for acetophenone type substrates.
Another interesting development in this field came recently from the group of Falck.[79] They combined the enantioselective borane reductions and enantioselective organocatalysis creating a method in which ketones can be reduced asymmetrically using a catecholborane in combination with a thiourea (**1.20**). With this method ketones could be reduced with selectivities up to 79-99% ee.

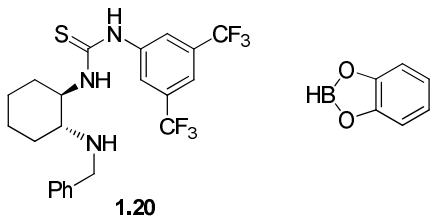


Figure 22: The thiourea, **1.20**, used by the group of Falck in the organocatalyzed borane reduction of acetophenones.[79]

1.4.3 Hydrosilylation

A second, indirect, way of reducing ketones in an asymmetric fashion is by hydrosilylation. In this process a ketone is reacted first with a silylhydride to obtain a silylether. This silylether is hydrolyzed upon acidic workup to provide the enantioenriched alcohol. The major advantage of using hydrosilylation for the reduction of ketones is the fact that some silanes used for this transformation are relatively cheap and easy to handle. From an atom economic point of view it

is, however, not a very good reaction. A lot of waste is produced just like in the borohydride reductions.

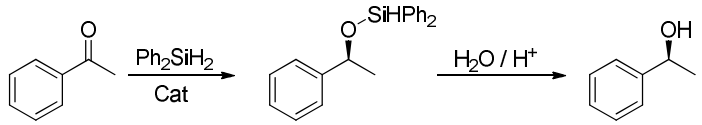


Figure 23: General scheme of asymmetric hydrosilylation.

The first hydrosilylation of a ketone was reported in 1972 by Ojima *et al.*[80] Using the classical Wilkinson catalyst they were able to hydrosilylate cyclohexanone and acetophenone to full conversion. Shortly after that first report, also the first asymmetric hydrosilylation was reported by Yamamoto *et al.*[81] They used a platinum catalyst containing the P-chiral phosphine benzylmethylphenyl phosphine obtaining up to 18.6% optical yield in the reduction of *t*-butylphenyl ketone. Since these first reports many Ir, Rh and Ru based catalysts have been developed that give high stereoselectivity.[62;82] But also the, in the classical asymmetric hydrogenation less common, metals like Cu,[83;84] Co[85] and Fe[85;86] have been successfully used in the asymmetric hydrosilylation of ketones.
In a recent paper by Inagaki *et al.*[85] the use of bis(oxazolinylphenyl)amine (bopa, Figure 24) ligands in the Co and Fe catalyzed hydrosilylation of acetophenones is described. They were able to reach full conversions and excellent ee's of up to 98 and 88% using cobalt and iron, respectively.

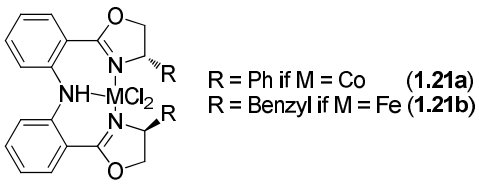


Figure 24: The Co- and Fe-Bopa catalysts (**1.21**) as used by Inagaki *et al.* in the hydrosilylation of acetophenones.[85]

Until the beginning of 2010, only one paper had been published in which the use of monodentate ligands in the hydrosilylation of ketones was reported. In 2001 it

were Suárez *et al.*[87] which reported the use of monodentate phosphite ligands obtaining up to 58% ee and 94% conversion in the rhodium-catalyzed hydrosilylation of acetophenone. It took till 2010 before Junge *et al.* improved this result using the from their group well known monodentate phosphepine ligands.[88] They obtained good yields and up to 96% ee in the asymmetric hydrosilylation of a broad range of ketones.[84]

1.4.4 Biocatalytic reductions

Besides chemical ways of reducing ketones also a biochemical pathway is possible. The enzymes that are capable of reducing ketones into alcohols are usually called alcohol dehydrogenases (ADH's) but are also known under the names ketoreductases and carbonyl reductases. Interesting enzymes have been identified in a large number of bacteria, yeasts and fungi. Ways of doing biochemical transformations can be divided into two main strategies:

1) Using whole cells
2) Using isolated enzymes

For both methods applies that the ketone is reduced by an enzyme with the consumption of a co-factor molecule (usually NADH or NADPH). When using whole cells, this co-factor is regenerated by other enzymes present in the cells but when isolated enzymes are used this co-factor has to be added stoichiometrically, which is very expensive, or a co-factor recycling system has to be added to the reaction in order to reduce the $NAD(P)^+$ back to NAD(P)H.

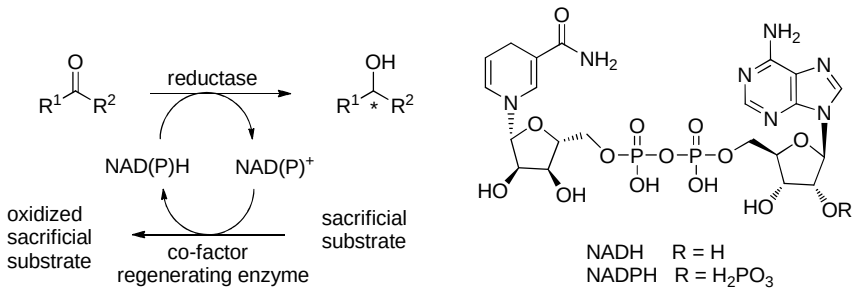


Figure 25: General scheme for biocatalytic reduction of ketones.

Several recycling systems are in use nowadays, like formate dehydrogenase, which transforms a molecule of formate into CO_2 and OH^- forming back one molecule of NAD(P)H from $NAD(P)^+$. In a similar fashion phosphite dehydrogenase can be used regenerating NAD(P)H while transforming a phosphite anion into a phosphate. The preferred recycling system however, uses the enzyme glucose dehydrogenase (GDH) to convert $NAD(P)^+$ back to NAD(P)H using one molecule of glucose which is converted into gluconic acid. The reason this system is preferred is the fact it is highly stable, active and it accepts both cofactors. Drawbacks of this system are firstly that in order to control the pH of the reaction medium the formed gluconic acid has to be neutralized by addition of a base during the reaction, secondly GDH is not very cheap. A cheaper method of reducing $NAD(P)^+$ back to NAD(P)H is by using an alcohol dehydrogenase (ADH) to oxidize ethanol or IPA to acetaldehyde or acetone, respectively. Drawback of this method is the low oxidation potential which makes it only available for the reduction of activated ketones.[89]

Over the years, several ADH's have been identified and used in carbonyl reductions reactions resulting in good conversions and excellent ee's for a variety of ketones[90;91] like acetophenones,[92-94] alkyl ketones,[93] benzophenones,[95] and α-ketoesters.[96;97] Despite the good progress that has been made, the major drawback of biocatalytic reactions still remains. Most of the enzymes used in carbonyl reduction have a fairly narrow substrate scope that gives good to excellent ee's. Even a small difference in substitution pattern (e.g. going from an H atom to an F atom) can lead to a significant drop in enzyme activity and ee. Also the fact that usually only one of the two enantiomers of the

product is accessible when using a particular enzyme can pose a problem and is something that can easily be overcome in chemical asymmetric catalysis by simply changing the enantiomer of the ligand used in the catalyst.

1.5 Phosphoramidites

As described above, phosphoramidite ligands were in 2000 one of three classes of monodentate ligands which induced excellent enantioselectivities in the rhodium catalyzed asymmetric olefin hydrogenation.[30] Since then, their easy synthesis and high structural variability have made them interesting ligands for a large number of asymmetric transformations which were recently extensively reviewed.[98]

1.5.1 Synthesis of phosphoramidite ligands

One of the major advantages of the use of monodentate phosphoramidites over the commonly used bidentate phosphorus ligands lies in their synthesis. Where the synthesis of the bidentate ligands requires multiple steps, including some very tedious ones,[99] the phosphoramidites can be readily synthesized in two or three steps. There are different routes towards the various phosphoramidites but the most common one, as depicted in Figure 25, starts off by a reaction of inexpensive, enantiopure, bis-β-naphthol in refluxing PCl_3 overnight to form the phosphochloridite. After removal of the excess PCl_3, the resulting chloridite is redissolved in toluene and by adding the appropriate amine in combination with Et_3N, as an HCl scavenger, the phosphoramidite ligand is formed in moderate to high yields. This simple two step synthesis route also proved to be very well suited to be automated thus making it very easy to screen a large number of ligands in a short period of time.[100-102]

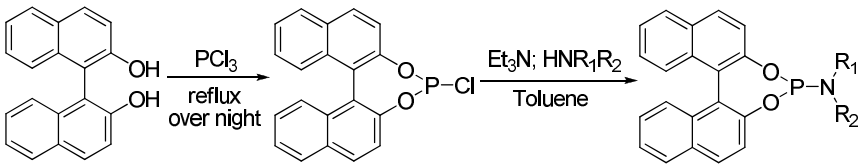


Figure 25: General scheme of the most common way of synthesizing phosphoramidite ligands. Refluxing the diol overnight in PCl_3 to form the phosphoryl chloride to which in the presence of Et_3N the desired amine can be coupled.

It is possible also, to start the synthesis of a phosphoramidite by transforming an amine into its dichloroaminophosphine and then adding the diol.[103]
A third alternative is to perform a transamination by taking a phosphoramidite, for instance MonoPhos, treat it with tetrazole and another amine. This results in an almost quantitative exchange of the amine groups.[104]

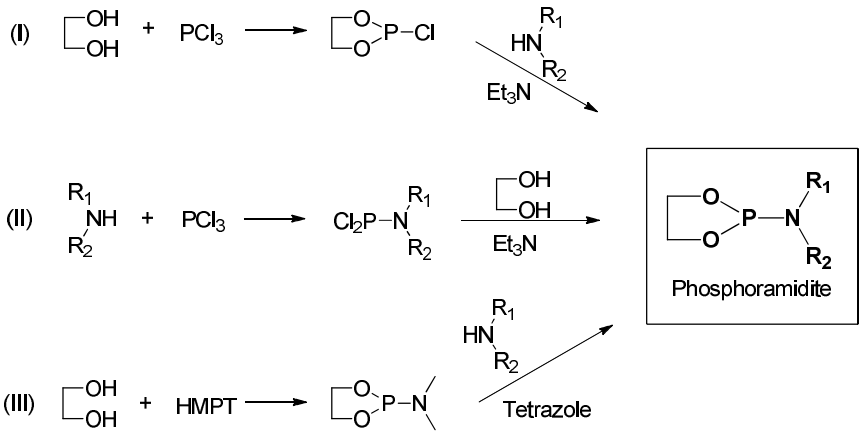


Figure 26: Three ways of synthesizing a phosphoramidite ligand. (I) Formation of the phosphoryl chloride from the diol followed by reaction with the desired amine. (II) Formation of the "PCl_2N" compound which is then reacted with the appropriate diol. (III) Synthesis of MonoPhos and subsequent transamination in tetrazole to get the desired ligand.

Of course, phosphoramidite ligands are not restricted to have a bis-naphthol backbone. Several other diol backbones (see Figure 27) have been used successfully in phosphoramidite synthesis. Among them substituted bis-naphthols (**1.22**), biphenols (**1.23**), cathechol (**1.24**) and others.[30;105-108] The ligands have been used with great success in several asymmetric reactions.

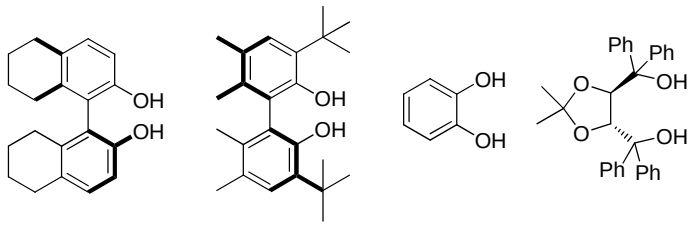


Figure 27: Examples of (a)chiral backbones, 8H-bis-β-naphthol (**1.22**), a biphenyl (**1.23**), catechol (**1.24**) and taddol (**1.25**), which have been used successfully in the synthesis of phosphoramidites.

1.5.2 Use of phosphoramidites in asymmetric hydrogenations

Since the discovery of the phosphoramidites as excellent ligands in the asymmetric hydrogenation of dehydroamino acids[30] a range of different substrates has been successfully hydrogenated using a catalyst based on phosphoramidites.[38;39;105;107-116] A few examples of successful rhodium catalyzed asymmetric hydrogenations, in which a phosphoramidite was used as chiral ligand, are depicted in Figures 29-34

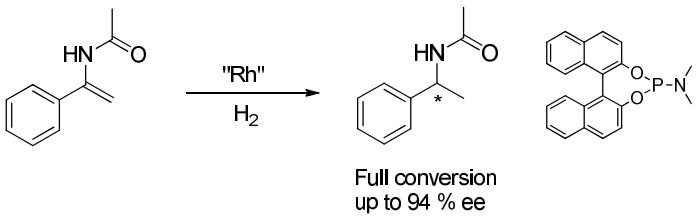


Figure 28: Enamide hydrogenation using MonoPhos as chiral ligand according to Van den Berg *et al.*.[115]

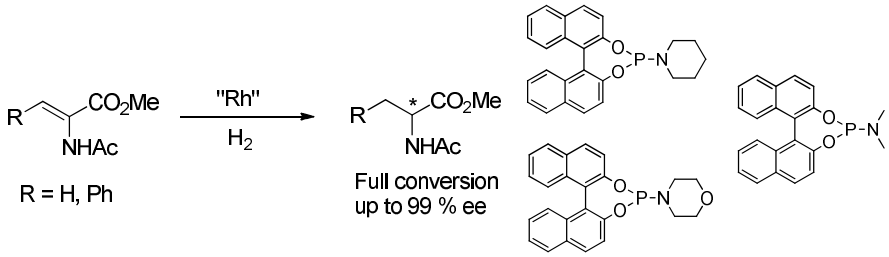


Figure 29: α-dehydroamino acid hydrogenation using MonoPhos, PipPhos or MorfPhos as chiral ligand by Van den Berg *et al.* and Bernsmann *et al.*.[30;105]

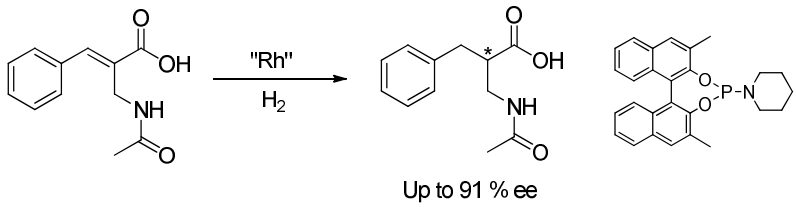


Figure 30: β^2-dehydroamino acid hydrogenation using 3-3'-dimethyl PipPhos according to Hoen *et al.*.[110]

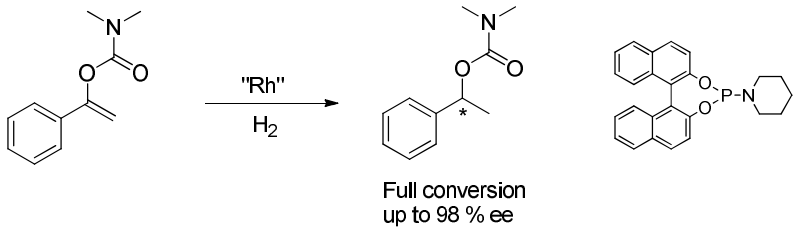


Figure 31: carbamate hydrogenation using PipPhos according to Panella *et al.*.[112]

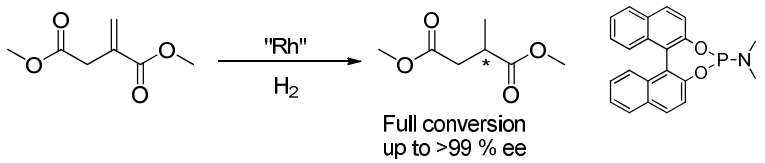


Figure 32: Itaconic acid methyl ester hydrogenation using MonoPhos according to Van den Berg *et al.*.[116]

A procedure was reported in which a phosphoramidite ligand was made water-soluble by attaching polyethyleneglycol units onto the backbone of the ligand. In this case good results (see Figure 33) were obtained in the asymmetric hydrogenation of dehydroalanine.[109]

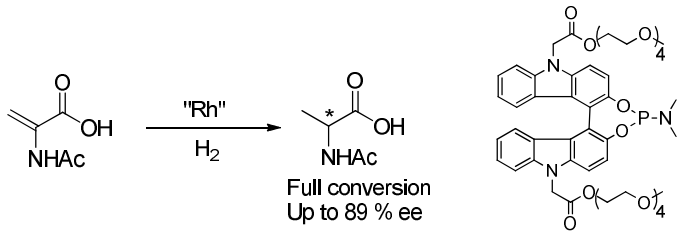


Figure 33: Asymmetric hydrogenation using a water soluble phosphoramidite ligand by Hoen *et al.*[109]

Phosphoramidites have not only been used in the rhodium catalyzed hydrogenation of olefinic double bonds. As already stated above, also in the iridium catalyzed asymmetric hydrogenation of the C=N double bonds of quino(xa)lines[38;111] and *N*-aryl imines[39] they perform excellent. When PipPhos was used as a ligand in combination with its hydrochloric salt, full conversions were reached in all three types of hydrogenations and ee's up to 99% could be obtained.

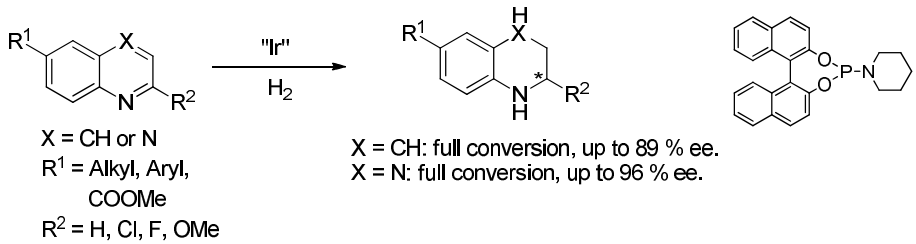


Figure 34: Quino(xa)line hydrogenation by Mršić *et al.*[38;111]

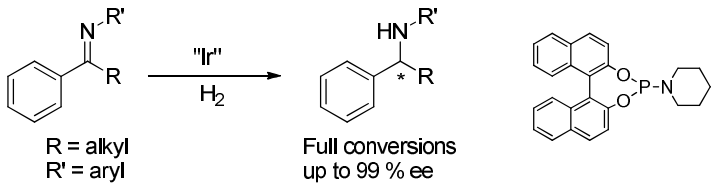


Figure 35: Imine hydrogenation by Mršić *et al.*[39]

When the iridium catalyzed hydrogenation of a dehydroamino acid was performed using a phosphoramidite based on a biphenol backbone, an interesting observation was made. It was found that when a biphenyl based Monophos type

phosphoramidite was used with t-butyl side groups on the 3 and 3' position only one monodentate ligand was needed per iridium for excellent stereoselectivity (Figure 36).[108] This was the first report in which only one monodentate ligand per metal still gives excellent result in asymmetric hydrogenation.

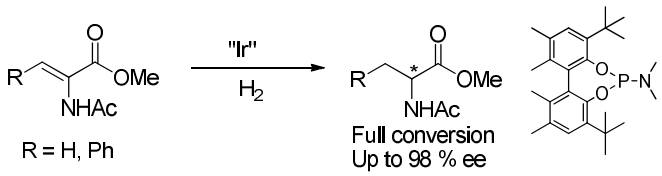


Figure 36: Iridium catalyzed hydrogenation of dehydroamino acids using only one monodentate ligand.[108]

1.5.3 Mixed ligands

Looking for a way to further improve the results in the asymmetric hydrogenation using monodentate ligands, some groups decided to see what would be the result if two different monodentate ligands are added to the catalyst precursor. In this case several chiral catalytic species can be formed; the two homo complexes, each containing two of the same ligands and a hetero complex in which both ligands are present once.[117-122]

Figure 37: The different metal ligand complexes that are formed when using a mixed ligand approach.

Depending on the most active and selective combination being formed by a self-assembly process in the reaction mixture, the reaction rate and selectivity are changed. This can lead to a great improvement in ee's and reaction rate, even when an achiral phosphine is used as second ligand. Hoen *et al.* were able to improve the conversions and ee's in the asymmetric hydrogenation of α,β-disubstituted unsaturated acids by adding simple achiral triaryl phosphines to the reaction mixture. In this way they were able to increase the rate up to tenfold and

induce a rise in ee from 2% to 85% by simply adding triphenylphosphine to the mixture. After a screening of different phosphines, it was found that when a bulky triarylphosphine was added, the ee went even further up to an excellent 99%. The same positive influence of an additional achiral triarylphosphine was found in the Ir-phosphoramidite catalyzed hydrogenation of quino(xa)lines and *N*-aryl imines.[38;39;111] How the mixed ligand approach will affect the outcome of the reaction is, however, not predictable beforehand and it is definitely not a guarantee for better results (*vide infra*).

1.6 Goal of this research

In view of the excellent results obtained with monodentate phosphoramidite ligands in the asymmetric hydrogenation of olefins, imines and heteroaromatics, the logical next step was to study the enantioselective hydrogenation of C=O double bonds using phosphoramidite ligands. Thus, we set out to develop one or more catalytic systems for the asymmetric, ruthenium or iridium catalyzed, hydrogenation of acetophenones, α- and β-ketoesters and α-aryl aldehydes.

1.7 Outline of the thesis

In this thesis the use of phosphoramidites as ligands in the hydrogenation of several carbonyl compounds is described. Chapter two will focus on the hydrogenation of simple aryl ketones, employing the classical Noyori type catalyst using a combination of a chiral phosphorus ligand and a chiral diamine.[44]
In chapter three, a switch is made from ruthenium to iridium as the metal of choice. Ir/PPA and Ir/SPO catalysts were tested in the asymmetric hydrogenation of a simple ketone.
In chapter four, the switch is made back again to ruthenium and the research focuses on the use of the phosphoramidite ligands in the asymmetric hydrogenation of α- and β-ketoesters.

The good results that were obtained with the experiments in chapters two and four are further explored in chapter five. In this chapter the results of the asymmetric hydrogenation of α-substituted β-ketoesters and α-aryl aldehydes under DKR conditions are described.
In the last chapter an overview is given of the conclusions drawn from this work and an outlook for further research in the field of asymmetric hydrogenations using monodentate (phosphoramidite) ligands in academia and industry.

1.8 References

[1.] R. Noyori, *Asymmetric Catalysis in Organic Chemistry*, Wiley, New York **1994**.

[2.] *Comprehensive Asymmetric Catalysis I*, first ed. (Eds.: E. N. Jacobson, A. Pfaltz, H. Yamamoto) Springer, Berlin-Heidelberg **1999**.

[3.] L. J. Eliel, S. H. Wilen, *Stereochemistry of Organic Compunds*, Wiley, Weinheim **2009**.

[4.] J. A. LeBel, *Bull.Soc.Chim.Fr.* **1874,** *22* 337-347.

[5.] J. H. Van 't Hoff, *Arch.Neerl.Sci.Exactes Nat.* **1874,** *9* 445-454.

[6.] L. A. Nguyen, H. He, C. Pham-Huy, *Int.J.Biomed.Sci.* **2006,** *2* 85-100.

[7.] J. R. Powell, J. J. Ambre, T. I. Ruo, in *Drug Stereochemistry. Analytical Methods and Pharmacology*, Ed.: I. W. Wainer), Marcel Dekker, New York, NY **1988**, pp. 245-270.

[8.] P. Barham, L. H. Skibsted, W. L. P. Bredie, M. B. Frøst, P. Møller, J. Risbo, P. Snitkjær, L. Mørch Mortensen, *Chem.Rev.* **2010,** *110* 2313-2365.

[9.] R. A. Sheldon, *Chirotechnology: Industrial synthesis of optically active compounds*, Marcel Dekker, New York **1993**.

[10.] A. N. Collins, G. N. Sheldrake, J. Crosby, *Chirality in industry II: developments in the commercial manufacture and applications of optically active compounds*, Wiley, Chichester **1997**.

[11.] J. P. Genet, *Acc.Chem.Res.* **2003,** *36* 908-918.

[12.] *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, (Eds.: H.-U. Blaser, H.-J. Federsel) Wiley-VCH, **2010**.

[13.] H. U. Blaser, *Tetrahedron: Asymmetry* **1991,** *2* 843-866.

[14.] *The Handbook of Homogeneous Hydrogenation*, 1 ed. (Eds.: J. G. de Vries, C. J. Elsevier) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**.

[15.] M. A. Bennett, G. Wilkinson, *J.Chem.Soc.* **1961,** 1418-1419.

[16.] J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *J.Chem.Soc.A* **1966,** 1711.

[17.] L. Horner, H. Siegel, H. Büthe, *Angew.Chem.Int.Ed.* **1968,** *7* 942.

[18.] W. S. Knowles, M. J. Sabacky, *Chem.Commun.(London)* **1968,** 1445-1446.

[19.] W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J.Am.Chem.Soc.* **1975,** *97* 2567-2568.

[20.] W. S. Knowles, *Acc.Chem.Res.* **1983,** *16* 106-112.

[21.] J. C. Poulin, T. P. Dang, H. B. Kagan, *J.organomet.chem.* **1975,** *84* 87-92.

[22.] T. P. Dang, J. C. Poulin, H. B. Kagan, *J.organomet.chem.* **1975,** *91* 105-115.

[23.] W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J.Chem.Soc.Chem.Commun.* **1972,** 10-11.

[24.] J. D. Morrison, R. E. Burnett, A. M. Aguiar, C. J. Morrow, C. Phillips, *J.Am.Chem.Soc.* **1971,** *93* 1301-1303.

[25.] J. A. Osborn, R. R. Schrock, *J.Am.Chem.Soc.* **1971,** *93* 2397-2407.

[26.] D. J. Ager, in *Handbook of Homogeneous Hydrogenation* ,*Vol. II*, (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 745-772.

[27.] W. Tang, X. Zhang, *Chem.Rev.* **2003,** *103* 3029-3069.

[28.] C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem.Commun.* **2000,** 961-962.

[29.] M. T. Reetz, G. Mehler, *Angew.Chem.Int.Ed.* **2000,** *39* 3889-3890.

[30.] M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J.Am.Chem.Soc.* **2000,** *122* 11539-11540.

[31.] C. Botteghi, M. Bianchi, E. Benedetti, U. Matteoli, *Chimia* **1975,** *29* 256-258.

[32.] H. B. Kagan, N. Langlois, T. Phat Dang, *J.Organomet.Chem.* **1975,** *90* 353-365.

[33.] S. Vastag, J. Bakos, S. Toros, N. E. Takach, R. B. King, B. Heil, L. Marko, *J.Mol.Catal.* **1984,** *22* 283-287.

[34.] J. Bakos, I. Tóth, B. Heil, G. Szalontai, L. Párkányi, V. Fülöp, *J.Organomet.Chem.* **1989,** *370* 263-276.

[35.] C. Lensink, J. G. de Vries, *Tetrahedron: Asymmetry* **1992,** *3* 235-238.

[36.] Y. Amrani, L. Lecomte, D. Sinou, J. Bakos, I. Tóth, B. Heil, *Organometallics* **1989,** *8* 542-547.

[37.] H. U. Blaser, H. P. Buser, K. Coers, R. Hanreich, H. P. Jalett, E. Jelsch, B. Pugin, H. D. Schneider, F. Spindler, A. Wegmann, *Chimia* **1999,** *53* 275-280.

[38.] N. Mršic, L. Lefort, J. A. F. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv.Synth.Catal.* **2008,** *350* 1081-1089.

[39.] N. Mršic, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J.Am.Chem.Soc.* **2009,** *131* 8358-8359.

[40.] P. Bonvicini, A. Levi, G. Modena, G. Scorrano, *Chem.Commun.* **1972,** 1188-1189.

[41.] S. Törös, B. Heil, L. Kollár, L. Markó, *J.Organomet.Chem.* **1980,** *197* 85-86.

[42.] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J.Am.Chem.Soc.* **1987,** *109* 5856-5858.

[43.] M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J.Am.Chem.Soc.* **1988,** *110* 629-631.

[44.] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J.Am.Chem.Soc.* **1995,** *117* 2675-2676.

[45.] V. Massonneau, P. Le Maux, G. Simonneaux, *J.Organomet.Chem.* **1985,** *288* c59-c60.

[46.] R. H. Morris, *Chem.Soc.Rev.* **2009,** *38* 2282-2291.

[47.] C. P. Casey, H. Guan, *J.Am.Chem.Soc.* **2007,** *129* 5816-5817.

[48.] C. Sui-Seng, F. Freutel, A. J. Lough, R. H. Morris, *Angew.Chem.Int.Ed.* **2008,** *47* 940-943.

[49.] R. A. Sánchez-Delgado, M. Rosales, M. A. Esteruelas, L. A. Oro, *J.Mol.Catal.A: Chem.* **1995,** *96* 231-243.

[50.] W. Baratta, M. Ballico, S. Baldino, G. Chelucci, E. Herdtweck, K. Siega, S. Magnolia, P. Rigo, *Chem.Eur.J.* **2008,** *14* 9148-9160.

[51.] W. Baratta, C. Barbato, S. Magnolia, K. Siega, P. Rigo, *Chem.Eur.J.* **2010,** *16* 3201-3206.

[52.] *Handbook of organopalladium chemistry for organic synthesis*, (Ed.: E. Negishi) John Wiley & Sons, Inc., Hoboken N.J. **2002**.

[53.] Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *Org.Lett.* **2005,** *7* 3235-3238.

[54.] C. Wang, G. Yang, J. Zhuang, W. Zhang, *Tetrahedron Lett.* **2010,** *51* 2044-2047.

[55.] N. S. Goulioukina, G. N. Bondarenko, A. V. Bogdanov, K. N. Gavrilov, I. P. Beletskaya, *Eur.J.Org.Chem.* **2009,** 510-515.

[56.] H. Shimizu, D. Igarashi, W. Kuriyama, Y. Yusa, N. Sayo, T. Saito, *Org.Lett.* **2007,** *9* 1655-1657.

[57.] A. J. Blacker, in *Handbook of Homogeneous Hydrogenation, Vol. III,* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 1215-1244.

[58.] E. Alberico, I. Nieddu, R. Taras, S. Gladiali, *Helv.Chim.Acta* **2006,** *89* 1716-1729.

[59.] S. Gladiali, E. Alberico, *Chem.Soc.Rev.* **2006,** *35* 226-236.

[60.] X. F. Wu, X. G. Li, F. King, J. L. Xiao, *Angew.Chem.Int.Ed.* **2005,** *44* 3407-3411.

[61.] R. Noyori, S. Hashiguchi, *Acc.Chem.Res.* **1997,** *30* 97-102.

[62.] R. Malacea, R. Poli, E. Manoury, *Coor.Chem.Rev.* **2010,** *254* 729-752.

[63.] D. A. Evans, S. G. Nelson, M. R. Gagne, A. R. Muci, *J.Am.Chem.Soc.* **1993,** *115* 9800-9801.

[64.] X. F. Wu, J. L. Xiao, *Chem.Commun.* **2007,** 2449-2466.

[65.] M. T. Reetz, X. Li, *J.Am.Chem.Soc.* **2006,** *128* 1044-1045.

[66.] M. Watanabe, K. Murata, T. Ikariya, *J.Org.Chem.* **2002,** *67* 1712-1715.

[67.] S. J. M. Nordin, P. Roth, T. Tarnai, D. A. Alonso, P. Brandt, P. G. Andersson, *Chem.Eur.J.* **2001,** *7* 1431-1436.

[68.] K. Everaere, A. Mortreux, J. F. Carpentier, *Adv.Synth.Catal.* **2003,** *345* 67-77.

[69.] J. C. Mao, J. Guo, *Chirality* **2010,** *22* 173-181.

[70.] W. Wang, Z. Li, W. Mu, L. Su, Q. Wang, *Catal.Commun.* **2010,** *11* 480-483.

[71.] X. F. Wu, C. Wang, J. L. Xiao, *Platinum Met.Rev.* **2010,** *54* 3-19.

[72.] R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim **2007**.

[73.] P. Daverio, M. Zanda, *Tetrahedron: Asymmetry* **2001,** *12* 2225-2259.

[74.] B. T. Cho, *Chem.Soc.Rev.* **2009,** *38* 443-452.

[75.] E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J.Am.Chem.Soc.* **1987,** *109* 7925-7926.

[76.] E. J. Corey, R. K. Bakshi, S. Shibata, *J.Am.Chem.Soc.* **1987,** *109* 5551-5553.

[77.] V. A. Glushkov, A. G. Tolstikov, *Russ.Chem.Rev.* **2004,** *73* 581-608.

[78.] T. Yamada, T. Nagata, K. D. Sugi, K. Yorozu, T. Ikeno, Y. Ohtsuka, D. Miyazaki, T. Mukaiyama, *Chem.Eur.J.* **2003,** *9* 4485-4509.

[79.] D. R. Li, A. He, J. R. Falck, *Org.Lett.* **2010,** *12* 1756-1759.

[80.] I. Ojima, M. Nihonyanagi, *J.Chem.Soc.Chem.Commun.* **1972,** 938a-938.

[81.] K. Yamamoto, T. Hayashi, M. Kumada, *J.Organomet.Chem.* **1972,** *46* C65-C67.

[82.] C. G. Arena, *Mini-Rev.Org.Chem.* **2009,** *6* 159-167.

[83.] S. Díez-González, S. P. Nolan, *Acc.Chem.Res.* **2008,** *41* 349-358.

[84.] K. Junge, B. Wendt, D. Addis, S. L. Zhou, S. Das, M. Beller, *Chem.Eur.J.* **2010,** *16* 68-73.

[85.] T. Inagaki, L. T. Phong, A. Furuta, J. Ito, H. Nishiyama, *Chem.Eur.J.* **2010,** *16* 3090-3096.

[86.] N. S. Shaikh, S. Enthaler, K. Junge, M. Beller, *Angew.Chem.Int.Ed.* **2008,** *47* 2497-2501.

[87.] A. Suárez, A. Pizzano, I. Fernández, N. Khiar, *Tetrahedron: Asymmetry* **2001,** *12* 633-642.

[88.] K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Tetrahedron Lett.* **2002,** *43* 4977-4980.

[89.] K. Faber, *Biotransformations in organic chemistry*, 4 ed. Springer-Verlag, Berlin, Heidelberg **2000**.

[90.] K. B. Borges, W. d. S. Borges, R. Durán-Patrón, M. T. Pupo, P. S. Bonato, I. G. Collado, *Tetrahedron: Asymmetry* **2009,** *20* 385-397.

[91.] J. C. Moore, D. J. Pollard, B. Kosjek, P. N. Devine, *Acc.Chem.Res.* **2007,** *40* 1412-1419.

[92.] D. M. Zhu, L. Hua, *J.Org.Chem.* **2006,** *71* 9484-9486.

[93.] I. Lavandera, A. Kern, B. Ferreira-Silva, A. Glieder, S. de Wildeman, W. Kroutil, *J.Org.Chem.* **2008,** *73* 6003-6005.

[94.] W. Yang, J. H. Xu, Y. Xie, Y. Xu, G. Zhao, G. Q. Lin, *Tetrahedron: Asymmetry* **2006,** *17* 1769-1774.

[95.] H. Li, D. Zhu, L. Hua, E. R. Biehl, *Adv.Synth.Catal.* **2009,** *351* 583-588.

[96.] D. Zhu, J. E. Stearns, M. Ramirez, L. Hua, *Tetrahedron* **2006,** *62* 4535-4539.

[97.] P. Hoyos, J. V. Sinisterra, F. Molinari, A. R. Alcántara, P. Domínguez de María, *Acc.Chem.Res.* **2010,** *43* 288-299.

[98.] J. F. Teichert, B. L. Feringa, *Angew.Chem.Int.Ed.* **2010,** *49* 2486-2528.

[99.] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J.Am.Chem.Soc.* **1980,** *102* 7932-7934.

[100.] L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, *Org.Lett.* **2004,** *6* 1733-1735.

[101.] R. B. C. Jagt, P. Y. Toullec, D. Geerdink, J. G. de Vries, B. L. Feringa, A. J. Minnaard, *Angew.Chem.Int.Ed.* **2006,** *45* 2789-2791.

[102.] J. G. de Vries, L. Lefort, *Chem.Eur.J.* **2006,** *12* 4722-4734.

[103.] Duursma, A., University of Groningen, **2004**.

[104.] R. Hulst, N. K. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1994,** *5* 699-708.

[105.] H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J.Org.Chem* **2005,** *70* 943-951.

[106.] R. Hoen, M. van den Berg, H. Bernsmann, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *Org.Lett.* **2004,** *6* 1433-1436.

[107.] A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc.Chem.Res.* **2007,** *40* 1267-1277.

[108.] F. Giacomina, A. Meetsma, L. Panella, L. Lefort, A. H. M. de Vries, J. G. de Vries, *Angew.Chem.Int.Ed.* **2007,** *46* 1497-1500.

[109.] R. Hoen, S. Leleu, P. N. M. Botman, V. A. M. Appelman, B. L. Feringa, H. Hiemstra, A. J. Minnaard, J. H. van Maarseveen, *Org.Biomol.Chem.* **2006,** *4* 613-615.

[110.] R. Hoen, T. Tiemersma-Wegman, B. Procuranti, L. Lefort, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *Org.Biomol.Chem.* **2007,** *5* 267-275.

[111.] N. Mršic, T. Jerphagnon, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv.Synth.Catal.* **2009,** *351* 2549-2552.

[112.] L. Panella, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Org.Lett.* **2005,** *7* 4177-4180.

[113.] L. Panella, A. M. Aleixandre, G. J. Kruidhof, J. Robertus, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *J.Org.Chem.* **2006,** *71* 2026-2036.

[114.] D. Pena, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J.Am.Chem.Soc.* **2002,** *124* 14552-14553.

[115.] M. van den Berg, R. M. Haak, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Adv.Synth.Catal.* **2002,** *344* 1003-1007.

[116.] M. van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv.Synth.Catal.* **2003,** *345* 308-323.

[117.] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew.Chem.Int.Ed.* **2005,** *44* 4209-4212.

[118.] M. T. Reetz, *Chim.Oggi* **2003,** *21* 5-8.

[119.] M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003,** *44* 4593-4596.

[120.] M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew.Chem.Int.Ed.* **2003,** *42* 790-793.

[121.] M. T. Reetz, *Angew.Chem.Int.Ed.* **2008,** *47* 2556-2588.

[122.] D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org.Biomol.Chem.* **2003,** *1* 1087-1089.

Chapter 2

Ruthenium Catalyzed Asymmetric Hydrogenation of Aryl Alkyl Ketones using Phosphoramidite Ligands

Abstract

In this chapter the use of a ruthenium complex based on a chiral diamine and a monodentate phosphoramidite as a catalyst for the asymmetric hydrogenation of aryl alkyl ketones is described. The best catalyst contains 3,3'-dimethyl PipPhos and 1,2-diamino-cyclohexane leading to full conversion and over 95% ee for a range of different substrates. The exact structure of the complex is not yet fully established, although a lot of evidence points towards a dimeric precatalyst containing just one phosphoramidite ligand. We were able to prove that two phosphoramidite ligands per ruthenium are necessary in order to obtain a high ee.

The work described here is covered by patent *WO*2008-077610 B. Stegink and J.G. de Vries, "*Asymmetric hydrogenation of prochiral compounds.*"

Parts of this chapter are published: B. Stegink, L. van Boxtel, L. Lefort, A. J. Minnaard, B. L. Feringa and J. G. de Vries, *Adv.Synth.Catal.*, **2010,** *352* 2621-2628.

2.1 Introduction

Even after the discovery of ruthenium-binap as catalyst for the asymmetric hydrogenation of functionalized ketones by the group of Noyori,[1;2] the acetophenone type ketones remained a problematic substrate for many years.

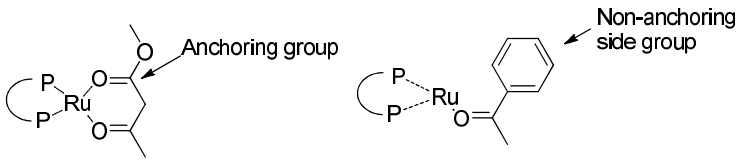


Figure 1: Noyori catalyst with an easy to hydrogenate, anchored, β-ketoester and a difficult to hydrogenate, non-anchored, acetophenone.

The reason for this was the fact that in order to get good results, when using the first Noyori type catalyst **2.1,** the substrate needed to possess an anchoring group which would keep the substrate in close proximity of the metal long enough for the reaction to take place. As is shown in Figure 1, acetophenone, and other non-functionalized ketones, do not possess such an anchoring group and therefore the reduction was neither efficient nor selective.

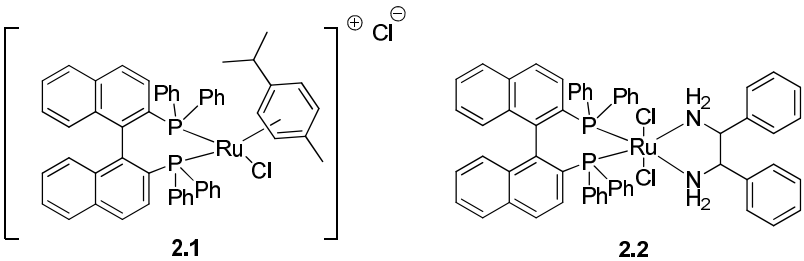
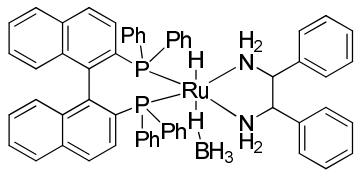


Figure 2: The Noyori catalysts for the asymmetric hydrogenation of functionalized ketones, without diamine (**2.1**) and for non-functionalized alkyl aryl ketones, with diamine. (**2.2**)

It took until 1995 before Noyori and co-workers were able to hydrogenate these substrates with high ee's.[3;4] It was found that adding a chiral 1,2-diamine to the catalyst improved the outcome of the reaction dramatically.
Besides the effect of the diamine they also found out that upon adding a small amount of base to the reaction mixture they were able to speed up the reaction

more than a 6000 fold compared to the original system without diamine and base, creating one of the most efficient catalysts in homogeneous catalysis.[5]
One of the drawbacks of this type of catalysts is that substrates which do not tolerate the presence of a base in the reaction can not be hydrogenated since the base is needed for the activation of the catalyst. This problem was overcome by treating the catalyst prior to use with 25 equivalents of $NaBH_4$.[6]



2.3

Figure 3: The BH_4-type Noyori catalyst which can be used under base-free conditions.

This led to a catalyst in which the two chlorides were replaced by a hydride and a η_1-HBH_3 group. This catalyst proved to be active in the hydrogenation of non-functionalized alkyl aryl ketones without adding a base to the mixture.
Since these discoveries numerous groups have developed their own catalysts for the hydrogenation of acetophenones.[7;8] The differences between these systems most often are found in the variation of the P-ligands. A few commonly used P-ligands are depicted in Figure 4.

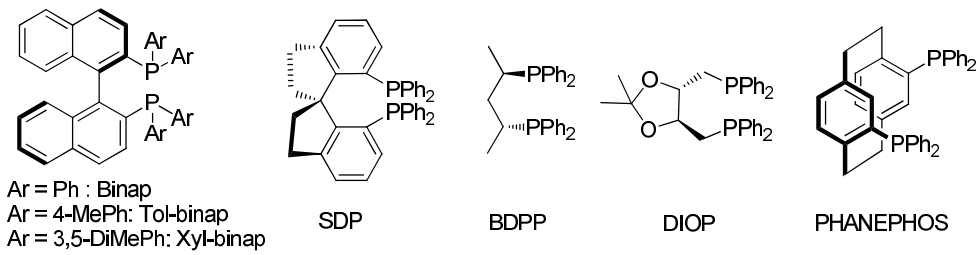


Figure 4: Representative examples of bidentate phosphine ligands that have been used successfully in the asymmetric hydrogenation of alkyl aryl ketones.[8]

Surprisingly, only a few chiral diamines have ever been used as ligands. Almost all groups use one of the three chiral 1,2-diamines depicted in Figure 5, 1,2-

diphenyl ethylenediamine (DPEN), 1,2-diamino cyclohexane (DACH) or 1,1-dianisole-2-isopropyl ethylenediamine (DAIPEN).

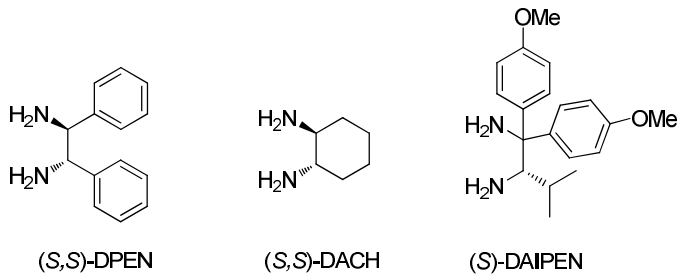


Figure 5: The three diamines most commonly used in the hydrogenation of acetophenones.

There is however one diamine variation which increased the versatility of the Noyori catalyst even further. The group of Noyori introduced the, non-chiral, α-picolylamine (**2.4**) as an amine which made it possible to hydrogenate even the, until then, very difficult substrate pinacolone (**2.6**).[9] They showed that by using this amine instead of the classically used diamines these *tert*-butyl type substrates could be hydrogenated in good yield and excellent enantioselectivities.

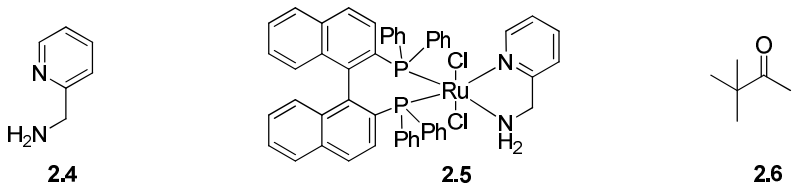


Figure 6: Picolylamine as used by Noyori to facilitate the hydrogenation of tert-butyl ketones like pinacolone.

2.2 The mechanism

The hydrogenation of acetophenone using a Noyori-type catalyst proceeds via a non-classical mechanism. In Figure 7 it can be seen that no direct interaction between the substrate and the metal center of the catalyst takes place. Instead the substrate binds in an outer sphere mode to the ligands of the catalyst before being reduced.[10-14] The ruthenium dichloride catalyst precursor (**I**) is activated

by the first equivalents of hydrogen under the influence of the base present turning it into the dihydride species (**II**). To this complex, the substrate binds in an outer sphere fashion in which one of the hydrides on the ruthenium center coordinates to the more electrophilic carbon of the carbonyl and a proton of the diamine coordinates to the more electronegative oxygen atom. In this way an, energetically favored, six-membered transition state is formed (**TS1**).

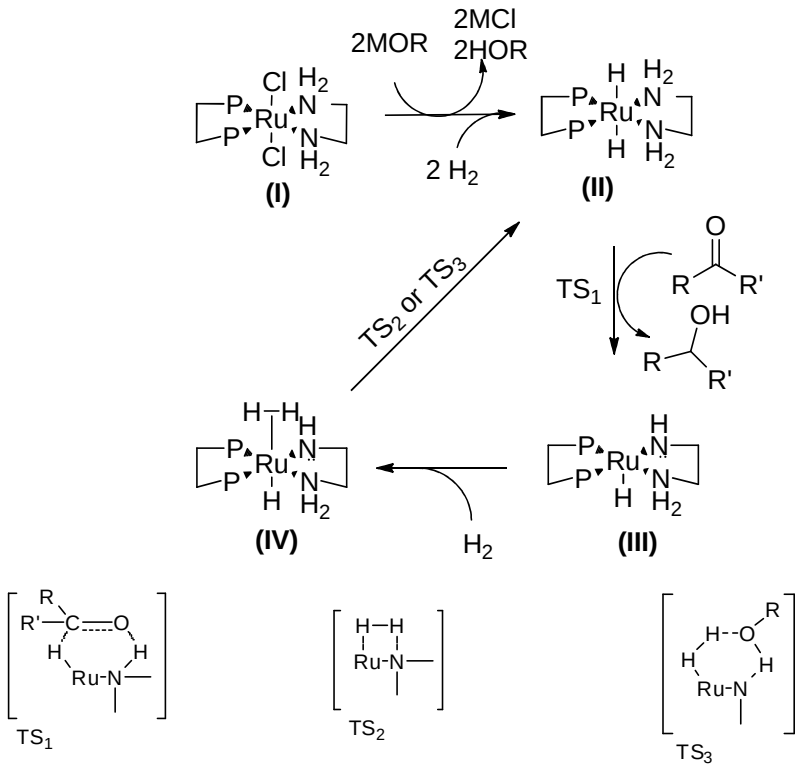


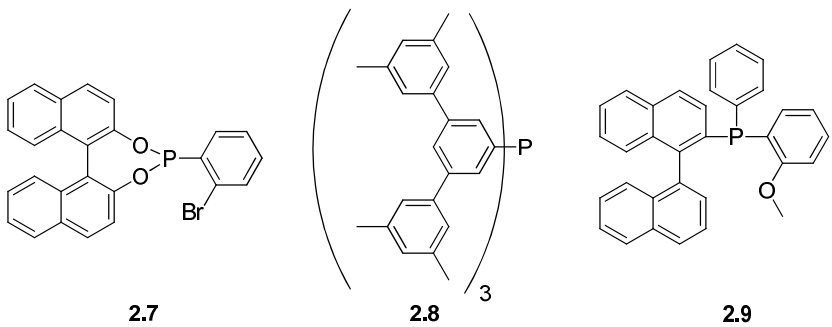
Figure 7: Mechanism of hydrogenation of alkyl aryl ketones catalyzed by a Noyori type catalyst.

The hydride and the proton are transferred to the substrate and the reduced product is released. To the resulting complex (**III**) a hydrogen molecule binds resulting in complex (**IV**) which then splits in one of two possible ways. Either it heterolytically splits and regenerates the active catalyst via a four-membered ring transition state (**TS2**), or the hydrogen splits heterolytically donating its hydride to the ruthenium and its proton gets transferred to a solvent molecule

which then donates its proton to the amine group regenerating the active complex via a six-membered transition state (**TS3**). Whether the regeneration goes via **TS2** or **TS3** depends on the nature of the solvent. In aprotic solvents the route via **TS2** will be followed whereas in protic solvents preferentially the **TS3** route will be followed.

2.3 Monodentate ligands in acetophenone-type asymmetric ketone hydrogenation

Until now only three reports are known in which a monodentate P-ligand is used for the asymmetric hydrogenation of alkyl aryl ketones, all in combination with a diamine co-ligand. The first report was from the group of Wills in 2004[15-17] who described full conversions and excellent ee's for a range of acetophenones when using phosphonite (**2.7**) type ligands.
The second report came from the group of Ding[18] who was able to achieve good chiral induction as well. Interestingly they used a non-chiral monodentate phosphine and only a chiral diamine. They were able to reach up to 95% ee in the hydrogenation of acetophenone using the bulky tris-(3,5-di(3,5-xylyl)-phenyl)phosphine (**2.8**).
The third and final example came from the group of Lemaire[19] who used a P-chiral monodentate phosphine ligand **2.9** with which they were able to get full conversion and up to 61% ee in the hydrogenation of acetophenone, but only when they use 1,4-butanediamine as co-ligand.



2.7 **2.8** **2.9**

Figure 8: The monodentate P-ligands as used by the groups of Wills (**2.7**), Ding (**2.8**) and Lemaire (**2.9**) in the hydrogenation of acetophenones.

2.4 Goal of the research

Our group already has a lot of experience in using monodentate ligands in asymmetric hydrogenation reactions.[20] As highlighted in chapter 1, phosphoramidite ligands are an interesting class of ligands to use because of their structural versatility, easy synthesis which is highly suited for high throughput screening and relatively cheap starting materials. We set out to further optimize the preliminary results obtained in DSM and create a ruthenium-based catalyst containing monodentate phosphoramidite ligands which would be able to hydrogenate acetophenone-type ketones in good yields and high ee's. The results obtained in this search for a good catalyst will be discussed in this chapter.

2.5 Results

Early 2005 some promising results were obtained at DSM in the first attempts of the asymmetric hydrogenation of acetophenone using a ruthenium catalyst containing phosphoramidite ligands. When using a ruthenium catalyst containing two phosphoramidites and a (chiral) diamine they were able to get up to 61% ee in the hydrogenation of acetophenone, at 50 bar and 50 ^{o}C.[21] To further optimize the results previously obtained in DSM we started with a phosphoramidite ligand screening.
As a starting point for the preparation of the pre-catalyst we used the catalyst preparation first described by Noyori[3] which has since then been used by most groups working in this field.

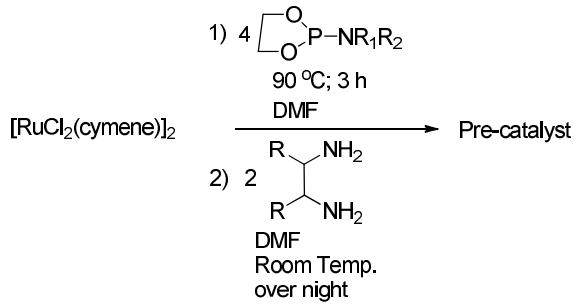


Figure 9: Preparation of the precatalyst for the hydrogenation of ketones.

As can be seen in Figure 9 the pre-catalyst was made by adding 4 equivalents of a monodentate phosphoramidite to the dimeric ruthenium precursor $[RuCl_2(cymene)]_2$. This mixture was heated in DMF for 3 h at 90 °C. After cooling the mixture down to room temperature, two equivalents of the desired 1,2-diamine were added and after overnight stirring the precatalyst was obtained by evaporating the DMF, stripping the residue twice with toluene and washing it twice with hexane, which should wash away any free ligand still present. The obtained powder was used directly in the hydrogenations. The precatalyst would be activated by the first equivalents of hydrogen gas after addition of base to the reaction mixture as has been previously shown in the mechanistic studies of similar catalysts (see also Figure 7 for the reaction mechanism).[12]

2.5.1 Screening of ligands

The search for a fast and enantioselective ketone hydrogenation catalyst started with a screening of phosphoramidite ligands. They were tested as P-ligands in the hydrogenation of acetophenone. As standard conditions 0.1 mol% ruthenium catalyst was used in the presence of 1 mol% of KO*t*Bu. The reaction mixtures were kept stirring in the Endeavor, a unit containing eight small stirred autoclaves, for 16 h under a hydrogen pressure of 25 bar. The results of this initial screening are depicted in Table 1. In all cases the catalysts displayed perfect chemoselectivity towards the carbonyl group, (partial) reduction of the aryl groups was never observed. The first try, using normal PipPhos (**L1**) immediately gave full conversion and an ee of 52%. In an attempt to improve

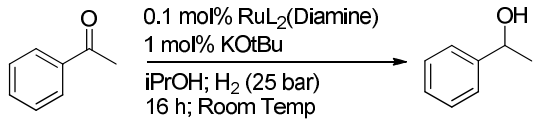
this ee a few other ligands were tested. The first thing we tried was to investigate whether a bidentate phosphoramidite ligand would give better selectivities. We tested three bidentate ligands (**L3**, **L4** and **L8**) with no success. In all three cases the ee turned out to be lower compared to the result with PipPhos as ligand. This, in combination with the fact that none of the reactions went to completion within the 16 h reaction time, made us decide to shift our focus back to the monodentate ligands.

The "Leggy"-ligand **L2** with a more bulky amine did also not give an improvement in terms of ee. Going to a smaller backbone by using a catechol based ligand **L5**, which gave good results in the olefin hydrogenations,[22] proved to be the worst choice of all, giving only 40% conversion and a racemic product. When, however, the backbone of the ligand was made bulkier, instead of smaller, by adding two methyl groups on the 3 and 3' position of the naphthyl unit the ee went up significantly. When 3,3'-dimethyl MonoPhos (**L6**) was used, the ee already increased to 90%, even exceeding the result obtained with Binap (entry 1) as a ligand. With DiMePip (**L7**) the ee went up even further to reach an excellent 97%.

Switching from the diamine DPEN to DACH proved not to be of influence on the outcome of the reaction (entry 8 vs. entry 11). The use of the non-chiral diamine 1,2-ethylenediamine (entry 13), however, made the importance of the chirality of the diamine co-ligand in the catalyst very clear, as this change resulted in a drop in ee to just 34%. Switching the stereochemistry of the diamine resulted in a drop in ee from 97% to 52% (entries 11 and 12). These results made it clear that there is a matched combination, with both the phosphoramidite and the diamine of the same absolute configuration, and a mismatched combination, with the phosphoramidite and the diamine both of opposite absolute configurations, of phosphoramidite and diamine and the best selectivities are achieved only when the phosphoramidites and diamine present are of the same absolute configuration.

To make sure the reaction is only operating through molecular hydrogen and no other background reactions with the substrate, such as transfer hydrogenation, take place, we also tried the reduction of acetophenone in the absence of hydrogen pressure. As can be seen in entry 14 no reaction takes place at all, establishing it is really a reduction by molecular hydrogen we are looking at.

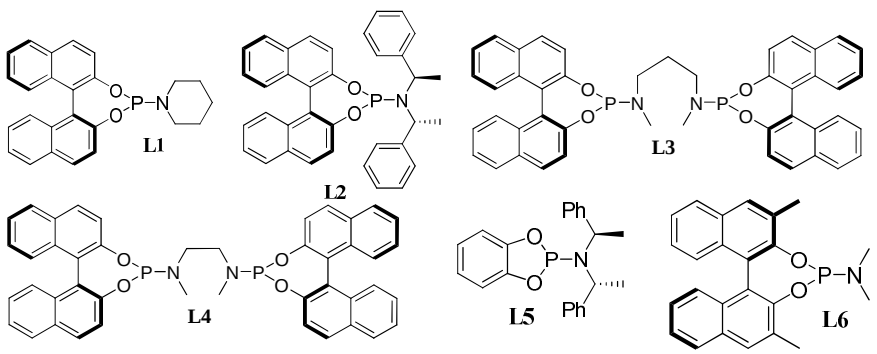
Table 1: Ligand screening in the acetophenone hydrogenation.

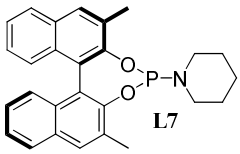


2.10a **2.11a**

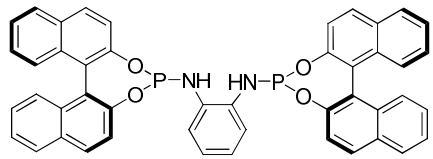
	Ligand	Diamine	Conversion[a] (%)	Ee[a] (%)
1	(*S*)-Binap	(*S*,*S*)-DPEN	100	87 (*R*)
2	**(*S*)-L1**	(*S*,*S*)-DPEN	100	52 (*R*)
3	**(*S*,*RR*)-L2**	(*S*,*S*)-DPEN	100	41 (*R*)
4	**(*S*)-L3**	(*S*,*S*)-DPEN	50	12 (*R*)
5	**(*S*)-L4**	(*S*,*S*)-DPEN	20	10 (*R*)
6	**(*R*,*R*)-L5**	(*R*,*R*)-DPEN	40	rac.
7	**(*R*)-L6**	(*R*,*R*)-DPEN	100	90 (*S*)
8	**(*R*)-L7**	(*R*,*R*)-DPEN	100	97 (*S*)
9	**(*S*)-L8**	(*S*,*S*)-DPEN	13	41 (*R*)
10	**(*S*)-L1**	(*S*,*S*)-DACH	100	55 (*R*)
11	**(*R*)-L7**	(*R*,*R*)-DACH	100	97 (*S*)
12	**(*R*)-L7**	(*S*,*S*)-DACH	100	52 (*S*)
13	**(*R*)-L1**	Ethylenediamine	100	34 (*S*)
14[b]	**(*R*)-L7**	(*R*,*R*)-DACH	0	Nd

All reactions were carried out in the Endeavor parallel autoclave on 2 mmol of **2.10a** in a total volume of 4 ml *i*PrOH with 0.1 mol% catalyst in the presence of 1 mol% KO*t*Bu. Hydrogen pressure was applied (25 bar) for 16 h while the reaction was stirred at room temperature. a) Conversion and ee were determined using ^{1}H-NMR and chiral GC, respectively. b) No hydrogen pressure applied.





L7

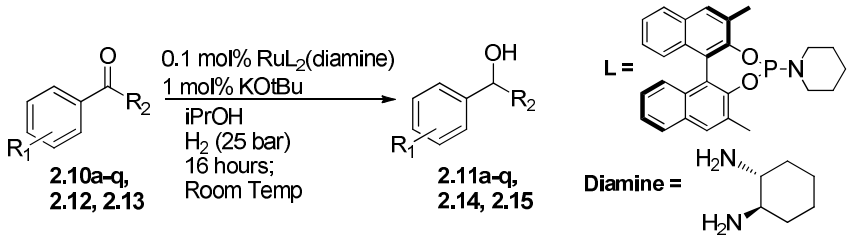


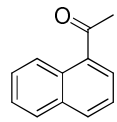
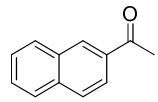
L8

2.5.2 Substrate scope

Having established the best phosphoramidite-diamine combination, DiMePip and DACH, the scope of the reaction was screened. As can be seen in Table 2 the system works very well for a large range of aromatic ketones. With most substrates it is possible to reach full conversion within 16 h. Only a few substrates are not hydrogenated to completion. *o*-Hydroxy acetophenone (**2.10c**) did not react at all which is probably due to the acidity of the substrate. The base that is added to the reaction mixture will immediately react with the phenol group of the substrate which prevents the catalyst from being activated. If the protected substrate, *o*-methoxy acetophenone (**2.10d**), is used the activity is restored again. Other problematic substrates are the sterically demanding 2-methyl-propiophenone (**2.10m**, entry 14) and the two substrates bearing strongly electron withdrawing substituents (**2.10o-p** entries 16 and 17). The selectivity of the hydrogenations is mostly excellent (ee >90%) except for the *meta*-substituted substrates where the enantiomeric excess drops.

Table 2: Substrate scope of the aromatic ketone hydrogenation.

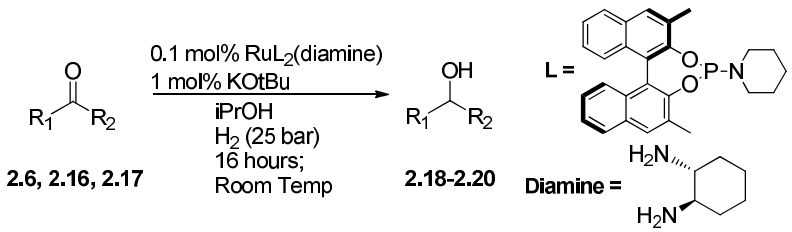


	Substrate	R1	R2	Conversion[a] (%)	Ee[a] (%)
1	**2.10a**	H	Me	100	97 (*S*)
2	**2.10b**	*o*-Me	Me	100	97 (*S*)
3	**2.10c**	*o*-OH	Me	0	Nd
4	**2.10d**	*o*-OMe	Me	100	96 (*S*)
5	**2.10e**	*p*-OMe	Me	100	97 (*S*)
6	**2.10f**	*p*-Cl	Me	100	95 (*S*)
7	**2.10g**	*m*-Br	Me	100	65 (*S*)
8	**2.10h**	*m*-Cl	Me	100	83 (*S*)
9	**2.10i**	*m*-OMe	Me	<10	Nd
10	**2.10j**	3,5-CF_3	Me	100	95 (*S*)
11	**2.12**	 1-acetonaphthone		100	93 (*S*)
12	**2.13**	 2-acetonaphthone		100	94 (*S*)
13	**2.10k**	H	Et	100	91 (*S*)
14	**2.10m**	H	*i*-Pr	<10	Nd
15	**2.10n**	H	*n*-Pr	100	93 (*S*)
16	**2.10o**	H	CH_2Cl	<10	Nd
17	**2.10p**	H	CF_3	<10	Nd
18	**2.10q**	o-Me	Ph	100	15 (*R*)

All reactions were carried out in the Endeavor parallel autoclave on 2 mmol substrate in a total volume of 4 ml *i*PrOH with 0.1 mol% catalyst, containing DiMePip and DACH as ligands, in the presence of 1 mol% KO*t*Bu. Hydrogen pressure was applied (25 bar) for 16 h while the reaction was stirring at room temperature. a) Conversion and ee were determined using ^{1}H-NMR and chiral GC respectively.

After testing a range of aromatic ketones we decided to investigate if the catalyst would also be able to hydrogenate alkyl ketones. As can be seen in Table 3 varying results were obtained.

Table 3: Results in the hydrogenation of aliphatic ketones.



Entry	Substrate	R1	R2	Conversion[a] (%)	ee[a] (%)
1	**2.6**	Me	*t*-Bu	50	41 (*S*)
2	**2.16**	Me	Bu	100	<5
3	**2.17**	2-cyclohexenone		85	<5

All reactions were carried out in the Endeavor parallel autoclave on 2 mmol substrate in a total volume of 4 ml *i*PrOH with 0.1 mol% catalyst, containing DiMePip and DACH as ligands, in the presence of 1 mol% KO*t*Bu. Hydrogen pressure was applied (25 bar) for 16 h while the reaction was stirring at room temperature. a) Conversion and ee were determined using chiral GC.

In the case of the, known to be difficult[9], substrate pinacolone (**2.6**, entry 1) the reaction did not proceed for more than 50%. There was some selectivity towards one of the two enantiomers but with an ee of 41% this is not very impressive. The hydrogenation of 2-hexanone (**2.16**, entry 2) did go to full completion. However, since no significant ee was found, the small difference between the methyl and butyl groups of the molecule apparently made it almost impossible for the catalyst to create any selection towards one of the two enantiomers. In the case of 2-cyclohexenone (**2.17**, entry 4) the conversion, although not complete, was good, also the hydrogenation went with complete selectivity for the carbonyl group. Products with a saturated cyclohexane ring were not detected. Sadly, no significant ee was detected in this case after 16 h of reaction.

2.5.3 Mixed ligands

As already mentioned in chapter 1, it is known from earlier work by the groups of Reetz[23;24] and our own[25;26] that mixing of monodentate chiral ligands with monodentate (a)chiral ligands can have a dramatic influence on the rate and enantioselectivity in the asymmetric hydrogenation of olefins. By mixing different monodentate ligands together in the reaction mixture, different metal ligand combinations can be formed (see Figure 10). In some cases the hetero combinations formed can outperform the homo combinations giving rise to faster and more selective reactions.

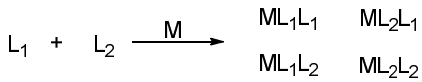


Figure 10: Schematic representation of the metal ligand combinations formed when using a mixed ligand approach.

We decided to examine if the same observations could be made in the hydrogenation of aryl ketones. To see if the mixed ligand approach would have the same positive outcome as in the olefin hydrogenations we preformed a dimeric precatalyst (*vide infra*) containing one ligand (*R*)-**L7** and one (*R,R*)-DACH molecule per ruthenium center. This dimeric complex was used in the hydrogenation of acetophenone with extra ligand added to it.

Table 4: Results of adding an achiral phosphine ligand.

	Added PPh_3[a]	**Added DiMePip[a]**	**Conversion[b]**	**Ee[c] (%)**
1	0	1	full (16 h)	97
2	1	0	full (13 h)	52
3	2	0	full (8 h)	28

Substrate **2.10a** was hydrogenated in *i*PrOH under 25 bar H_2 pressure, using 1 mol% of KO*t*Bu and 0.05 mol% "$[RuCl_2$(**L7**)$(DACH)]_2$ " to which the given amount of PPh_3 and/or DiMePip were added prior to pressurizing the autoclave. a) Given number is number of equivalents wrt the amount of ruthenium. b) Conversions were monitored using the Endeavor parallel autoclave gas uptake graph c) ee was determined via chiral GC.

As can be seen in Table 4 the results were not the same as for the olefin hydrogenation. The dimeric complex performed equally well, compared to the previous results, if an extra equivalent of **L7** was added to the reaction mixture. Upon adding triphenylphosphine to the reaction mixture the reaction rate was enhanced. Two equivalents of PPh_3 added to the reaction mixture made the reaction time drop by 8 h. The product, however, had a much lower ee compared to the product of the reaction without added triphenylphosphine. It looks like the complex with the highest catalytic activity bears achiral triphenylphosphine ligands, which lead to a higher reaction rate but also less selectivity.

2.6 Characterization of the complex

When analyzing the complex we used for the hydrogenation experiments containing two phosphoramidites and a diamine ligand per ruthenium center, the first observations we made were the two absorptions in the ^{31}P-NMR spectrum (Figure 11). The chemical shift of the two absorptions corresponded nicely to that of free ligand (147 ppm) and to that of a phosphoramidite coordinated to ruthenium (173 ppm).[27;28] This observation was somewhat puzzling since we expected only one absorption, namely that of bound phosphoramidite ligand.

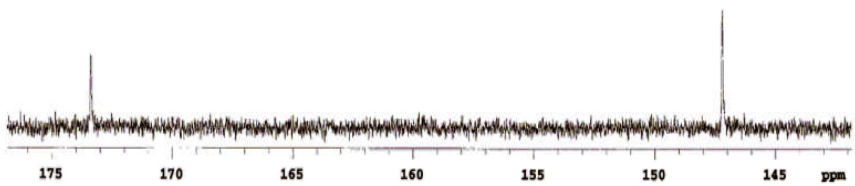
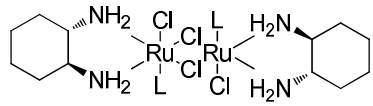


Figure 11: ^{31}P-NMR ($CDCl_3$) of the complex made with two PPA's per Ru center.

The mass spectrum that was recorded from the complex did not show the expected mass of 1104 $[M\text{-}Cl]^+$ corresponding to the ruthenium complex containing two phosphoramidite ligands, a diamine and one chloro atom. Instead a peak was found at a much higher m/z ratio of 1389. The isotope pattern of the

spectrum suggested the presence of a dimeric ruthenium complex (**2.21**) containing only one phosphoramidite ligand per ruthenium center in combination with one diamine and two chloride ions.



2.21

Figure 12: Dimeric complex based upon the mass spectrum results.
With **L** = monodentate phosphoramidite ligand.

When we tried to preprepare the complex with only one ligand per ruthenium center instead of two, a complex was obtained which was still an active catalyst (see Table 5, entry 1). As can be seen in Figure 13 the ^{31}P-NMR of this complex still showed the presence of some free phosphoramidite ligand in solution, indicating an indeed very weak coordination of the phosphoramidite to the ruthenium. It was previously found in DSM, that after an overnight washing step with hexane after the complex preparation, no phosphoramidite was found to be present in the complex.[29] This also indicates weak ligand coordination to the ruthenium center.

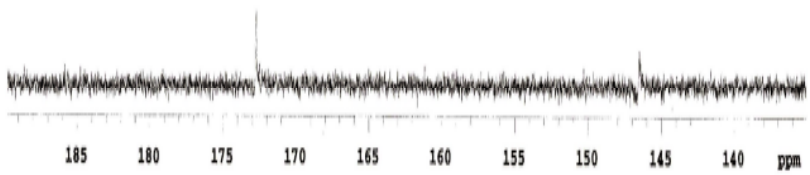
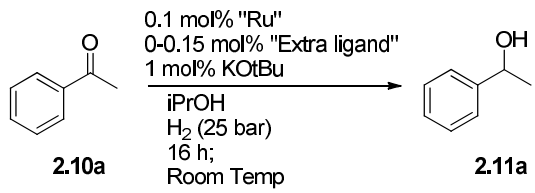


Figure 13: ^{31}P-NMR ($CDCl_3$) of complex made with one equivalent PPA per Ru center.

The complex obtained with the adjusted preparation method of adding only one phosphoramidite per ruthenium proved to be able to get the hydrogenation reaction to completion, although with lower selectivity as can be seen from the result in entry 1 in Table 5.

Table 5: Adding extra ligand to the preformed catalyst.



	"catalyst"[a]	Extra ligand[b]	Conversion[c] (%)	Ee[d] (%)
1	$RuCl_2$(L)(DACH)	0	100 (18h)	75
2	$RuCl_2$(L)(DACH)	0.5 (DiMePip)	100 (17h)	90
3	$RuCl_2$(L)(DACH)	1.0 (DiMePip)	100 (16h)	97
4	$RuCl_2$(L)(DACH)	1.5 (DiMePip)	100 (14h)	89
5	$RuCl_2$(L)(DACH)	0.5 (PPh_3)	50 (24h)	31
6	$RuCl_2$(L)(DACH)	1.0 (PPh_3)	50 (24h)	38

Substrate **2.10a** was hydrogenated in *i*PrOH under 25 bar H_2 pressure, using 1 mol% of base and 0.1 mol% "Ru" to which the given amount of extra ligand was added prior to pressurizing the autoclave. a) The catalyst was added as 0.05 mol% dimer; L = (*R*)-DiMePip; DACH = (*R*,*R*)-DACH. b) given number is number of equivalents wrt the amount of ruthenium. c) Conversions were monitored using the Endeavor parallel autoclave gas uptake graph. d) ee was determined via chiral GC.

Adding one equivalent of ligand to the reaction mixture just before placing it in the Endeavor proved to work in restoring the selectivity to the original. Adding more than one extra equivalent led to an, although faster, less selective reaction again. Surprisingly adding PPh_3 in this case did not speed up the reaction, as was the case when the catalyst was preprepared with two ligands per metal center, but slowed it down significantly.

Since the mass spectrum did not give a conclusive results about the nature of the complex we decided to try to grow crystals for X-ray analysis to get a better insight into how the different ligands are arranged around the metal center. This proved to be a difficult task. In the end we were able to grow some crystals which were suitable for X-Ray analysis. To our surprise however, the X-Ray structure showed no phosphoramidites were present at all bound to the metal center but only the diamine was present together with one of the cymene

molecules. Not finding any phosphoramidite in the crystal structure was very surprising to us but does relate to the previously described findings done at DSM where no phosphoramidite was found in the complex after a prolonged washing step. Since the growing of the crystals took several days this could also been seen as such a washing.

Experimental results, however, still show that the presence of the phosphoramidites play a crucial role in the selectivity of the reaction. As is clearly shown in Table 5, adding extra ligand to the reaction mixture is necessary in order to reach the optimal selectivity. This suggests that during the catalytic cycle the ligands definitely play a role in the reaction and the selectivity of the reaction is not only determined by the diamine. This is also suggested by the different results obtained when different phosphoramidites are being used (see Table 1). Despite the fact that the different analyses done on the complex, NMR, mass and X-Ray, do not clearly show the presence of phosphoramidite ligands around the metal, we think it is safe to say they are present around the ruthenium center during the hydrogenation reaction.

2.7 Conclusions

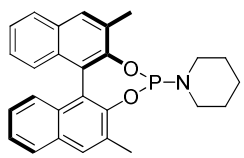
It was found that phosphoramidite ligands can be used as ligands in the asymmetric hydrogenation of aromatic ketones. When 3,3'-dimethyl PipPhos is used in combination with DACH or DPEN, the ruthenium catalyzed hydrogenations go to full conversion and provide the product with over 95% ee for a range of acetophenone derivatives. The exact structure of the catalyst turned out to be harder to prove than expected but all the results of the hydrogenation experiments point towards a catalyst which carries two phosphoramidite ligands per ruthenium in the catalytic cycle.

2.8 Experimental

General remarks.

Starting materials were purchased from Aldrich, Alfa Aesar or Acros and used as received unless stated otherwise. $[RuCl_2(cymene)]_2$ was bought from Strem and used as received. (*R*)-3,3'-dimethyl bis-β-naphthol was kindly provided by DSM. All solvents were reagent grade and, if necessary, dried and distilled prior to use. Column chromatography was performed on silica gel (Aldrich 60, 230-400 mesh). TLC was performed on silica gel 60/Kieselguhr $F_{254.}$ ^1H and ^{13}C NMR spectra were recorded on a Varian AMX400 (399.93 MHz for ^1H, 100.59 MHz for ^{13}C and 161.9 MHz (^1H-decoupled) for ^{31}P) spectrometer or a Mercury-200 (199.99 MHz for ^1H and 50.3 MHz for ^{13}C). Mass spectra (HRMS) were performed on a Jeol JMS-600H.

Synthesis of (L7) (R)-1-(2,6-dimethyl-3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)piperidine; ((*R*)-DiMePipPhos)



(*R*)-3,3'-Dimethyl-bis-β-naphthol, (2 g. 6.4 mmol), was dissolved in 10 ml of PCl_3. After heating overnight at reflux the excess of PCl_3 was distilled of *in vacuo*. The residual solid was subjected to azeotropic distillation with toluene (2 x 10 ml), affording the crude chlorophosphite.

The chlorophosphite was redissolved in toluene (10 ml). To the solution 2 ml Et_3N (14.1 mmol, 2.2 equiv) was added, followed by 0.7 ml piperidine (7 mmol, 1.1 equiv) in small portions. After two hours of stirring 10 ml MTBE was added. The resulting suspension was filtered over Celite and concentrated. The residue was purified over SiO_2 using pentane : ethyl acetate (9:1) as eluent, affording 1.9 g (4.4 mmol, 68%) of the pure solid white product.

^1H (400 MHz, $CDCl_3$) δ (ppm) 7.79-7.71 (m, 4H), 7.34-7.11 (m, 6H), 2.94-2.85 (m, 4H), 2.53 (d, *J* = 29 Hz, 6H), 1.51-1.47 (m, 2H), 1.39-1.28 (m, 4H); ^{31}P (161 MHz, $CDCl_3$) δ (ppm) 143.0.

A typical precatalyst synthesis: Synthesis of $[RuCl_2((R)\text{-}3\text{-}3'\text{-}DiMe\text{-}PipPhos)_2((R,R)\text{-}DACH)]$

A Schlenk flask was flame-dried and 62 mg $[RuCl_2(cymene)]_2$ (0.1 mmol) and 171 mg (*R*)-3-3'-Dimethyl-PipPhos (0.4 mmol, 4 equiv.) were added. The Schlenk flask was degassed by three cycles of vacuum/N_2 and then put under N_2 and the solids were dissolved in 5 ml DMF. This mixture was heated for 3 h at 90 ^oC and subsequently the mixture was cooled to room temperature and 23 mg (*R,R*)-DACH (0.2 mmol, 2 equiv.)

was added. The solution was stirred overnight after which the DMF was evaporated under reduced pressure. The resulting solid mass was subjected to azeotropic distillation with toluene (2 x 5 ml) and washed twice with 5 ml hexane. The obtained solid was used in hydrogenation reactions without further purification.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 (d, 1H, J = 36 Hz), 7.90-7.70 (m, 6H), 7.39-7.11 (m, 13H), 5.87 (dd, 2H, J = 22 Hz, J = 120 Hz), 5.85 (d, 2H, J = 22 Hz), 2.95-2.51 (m, 15H), 2.37-2.36 (m, 6H) 1.99-0.79 (m, 50H). ^{31}P-NMR (161 MHz, $CDCl_3$): δ (ppm): 173, 147.

A typical precatalyst synthesis: Synthesis of $[RuCl_2(DiMePip)(DACH)]_2$
A Schlenk flask was flame-dried and 62 mg $[RuCl_2(cymene)]_2$ (0.1 mmol) and 85 mg (*R*)-3,3'-dimethyl PipPhos (0.2 mmol, 2 equiv.) were added. The Schlenk flask was degassed by three cycles of vacuum/N_2 and then put under N_2. The solids were dissolved in 5 ml DMF. This mixture was heated for 3 h at 90 ^{o}C. Subsequently the mixture was cooled down to room temperature and 23 mg (*R*,*R*)-DACH (0.2 mmol, 2 equiv.) was added. The solution was stirred overnight after which the DMF was evaporated under reduced pressure. The resulting solid mass was subjected to azeotropic distillation with toluene (2 x 5 ml) and washed twice with 5 ml hexane. The obtained solid was used in hydrogenation reactions without further purification up on adding an extra equivalent of ligand per ruthenium center.
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.05 (d, 1H, J = 36 Hz), 7.90-7.70 (m, 6H), 7.39-7.11 (m, 13H), 5.87 (dd, 2H, J = 22 Hz, J = 120 Hz), 5.85 (d, 2H, J = 22 Hz), 2.95-2.51 (m, 15H), 2.37-2.36 (m, 6H) 1.99-0.79 (m, 50H). ^{31}P-NMR (161 MHz, $CDCl_3$): δ (ppm): 173 (major), 147 (minor).

A typical procedure for the hydrogenation of acetophenones using $[RuCl_2(L)_2(diamine)]$
To a glass liner for the Endeavor, 2 mmol of substrate and 2 μmol of preformed catalyst (0.1 mol%) were added. The compounds were dissolved in 4 ml *i*-PrOH. To the resulting solution, 10 μl of a 1 M solution of KO*t*Bu in *i*-PrOH was added just prior to inserting the liner into the Endeavor parallel autoclave. After the Endeavour was tightly closed, the system was purged 3 times with 5 bar N_2 and 3 times with 5 bar H_2, while stirring at 400 rpm. After the six purging cycles the stirring speed was increased to 750 rpm and a pressure of 25 bar H_2 was applied. This situation was kept for 24 h, subsequently the Endeavor was carefully vented and opened and the glass liner was taken out. From the reaction mixture a sample was taken and run over a silica plug to prepare a GC sample.

A typical procedure for the hydrogenation of acetophenones using $[RuCl_2(L)(diamine)]_2$
To a glass liner for the Endeavor, 2 mmol of substrate was added. To the substrate 1 μmol of preformed complex (0.05 mol%) and 2 μmol ligand (0.1 mol%) were added. Everything was dissolved in 4 ml *i*-PrOH. Just prior to inserting the liner into the Endeavor 10 μl of a 1 M solution of KO*t*Bu in *i*-PrOH was added to the mixture. After the Endeavour was tightly closed the system was purged 3 times with 5 bar N_2 and 3 times with 5 bar H_2, while stirring at 400 rpm. After the six purging cycles the stirring speed was increased to 750 rpm and a pressure of 25 bar H_2 was introduced. This situation was kept for 24 h, subsequently the Endeavor was carefully vented and the glass liner taken out. From the reaction mixture a sample was taken and run over a silica plug to prepare a GC sample.

All alcohols described below were obtained after a hydrogenation using a $[RuCl_2(L)(diamine)]_2$ type catalyst in which L = (*R*)-3-3'dimethyl PipPhos and the diamine (*R,R*)-DACH. To the reaction mixture one equivalent of (*R*)-3-3'-dimethyl PipPhos per ruthenium center was added.

(*S*)-1-phenyl ethanol (2.11a)[16] was obtained as a colorless oil (full conversion, 92% isolated yield, 97% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.37-7.26 (m, 5H), 4.85 (q, *J* = 6.4 Hz, 1H), 2.49 (s, 1H), 1.48 (d, *J* = 6.4 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 144, 127, 126, 124, 68, 23. $[\alpha]_D = -48.9$ (c 1.0, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (isotherm); $T_S = 7.5$ min, $T_R = 7.2$ min.

(*S*)-1-(2-methyl phenyl) ethanol (2.11b)[16] was obtained as a light yellow oil (full conversion, 96% isolated yield, 97% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.52 (d, *J* = 7.9 Hz, 1H), 7.27-7.02 (m, 3H), 5.17 (q, *J* = 6.4 Hz, 1H), 2.35 (s, 3H), 1.76 (bs, 1H), 1.47 (d, *J* = 6.4, 3H Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 144, 134, 130, 127, 126, 124, 67, 24, 19. $[\alpha]_D = -62.8$ (c 1.09, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (25 min) – (10 ^oC / min) → 180 ^oC. $T_S = 13.6$ min; $T_R = 12.0$ min.

(*S*)-1-(2-methoxyphenyl) ethanol (2.11d)[30] was obtained as a yellow oil (full conversion, 96% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.39-7.19 (m, 2H), 7.00-6.83 (m, 2H), 5.09 (quin, *J* = 6.4 Hz, 1H), 3.87 (s, 3H), 2.59 (bs, 1H), 1.51 (d, *J* = 6.4 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 156, 134, 128, 126, 121, 110, 67, 55, 23. $[\alpha]_D = -18.9$ (c 0.98, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x

250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (isotherm); $T_S = 20.1$ min, $T_R = 19.2$ min.

(*S*)-1-(4-methoxyphenyl) ethanol (2.11e)[31] was obtained as a brown oil (full conversion, 97% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.32-7.26 (m, 2H), 6.92-6.86 (m, 2H), 4.85 (q, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 1.79 (bs, 1H), 1.48 (d, *J* = 6.5 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 158, 138, 127, 114, 70, 55, 25. $[\alpha]_D = -52.1$ (c 1.08, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (isotherm); $T_S = 11.9$ min, $T_R = 11.5$ min.

(*S*)-1-(4-chlorophenyl) ethanol (2.11f)[16] was obtained as a yellow oil (full conversion, 95% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.31-7.26 (m, 4H), 4.88 (q, *J* = 6.8 Hz, 1H), 1.86 (bs, 1H), 1.47 (d, *J* = 6.5 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 144, 133, 129, 127, 70, 25. $[\alpha]_D = -47.9$ (c 0.98, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (isotherm); $T_S = 15.8$ min, $T_R = 15.3$ min.

(*S*)-1-(3-bromophenyl) ethanol (2.11g)[32] was obtained as a brown oil (full conversion, 65% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.58 (s, 1H), 7.42-7.37 (m, 1H), 7.32-7.21 (m, 2H), 4.83 (q, *J* = 6.5 Hz, 1H), 1.86 (bs, 1H), 1.49 (d, *J* = 6.5 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 148, 131, 130, 129, 124, 123, 70, 25. $[\alpha]_D = -20.8$ (c = 1.03, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (isotherm); $T_S = 28.3$ min, $T_R = 17.2$ min.

(*S*)-1-(3-chlorophenyl) ethanol (2.11h)[16] was obtained as a brown oil (full conversion, 83% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.39 (s, 1H), 7.23-7.19 (m, 3H), 4.86 (q, *J* = 6.5 Hz, 1H), 1.83 (bs, 1H), 1.49 (d, *J* = 6.5 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 148, 130, 128, 126, 124, 70, 25. $[\alpha]_D = -36.2$ (c 1.01, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (isotherm); $T_S = 16.4$ min, $T_R = 14.9$ min.

(*S*)-1-(3,5-di(trisfluoromethyl)phenyl) ethanol (2.11j)[33] was obtained as a colorless oil (full conversion, 95% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.85 (s, 2H), 7.79 (s, 1H), 5.05 (q, *J* = 6.6 Hz, 1H), 2.03 (bs, 1H), 1.55 (d, *J* = 6.6 Hz, 3H). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (isotherm); $T_S = 5.8$ min, $T_R = 6.5$ min.

(*S*)-1-phenyl propanol (2.11k)[16] was obtained as a dark yellow oil (full conversion, 91% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.37-7.20 (m, 5H), 4.59 (t, *J* = 7.4 Hz, 1H), 1.86-1.68 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 144, 128, 127, 126, 76, 32, 10. $[\alpha]_D$ = −42.4 (c 0.93, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det}$ = 250 ^{o}C; T_{start} = 110 ^{o}C (isotherm); T_S = 12.1 min, T_R = 11.5 min.

(*S*)-1-phenyl butanol (2.11n)[34] was obtained as a white solid (full conversion, 96% isolated yield, 93% ee), mp = 45.9 - 46.1 ^{o}C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.41-7.19 (m, 5H), 4.68 (t, *J* = 5.9 Hz, 1H), 1.87-1.21 (m, 5H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 128, 127, 126, 54, 41, 19, 14. $[\alpha]_D$ = −44.2 (c 0.99, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det}$ = 250 ^{o}C; T_{start} = 120 ^{o}C (2 min) - (1 ^{o}C / min) - 180 ^{o}C; T_S = 12.5 min, T_R = 11.5 min.

(*R*)-Phenyl-o-tolylcarbinol (2.11q) Conversion (100%) and ee (15%) were determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det}$ = 250 ^{o}C; T_{start} = 160 ^{o}C (60 min) - (1 ^{o}C / min) → 170 ^{o}C. T_S = 61.1 min; T_R = 63.5 min.

(*S*)-1-naphthyl ethanol (2.14)[16] was obtained as a green oil (full conversion, 93% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 8.19-8.11 (m, 1H), 7.91-7.83 (m, 1H), 7.79 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.59-7.42 (m, 3H), 5.78-5.59 (m, 1H), 1.99 (bs, 1H), 1.69 (d, *J* = 6.5 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 142, 134, 130, 129, 128, 126, 125, 123, 122, 67, 24. $[\alpha]_D$ = 71.6 (c 0.96, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det}$ = 250 ^{o}C; T_{start} = 140 ^{o}C (isotherm); T_S = 62.2 min, T_R = 59.9 min.

(*S*)-2-naphthyl ethanol (2.15)[31] was obtained as a white solid (full conversion, 94% ee), mp = 70.1 - 70.9 ^{o}C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.82-7.79 (m, 3H), 7.52-7.41 (m, 3H), 7.26 (s, 1H), 5.07 (q, *J* = 6.5 Hz, 1H), 1.92 (bs, 1H), 1.59 (d, *J* = 6.5 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm): 143, 129, 128, 128, 127, 126, 124, 70, 25. $[\alpha]_D$ = −47.8 (c 1.12, $CHCl_3$). Ee was determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det}$ = 250 ^{o}C; T_{start} = 120 ^{o}C (2 min) - (1 ^{o}C / min) – 180 ^{o}C; T_S = 31.1 min, T_R = 30.5 min.

(*S*)-3,3-dimethyl butan-2-ol (2.18) Conversion (50%) and ee (41%) were determined using a GTA column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 70\ ^oC$ (35 min) – (10 ^oC / min) → 170 ^oC. $T_S = 16.5$ min; $T_R = 16.9$ min.

2-hexanol (2.19) Conversion (100%) and ee (<5%) were determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 80\ ^oC$ (12 min) – (10 ^oC / min) → 170 ^oC. $T_S = 5.3$ min; $T_R = 7.5$ min.

Cyclohexenol (2.20)[35] Conversion (85%) and ee (<5%) were determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (12 min) – (1 ^oC / min) → 170 ^oC. $T_S = 28.6$ min; $T_R = 29.1$ min.

2.9 References

[1.] M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J.Am.Chem.Soc.* **1988,** *110* 629-631.

[2.] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J.Am.Chem.Soc.* **1987,** *109* 5856-5858.

[3.] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J.Am.Chem.Soc.* **1995,** *117* 2675-2676.

[4.] T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J.Am.Chem.Soc.* **1995,** *117* 10417-10418.

[5.] R. Noyori, T. Ohkuma, *Angew.Chem.Int.Ed.* **2001,** *40* 40-73.

[6.] H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew.Chem.Int.Ed.* **1998,** *37* 1703-1707.

[7.] T. Ohkuma, R. Noyori, in *Handbook of Homogeneous Hydrogenation* ,*Vol. III*, (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 1105-1163.

[8.] W. Tang, X. Zhang, *Chem.Rev.* **2003,** *103* 3029-3069.

[9.] T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J.Am.Chem.Soc.* **2005,** *127* 8288-8289.

[10.] R. Abbel, K. Abdur-Rashid, M. Faatz, A. Hadzovic, A. J. Lough, R. H. Morris, *J.Am.Chem.Soc.* **2005,** *127* 1870-1882.

[11.] T. Leyssens, D. Peeters, J. N. Harvey, *Organometallics* **2008,** *27* 1514-1523.

[12.] C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J.Am.Chem.Soc.* **2003,** *125* 13490-13503.

[13.] M. Zimmer-De Iuliis, R. H. Morris, *J.Am.Chem.Soc.* **2009,** *131* 11263-11269.

[14.] R. J. Hamilton, S. H. Bergens, *J.Am.Chem.Soc.* **2008,** *130* 11979-11987.

[15.] Y. Xu, N. W. Alcock, G. C. Clarkson, G. Docherty, G. Woodward, M. Wills, *Org.Lett.* **2004,** *6* 4105-4107.

[16.] Y. Xu, G. C. Clarkson, G. Docherty, C. L. North, G. Woodward, M. Wills, *J.Org.Chem.* **2005,** *70* 8079-8087.

[17.] Y. J. Xu, G. F. Docherty, G. Woodward, M. Wills, *Tetrahedron: Asymmetry* **2006,** *17* 2925-2929.

[18.] Q. Jing, X. Zhang, J. Sun, K. Ding, *Adv.Synth.Catal.* **2005,** *347* 1193-1197.

[19.] M. Jahjah, R. Jahjah, S. Pellet-Rostaing, M. Lemaire, *Tetrahedron: Asymmetry* **2007,** *18* 1224-1232.

[20.] A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc.Chem.Res.* **2007,** *40* 1267-1277.

[21.] L. Van Boxtel, Report of internship done at DSM Geleen 2001.

[22.] R. Hoen, M. van den Berg, H. Bernsmann, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *Org.Lett.* **2004,** *6* 1433-1436.

[23.] M. T. Reetz, *Chim.Oggi* **2003,** *21* 5-8.

[24.] M. T. Reetz, *Angew.Chem.Int.Ed.* **2008,** *47* 2556-2588.

[25.] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew.Chem.Int.Ed.* **2005,** *44* 4209-4212.

[26.] N. Mrsic, L. Lefort, J. A. F. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv.Synth.Catal.* **2008,** *350* 1081-1089.

[27.] S. Costin, S. L. Sedinkin, E. B. Bauer, *Tetrahedron Lett.* **2009,** *50* 922-925.

[28.] S. Costin, N. P. Rath, E. B. Bauer, *Inorg.Chim.Acta* **2009,** *362* 1935-1942.

[29.] Personal communication with J.A.F. Boogers and J.G. de Vries.

[30.] T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, R. Noyori, *J.Am.Chem.Soc.* **1998,** *120* 13529-13530.

[31.] H. L. Ngo, W. Lin, *J.Org.Chem* **2005,** *70* 1177-1187.

[32.] Y. Li, K. Ding, C. A. Sandoval, *Org.Lett.* **2009,** *11* 907-910.

[33.] D. M. Zhu, Y. Yang, J. D. Buynak, L. Hua, *Org.Biomol.Chem.* **2006,** *4* 2690-2695.

[34.] H. Ooka, N. Arai, K. Azuma, N. Kurono, T. Ohkuma, *J.Org.Chem.* **2008,** *73* 9084-9093.

[35.] B. J. Lussem, H. J. Gais, *J.Org.Chem.* **2004,** *69* 4041-4052.

Chapter 3

The use of SPO Ligands in the Ruthenium and Iridium Catalyzed Asymmetric Hydrogenation of Ketones

Abstract

In this chapter the use of an SPO ligand in the ruthenium and iridium catalyzed asymmetric hydrogenation of 2-methyl acetophenone is described. The best results were obtained when iridium was used as the metal in the presence of KOtBu, pyridine and the diamine DPEN. Under those conditions 91% conversion and 30 % ee were obtained. In the iridium/phosphoramidite based asymmetric hydrogenation of 2-methyl acetophenone 85 % conversion and 68 % ee were obtained when the hydrogenation was carried out in the presence of 1 phosphoramidite and 0.5 DPEN per metal center in the absence of KOtBu.

3.1.1 Secondary Phosphine Oxides

Secondary phosphine oxides (SPO's) are an interesting new class of ligands.[1-4] They are easily synthesized in racemic form by adding a Grignard reagent to a $RPCl_2$ substrate followed by acidic aqueous work-up.[5] The obtained substances are air and moisture stable for long periods of time.

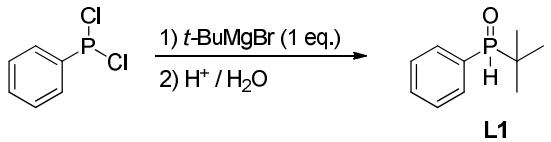


Figure 1: Racemic SPO's can be synthesized via a simple Grignard addition followed by aqueous acidic work-up.

The free SPO's exits in an equilibrium in which the phosphorus atom can easily switch between a pentavalent configuration (**L1$^{(V)}$**) and a trivalent one (**L1$^{(III)}$**) as depicted in Figure 2. Under ambient conditions this equilibrium lies far on the side of the pentavalent configuration. For catalysis, the trivalent configuration is however the most interesting one. When the SPO is in its trivalent configuration it has a free electron pair which can coordinate to a transition metal via σ-donation. This makes them an interesting class of ligand for transition metal catalysis.

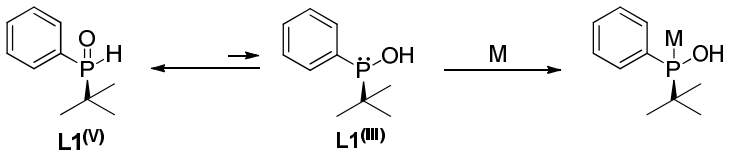
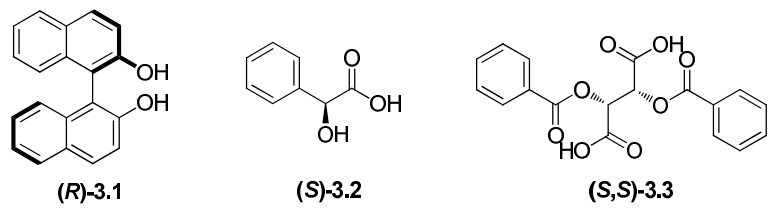


Figure 2: The two existing forms of SPO ligands (P(V) & P(III)) and its transition metal binding mode.

A major drawback of using SPO's in asymmetric catalysis, however, is the fact that there are no general methods available for synthesizing them in an asymmetric fashion. The main method for obtaining SPO's in enantiomerically pure form is by performing preparative chiral HPLC separations of a racemic mixture. This is, of course, not ideal since only small amounts of product can be

obtained that way. Also, the SPO ligands are not very soluble so only very dilute mixtures can be used in the resolution.

Another way of separating the two enantiomers is by selective crystallization. In this technique a resolving agent is added to a racemic mixture of the desired product. The resolving agent is chosen in such a way that only one of the two enantiomers of the product interacts with the resolving agent and forms a complex which crystallizes from the solution. Mostly the interactions between the resolving agents and the desired product are based on salt formation or hydrogen bonding. In 1999 Drabowicz *et al.*[6] found that they could separate a racemic mixture of *t*-butylphenylphosphine oxide via a resolution using (*R*)-bis-β-naphthol (**3.1**) or (*S*)-mandelic acid (**3.2**) as complexing agents. They were able to get a single enantiomer in excellent optical purity, however, the overall yield of these resolutions was low (28-52 %). Despite the low yield it seemed to be a good alternative for an earlier method[7;8] which involved conversion of the SPO into the corresponding thiophosphoric acid, followed by resolution with α-methylbenzylamine and finally desulfurization which is a lengthy and time consuming method. The method turned out, however, to be irreproducible.



(*R*)-3.1 (*S*)-3.2 (*S,S*)-3.3

Figure 3: Resolving agents (*R*)-bis-β-naphthol, (*S*)-mandelic acid and (*S,S*)-DBTA used for the separation SPO enantiomers.[6;9]

In 2009 Holt *et al.*[9] found a method to separate the two enantiomers of tert-butylphenylphosphine oxide by selective crystallization using the resolving agent DBTA (Dibenzoyl tartaric acid, **3.3**). They were able to obtain high yields and crystallize large batches of racemic ligand into single enantiomers with over 99% ee. This easy way of separating the two enantiomers makes them even more interesting as ligands in transition metal catalysis.

3.1.2 Previous use of SPO ligands in asymmetric catalysis

SPO ligands have been used successfully in several transition metal catalyzed reactions like hydroformylations,[10] the Pd catalyzed Stille coupling,[11] the Suzuki coupling,[12] the Ni catalyzed Grignard addition,[13] the Ru catalyzed arylation[14] and others[4].

Of course, SPO ligands have not only been used in non-asymmetric transformations. Various iridium and rhodium complexes of SPO ligands have been prepared and applied in several asymmetric hydrogenation reactions. In the iridium-catalyzed hydrogenation of imines[5] it was shown that the SPO ligand **L1** in combination with one equivalent of pyridine leads to full conversions and ee's up to 83% (Figure 4).

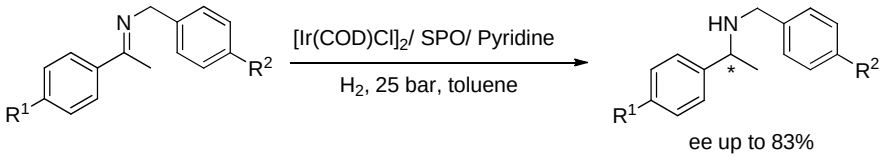


Figure 4: Iridium catalyzed asymmetric hydrogenation of imines using an SPO ligand.[5]

In the rhodium-catalyzed hydrogenation of several β-dehydroamino acids, itaconates, and carbamates the SPO ligands also proved to be suitable as chiral P-ligands.[15;16] Besides being used in asymmetric hydrogenations, Dai *et al.* have shown that SPO ligands can be used in palladium catalyzed allylic substitution reactions.[17] They were able to reach up to 80% ee in the allylic alkylation of 1,3-diphenyl prop-2-enyl acetate and dimethyl malonate as shown in Figure 5.

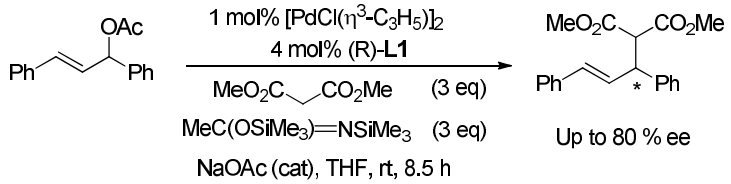


Figure 5: Pd-catalyzed allylic alkylation reaction using an SPO as chiral ligand as performed by Dai *et al.*.[17]

3.1.3 Previously obtained results obtained in Ir catalyzed hydrogenations of ketones

In the field of asymmetric hydrogenation, iridium is one of the preferred transition metals.[18] In particular, it is the metal of choice for imine hydrogenation.[19] In the field of ketone hydrogenation, however, iridium plays a less important role. Nevertheless, a few examples are known in which the iridium-catalyzed hydrogenation of ketones gives good results.
Le Roux *et al.*[20] obtained very good results when using a ferrocenyl based *P,S*-ligand. They were able to hydrogenate *para*-substituted acetophenones with selectivities up to 99 %.

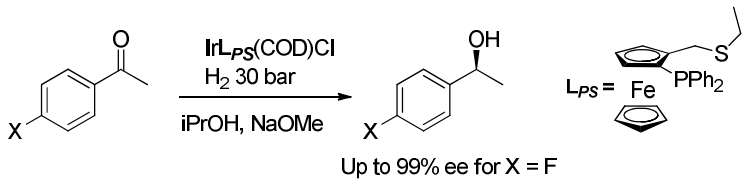


Figure 6: Iridium catalyzed asymmetric hydrogenation of acetophenones as described by Le Roux *et al.*[20].

Using Binap as a ligand in combination with bis(*o*-dimethylaminophenyl)phenylphosphine (**3.4**) Zhang *et al.*[21] were able to reach up to 84% ee in the asymmetric hydrogenation of acetophenones.

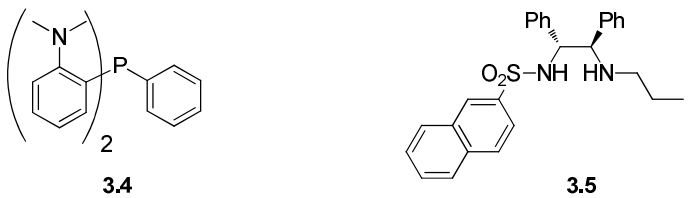


Figure 7: Bis(*o*-dimethylaminophenyl) phenylphosphine (**3.4**) as used by Zhang et al.[21] and the best performing diamine ligand **3.5** as used by the group of Wills[22] in the Ir(III) catalyzed asymmetric hydrogenation of acetophenones.

In 2009 the group of Wills reported the iridium(III) catalyzed asymmetric hydrogenation of acetophenones using chiral diamines as a ligand.[22] They were able to hydrogenate several acetophenones; reaching full conversion and

moderate ee's up to 85%. This was an improvement of the results of Ferrand *et al.* who, in 2002, did not surpass 68% ee in the hydrogenation of acetophenones using a similar diamine-Ir(I) catalyst.[23]

3.2 Goal

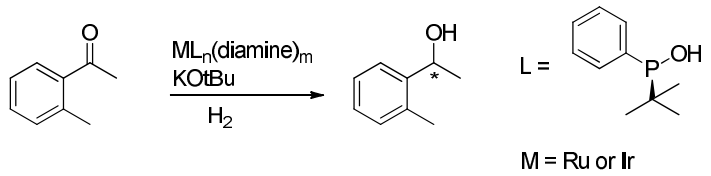
Monodentate phosphoramidites work very well in the asymmetric hydrogenation of acetophenones, as has been shown in chapter 2 of this thesis. We decided to investigate whether the use of an SPO ligand would also result in an active catalyst as has been the case in other hydrogenations.[5;15;16] As a starting point we took the ruthenium based catalyst as described in chapter two and simply replaced the phosphoramidite ligands with the SPO ligand. Since it is known that SPO ligands can perform very well as ligands for iridium we also investigated the performance of such a catalyst in the asymmetric hydrogenation of acetophenone.

3.3 Results

Tert-butyl(phenyl)phosphane oxide (**L1**) was synthesized in our labs and separated in its enantiomers by J. Holt via selective crystallization using (-)-**3.3**.[9] The ligand was liberated from its complexing salt by washing with an aqueous solution of 5% $NaHCO_3$ and extracting it with Et_2O resulting in the free ligand as a white powder. The free ligand was used in the hydrogenations described in this chapter.

3.3.1 SPO ligands in a ruthenium catalyst

To test the versatility of the SPO ligand **L1** in the aryl ketone hydrogenation we decided to replace the phosphoramidite ligands in the catalyst used in chapter 2 by SPO ligands. The catalysts used in the reactions were all formed in situ, in accordance with the methods described in Jiang *et al.*[5]

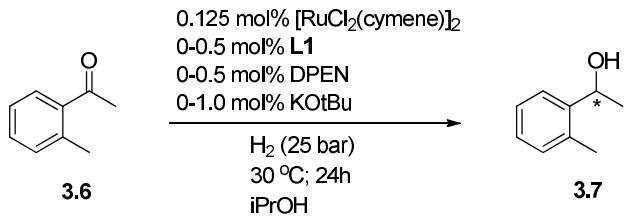


The results of these ruthenium/**L1** catalyzed hydrogenations are depicted in Table 1.

From the experiments it became clear that addition of a base is necessary to activate the complex. Without a base (entries 1, 4 and 8) present in the reaction mixture no reaction takes place. Also it is obvious that the presence of the diamine is crucial in order to get any enantioselectivity. Without diamine present (entries 1, 8 and 9) only racemic product was found, if any. The best results were obtained when both a base and diamine were used. Using only **L1** as phosphorus ligand in the reaction (entries 1-4) did not lead to very good results. After 24 hours only 20% conversion was observed and the product had a negligible ee (entry 2). Pre-forming the catalyst, as was done for the hydrogenations described in chapter 2, did give some improvement (entry 3). The conversion after 24

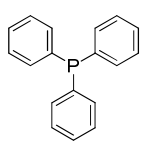
hours went up to 52% although unfortunately the ee was still very poor reaching a value of only 14%.

Table 1: Results obtained in the ruthenium-catalyzed asymmetric hydrogenation of **3.6** using SPO ligand **L1**.

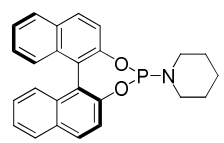


	Added P-Ligand	(*S,S*)-DPEN	Additive	Conversion[d] (%)	ee[d] (%)
1	-	no	no	0	nd
2	-	yes	KO*t*Bu	20	6
3[a]	-	yes	KO*t*Bu	52	14
4[a]	-	yes	no	0	nd
5	**L2**[b]	yes	KO*t*Bu	60	rac (0)
6	**L2**[b]	yes	KO*t*Bu	65	7
7	**L2**[b]	yes	KO*t*Bu	56	9
8	(*S*)-**L3**[c]	no	no	0	nd
9	(*S*)- **L3**[c]	no	KO*t*Bu	14	rac (1)
10	(*S*)- **L3**[b]	yes	KO*t*Bu	76	17

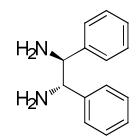
Unless stated otherwise reactions were carried out in the Endeavor with (*S*)-**L1,** $[RuCl_2(cymene)]_2$ and (*S,S*)-DPEN. 2 mmol **3.6** (4/1/2/800) in 4 mL *i*PrOH. 25 bar H_2 at 30 °C for 24 h. a) catalyst was pre-prepared via the M:L = 1:2 method as described in chapter 2. b) **L1**/"extra ligand/DPEN/"Ru" = 2/2/2/1 c) **L1**/"extra ligand"/DPEN/"Ru" = 4/4/0/1. d) Conversions and ee's were determined via chiral GC using a Chiralsil Dex-CB column (110 °C isotherm)



L2



(S)-**L3**



(S,S)-DPEN

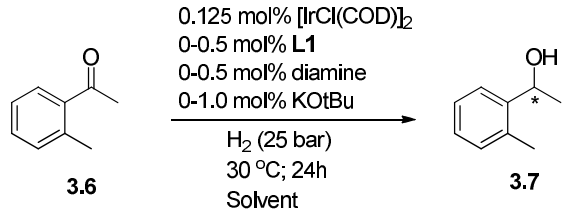
As described in previous chapters of this thesis (see chapters 1 and 2), employing a mixed ligand approach can sometimes lead to a great enhancement of the activity and selectivity of the used catalyst. Adding other ligands, like PPh_3 (**L2**) or PipPhos (**L3**) (entries 6 & 10) to the reaction mixture in this case gave some improvement. When **L2** was added (entry 6) the conversion went up to 65% but the ee went down again to a mere 7%. When the chiral phosphoramidite ligand **L3** was added (entry 10) the conversion increased to 76% and an ee of 17% was found. Although this is an improvement compared to the cases in which only SPO ligands are used, the enantioselectivity of the hydrogenation is still very poor.

3.3.2 SPO ligands in an iridium catalyst

The results of the ruthenium catalyzed hydrogenation of **3.6** using ligand **L1** did not give satisfactory results. From the work of X.-B. Jiang it is known that **L1** bound to iridium(I) can act as a hydrogenation catalyst for several olefins and imines.[5;15;16]

We decided to see if a change of metal from ruthenium to iridium would lead to a better acetophenone hydrogenation catalyst. The results of this screening can be found in Table 2.
As can be seen in Table 2 the results of the Ir/SPO catalyzed hydrogenation are slightly better than those for the Ru/SPO catalyzed hydrogenations. The best results were obtained when the reaction was performed in *i*PrOH or toluene in the presence of diamine and base (entries 4 and 6). In these cases over 90% conversion and up to 30% ee was obtained.

Table 2: Iridium/SPO catalyzed hydrogenation of **3.6**.



3.6 3.7

	Added Ligand	DPEN (*S,S*)	Additive	Solvent	Conversion[c] (%)	Ee[c] (%)
1	**L2**[a]	yes	KO*t*Bu	*i*PrOH	68	15
2	**L2**[b]	no	KO*t*Bu	*i*PrOH	15	11
3	-	yes	KO*t*Bu	*i*PrOH	26	22
4	-	yes	KO*t*Bu/ Pyridine	*i*PrOH	91	30
5	-	yes	KO*t*Bu/ Pyridine	DCM	17	9
6	-	yes	KO*t*Bu/ Pyridine	Toluene	90	29
7[d]	**L2**	yes	KO*t*Bu	*i*PrOH	100	8
8	*(S)*-**L3**[b]	no	KO*t*Bu	*i*PrOH	7	-2
9	*(S)*-**L3**[b]	no	-	*i*PrOH	30	7
10	*(S)*-**L3**[a]	yes	KO*t*Bu	*i*PrOH	100	7

Unless stated otherwise all reactions were carried out in the Endeavor with 2 mmol **3.6**, $[Ir(COD)Cl]_2$, (*S*)-**L1**, (*S,S*)-DPEN, KO*t*Bu and pyridine (800/1/4/2/8/2) in 4 mL total reaction volume, 25 bar H_2 at 30 °C for 24 h. a) Ir/**L1**/"extra ligand"/DPEN becomes 1/2/2/2; b) Ir/**L1**/"extra ligand"/DPEN becomes 1/4/4/0 c) ee's and conversions were determined via chiral GC using a Chiralsil Dex-CB column (110 °C isotherm); d) No SPO ligand was added so Ir/**L1**/"extra ligand"/DPEN (1/0/4/2).

All attempts to improve this result unfortunately failed. When **L3** was used as an additional ligand (entry 10), full conversion was reached but almost all enantioselectivity was lost in that case. Adding an achiral phosphine **L2** (entries 1 and 2) affected both conversion and ee in a negative way. One interesting observation that was made was a huge improvement in conversion when an equivalent of pyridine was added to the reaction, however, the selectivity, again, was not affected by this additive.

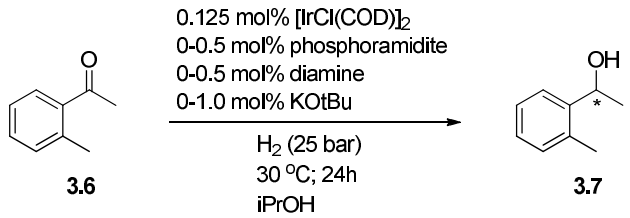
So despite the fact that the Ir/SPO based catalyst gives better results compared to the Ru/SPO based catalyst, the results are still nowhere near the results that were obtained when the phosphoramidite ligands were used.

3.3.3 Phosphoramidite ligands in an iridium catalyst

Since use of the SPO ligand **L1** did not lead to good results in the hydrogenation of acetophenones we decided to try the combination of phosphoramidites with iridium.
Previously it was found that in the iridium catalyzed asymmetric hydrogenation of enamides, it was possible to obtain good conversions and, more important, very good selectivities when only one phosphoramidite ligand per metal center was used.[24]

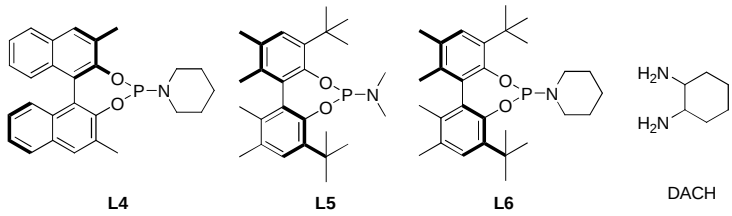
The use of phosphoramidite ligands in the iridium catalyzed hydrogenation of **3.6** gave better results compared to the catalyst in which SPO ligands were used but did not give the improvement we hoped for. We did, however, observe some striking differences in comparison to the iridium catalyzed hydrogenations in which the SPO ligand was used. What was not different was the need for the presence of a chiral diamine in order to obtain good ee's (entries 3, 4), also here it was observed that the use of a diamine in the reaction is necessary to obtain reasonable ee's (>15 %).

Table 3: Results obtained in the iridium/Phosphoramidite catalyzed asymmetric hydrogenation of **3.6**.



Entry	Phosphor amidite	Diamine	Amidite/ metal	Diamine/ metal	Conv.[c] (%)	Ee[c] (%)
1	L4	DPEN	2	1	28	68
2	**L4**	**DPEN**	**1**	**0.5**	**85**	**68**
3	L4	-	1	0	41	15
4	L4	-	2	0	12	9
5	L4	DPEN	1.5	0.5	18	34
6	-	DPEN	0	0.5	100	25
7	-	DPEN	0	1	95	31
8	-	DPEN	0	2	65	21
9	L4	DPEN	2	2	40	31
10[a]	L4	DPEN	1	0.5	33	20
11	L4	DACH	1	0.5	25	25
12[a]	L4	DACH	1	0.5	53	18
13	L5	-	1	0	0	Nd
14	L6	-	1	0	100	5
15	L5	-	1	0[b]	0	Nd
16	L6	-	1	0[b]	100	1

Reactions were carried out in the Endeavor with 2 mmol **3.6** and 0.125 mol% Ir with various amounts of phosphoramidite and diamine in 4 mL *i*PrOH. 25 bar H_2 at 30 °C for 24 h. In all cases the diamine had the same absolute configuration as the phosphoramidite ligand. The predominant configuration in the product was the opposite from the ligand and diamine i.e. *R*-ligand and *R,R*-diamine gave *S*-product. a) KO*t*Bu was added to the reaction mixture b) 1 equivalent of pyridine was added per metal centre. c) conversions and ee's were determined via chiral GC using a Chiralsil Dex-CB column (110 °C isotherm).



One of the most striking differences was the fact that no base was needed to get the reaction to proceed. On the contrary even, when base was added to the reaction mixture, the catalyst performed actually worse, compared to the base free one (entries 2, 11 and 10, 12). When DPEN was used as the diamine (entries 2 and 10) both conversion and ee dropped dramatically when base was added. When DACH was used as diamine, addition of base raised the conversion but the ee went down to a mere 18 %.

Another difference between the SPO and phosphoramidite catalysts is the fact that phosphoramidite ligands give the best results when only one phosphoramidite ligand per metal center is used. Also the number of diamine molecules per metal center has a lower optimum, at one diamine per two iridium centers. Noteworthy was the fact that the phosphoramidite ligands that previously were used successfully in an iridium catalyzed asymmetric hydrogenation with only one ligand per metal center (**L5** & **L6**) did not lead to any enantioselectivity.[24] Use of **L5** did not lead to any conversion whereas use of **L6** did result in full conversion but no selectivity whatsoever was observed. When **L4** was used in combination with 0.5 equivalents of DPEN per iridium dimer the best results were obtained leading to 85% conversion with an ee of 68%. This is a reasonably result for an iridium catalyzed hydrogenation of ketones,[20-23] but for the hydrogenation of ketones with phosphoramidite ligands the use of ruthenium is preferred. However, being able to perform the reaction without a base present, might make the catalyst interesting for ketones which cannot withstand basic conditions as they are being used in the typical ruthenium catalyzed hydrogenation reaction.[25-27]

3.4 Conclusions

The results discussed in this chapter show that, despite success in other types of hydrogenations, SPO ligand **L1** is not suitable for the use in the ruthenium or iridium catalyzed asymmetric hydrogenations of ketones. Although we were able to reach full conversion in the case where PipPhos was used as an additional ligand in the reaction, in none of the reactions ee's were obtained over 30%. Perhaps a screening of other SPO ligands might come up with a better suited ligand for this type of hydrogenation.
When, instead of an SPO ligand, a phosphoramidite ligand was used in the iridium catalyzed hydrogenation of **3.6**, somewhat better results were obtained. A conversion of 85% and an ee of 68% was a promising result but these results compare very poorly with the ones obtained with the Ru/phosphoramidite catalyst described in chapter 2. Noteworthy is the fact that in the Ir/phosphoramidite catalyst the use of only one bulky phosphoramidite ligand per metal center in the end gave the best result. Also no base was needed in this case in order to activate the catalyst. This in contrast to the catalysts used in Chapter 2 where a second phosphoramidite is needed and also the reaction does not proceed without the presence of a base, making the two procedures somewhat complementary.

3.5 Experimental

General experimental

For general experimental remarks see Chapter 2. The SPO ligand **L1** was synthesized by E.P. Schudde in our labs and separated by J. Holt into the **L1**-(-)-**3.3** complex with an ee >98%. **L2** was purchased from Aldrich, **L3** and **L4** were prepared as described in Chapter 2, **L5** and **L6** were kindly provided by N. Mršić. $[IrCl(COD)]_2$ was purchased from Strem, used as received and stored in the glove box.

Liberation of *tert*-butyl(phenyl)phosphine oxide (L1) from its resolving agent.[15]

L1-(-)-**3.3** complex, 595 mg (1.1 mmol), was washed with 5% $NaHCO_3$ for 15 minutes, after which the free (*S*)-**L1** ligand was extracted from the aqueous solution using diethyl

ether. After extraction the organic layer was dried over $NaSO_4$ and the solvent was removed *in vacuo* resulting in 145 mg (0.80 mmol, 73%) of free ligand as a white powder. Mp: 74-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38-7.67 (m, 5H), 6.98 (d, 1H, $^1J_{H-P}$ = 454.6 Hz), 1.08 (d, 9H, $^3J_{H-P}$ = 16.6 Hz). ^{31}P NMR (161 MHz, $CDCl_3$) δ (ppm) 47.3 (s). [α] = –32.5 (0.91)

General procedure for the ruthenium catalyzed asymmetric hydrogenation of *o*-methyl acetophenone

0.31 mg (0.5 μmol) $[RuCl_2(cymene)]_2$, 0.36 mg (2.0 μmol) (*S*)-**L1** and 0.21 mg (1 μmol) (*S*,*S*)-DPEN are weighted and together with 0.26 mL (2 mmol) **3.6** dissolved in 3.7 mL *i*PrOH till a final volume of 4 mL. As last component the base (KO*t*Bu) is added as a 1 M solution in *i*PrOH. The solution is put in the Endeavor where hydrogenation takes place at 30^o C, 25 bar H_2 and stirring at 750 rpm for 24 hours. After 24 hours the pressure was released and from the reaction mixture a small sample was run over a short silica plug and made into a sample for the GC. Conversion and ee were determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) with an isothermal program at 110 ^{o}C. T_S = 13.6 min T_R = 12.0 min

General procedure for the iridium catalyzed asymmetric hydrogenation of *o*-methyl acetophenone

0.34 mg (0.5 μmol) $[Ir(COD)Cl]_2$, 0.36 mg (2.0 μmol) (*S*)-**L1** and 0.21 mg (1 μmol) (*S*,*S*)-DPEN were weighed and together with 0.26 mL (2 mmol) **3.6** dissolved in 3.7 mL *i*PrOH till a final volume of 4 mL. As last component the base (KO*t*Bu) was added as a 1M solution in *i*PrOH. The solution was placed in the Endeavor where hydrogenation took place at 30^o C, 25 bar H_2 and stirring at 750 rpm for 24 hours. After 24 h the pressure was released and from the reaction mixture a small sample was run over a short silica plug and made into a sample for the GC. Conversion and ee were determined using a Chiralsil DEX-CB column (25m x 250 μm x 0.25 μm) with an isothermal program at 110 ^{o}C. T_S = 13.6 min T_R = 12.0

3.6 References

[1.] H. J. Klein, in *Methoden der Organischen Chemie (Houben-Weyl)*Ed.: M. Regitz), Georg Thieme Verlag, Stuttgart **1982**, p. p. 240.

[2.] K. Sasse, in *Methoden der Organischen Chemie (Houben-Weyl)*Ed.: E. Muller), Georg Thieme Verlag, Stuttgart **1963**, p. p. 193.

[3.] M. J. Gallagher, in *The Chemistry of the Organophosphorus Compounds ,Vol. II*, (Ed.: F. R. Hartley), Wiley, Chichester **1992**, p. p. 53.

[4.] L. Ackermann, *Synthesis* **2006,** 1557-1571.

[5.] X. B. Jiang, A. J. Minnaard, B. Hessen, B. L. Feringa, A. L. L. Duchateau, J. G. O. Andrien, J. A. F. Boogers, J. G. de Vries, *Org.Lett.* **2003,** *5* 1503-1506.

[6.] J. Drabowicz, P. Lyzwa, J. Omelanczuk, K. M. Pietrusiewicz, M. Mikolajczyk, *Tetrahedron: Asymmetry* **1999,** *10* 2757-2763.

[7.] R. K. Haynes, R. N. Freeman, C. R. Mitchell, S. C. Vonwiller, *J.Org.Chem.* **2002,** *59* 2919-2921.

[8.] R. Freeman, R. K. Haynes, W. A. Loughlin, C. Mitchell, J. V. Stokes, *Pure App.Chem.* **1993,** *65* 647-654.

[9.] J. Holt, A. M. Maj, E. P. Schudde, K. M. Pietrusiewicz, L. Sieron, W. Wieczorek, T. Jerphagnon, I. W. C. E. Arends, U. Hanefeld, A. J. Minnaard, *Synthesis-Stuttgart* **2009,** 2061-2065.

[10.] P. W. N. M. van Leeuwen, C. F. Roobeek, R. L. Wife, J. H. G. Frijns, *Journal of the Chemical Society-Chemical Communications* **1986,** 31-33.

[11.] C. Wolf, R. Lerebours, *Journal of organic chemistry* **2003,** *68* 7077-7084.

[12.] M. Miura, *Angewandte Chemie-International Edition* **2004,** *43* 2201-2203.

[13.] L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angewandte Chemie-International Edition* **2005,** *44* 7216-7219.

[14.] L. Ackermann, R. Born, J. H. Spatz, A. Althammer, C. J. Gschrei, *Pure and Applied Chemistry* **2006,** *78* 209-214.

[15.] Jiang, X.-B., University of Groningen, **2004**.

[16.] X. B. Jiang, M. van den Berg, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Tetrahedron: Asymmetry* **2004,** *15* 2223-2229.

[17.] W. M. Dai, K. K. Y. Yeung, W. H. Leung, R. K. Haynes, *Tetrahedron: Asymmetry* **2003,** *14* 2821-2826.

[18.] R. H. Crabtree, in *Handbook of Homogeneous Hydrogenation* ,*Vol. 1*, (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 31-44.

[19.] F. Spindler, H.-U. Blaser, in *Handbook of Homogeneous Hydrogenation* ,*Vol. III*, (Eds.: C. J. Elsevier, J. G. de Vries), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 1193-1214.

[20.] E. Le Roux, R. Malacea, E. Manoury, R. Poli, L. Gonsalvi, M. Peruzzini, *Adv.Synth.Catal.* **2007,** *349* 309-313.

[21.] X. Zhang, H. Kumobayashi, H. Takaya, *Tetrahedron: Asymmetry* **1994,** *5* 1179-1182.

[22.] J. E. D. Martins, M. Wills, *Tetrahedron* **2009,** *65* 5782-5786.

[23.] A. Ferrand, M. Bruno, M. L. Tommasino, M. Lemaire, *Tetrahedron: Asymmetry* **2002,** *13* 1379-1384.

[24.] F. Giacomina, A. Meetsma, L. Panella, L. Lefort, A. H. M. de Vries, J. G. de Vries, *Angew.Chem.Int.Ed.* **2007,** *46* 1497-1500.

[25.] T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J.Am.Chem.Soc.* **1995,** *117* 10417-10418.

[26.] T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J.Am.Chem.Soc.* **1995,** *117* 2675-2676.

[27.] T. Ohkuma, R. Noyori, in *Handbook of Homogeneous Hydrogenation* ,*Vol. III*, (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 1105-1163.

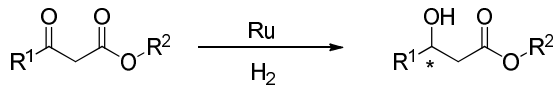
Chapter 4

Enantioselective Hydrogenation of α- and β-Ketoesters using Monodentate Phosphoramidite Ligands

Abstract

*In this chapter the ruthenium catalyzed enantioselective hydrogenation of α- and β-ketoesters using phosphoramidite ligands is discussed. It was shown that the hydrogenation of α-ketoesters proceeds to furnish essentially racemic product with such a catalytic system. However, the hydrogenation of several β-ketoesters was achieved reaching full conversions and up to 99% ee for a range of substrates when using the 8H-DiMePip (**L9**) ligand.*

4.1 Introduction



The asymmetric hydrogenation of ketoesters has been a topic of interest for many years. Since the discovery of the Ru-Binap catalyst by the group of Noyori[1;2], for the reduction of β-ketoesters in an enantioselective manner by means of hydrogenation, a lot of work has been done in this field. The groups of Genêt,[3] Weissensteiner,[4] Imamoto,[5] Knochel,[6] Zhang,[7] Reetz[8] and many others[9;10] successfully developed new ligands for this reaction. All these groups, however, designed synthetically laborious chiral bidentate phosphorus ligands, as shown in Figure 1, to be used in this transformation.

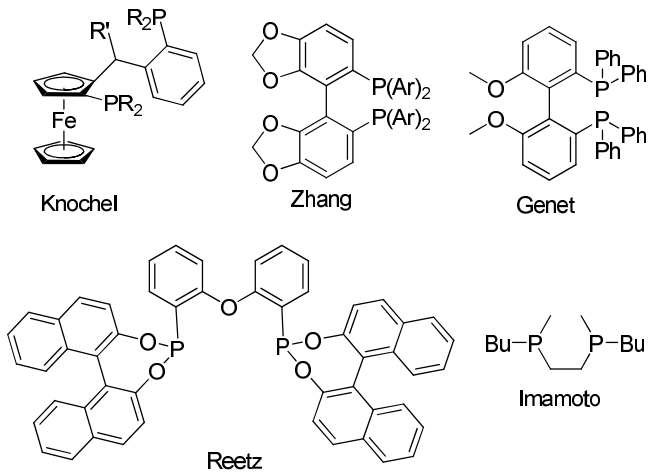
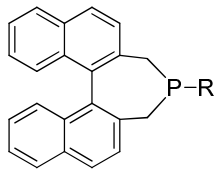


Figure 1: A selection of bidentate phosphorus ligands which have been used successfully in the asymmetric hydrogenation of β-ketoesters.

All previously mentioned ligands are able to induce excellent ee's and conversions in the asymmetric hydrogenations of several β-ketoesters. Despite numerous examples of the use of monodentate ligands in other types of asymmetric hydrogenations, such as the reduction of various olefins[11-14], imines[15;16] and acetophenone type ketones[17;18] up to date only one study has been reported on the asymmetric hydrogenations of β-ketoesters. The group of

Beller tested several phosphepine ligands (Figure 2), with different alkyl and aryl substituents on the phosphorus atom. They were able to reach full conversion and up to 95% ee for several β-ketoesters when the *p*-anisyl substituent was used.[19;20]



R = Et, *i*-Pr, *t*-Bu, Ph, *o*-anisyl, *m*-anisyl, *p*-anisyl, 3,4-(OMe)$_2$-Ph, *o*-F-Ph, *p*-F-Ph, 3,4,5-(F)$_3$-Ph, PhF$_5$, *p*-CF$_3$-Ph, *p*-NMe$_2$-Ph, 3,5-(Me)$_2$-Ph, 3,5-(*n*-Bu)$_2$-Ph, 2-Naphthyl

Figure 2: Monodentate phosphepine ligands as used by the group of Beller in the asymmetric hydrogenation of β-ketoesters

4.1.1 Use of β-ketoester hydrogenation in synthesis

The hydroxy-ester products of the asymmetric hydrogenation of β-ketoesters can be used in the synthesis of a wide variety of natural and biologically active compounds. A few examples of compounds that were synthesized, involving an asymmetric hydrogenation of a β-ketoester as a key step are given in Figure 3.

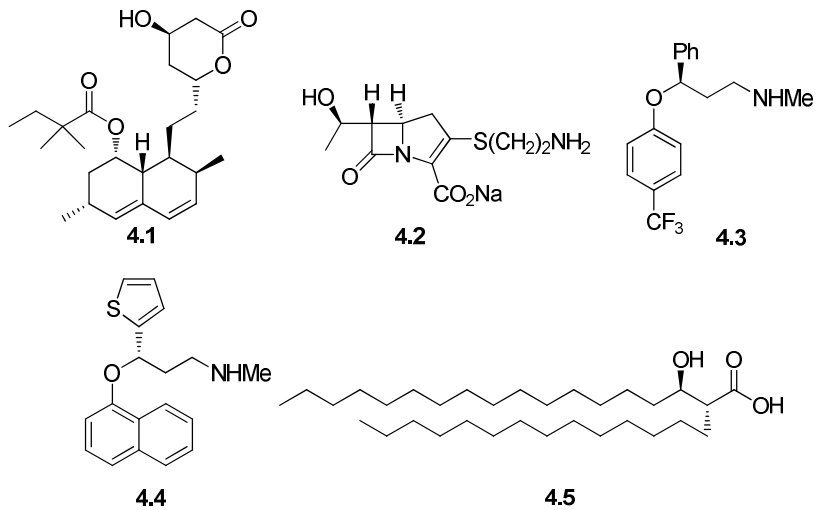


Figure 3: 4.1) Simvastatin; **4.2**) Carbapenem; **4.3**) Fluoxetin; **4.4**) Duloxetin; **4.5**) Corynomycolic acid.

A class of compounds that is very well accessible through β-ketoester hydrogenation is the class of statins.[21-23] But also biologically active and widely used compounds like the class of anti-biotics Carbapenem,[24] Fluoxetin (**4.3**), the active ingredient of Prozac® and Duloxetin (**4.4**), another anti-depressive, can have their stereogenic center introduced by means of hydrogenation of a β-ketoester.[3] The final example of a natural product given in Figure 3 which is accessible through the hydrogenation of a β-ketoester is corynomycolic acid (**4.5**) which is a fatty acid from the cell walls of *Corynebacterium sp.* and shows significant biological activity.[3]

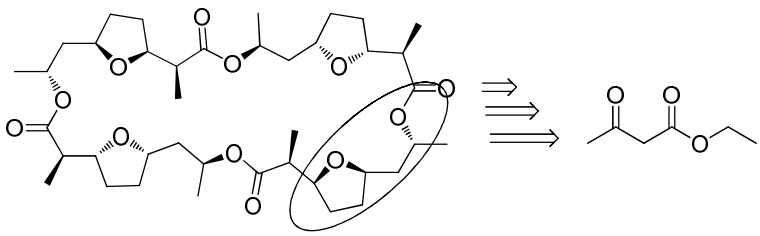


Figure 4: Nonactin, with in the encircled the the part of the molecule where the chiral center is introduced via an asymmetric hydrogenation of ethyl acetoacetate.[25]

Even in the synthesis of the complex macrocycle nonactin (Figure 4) the starting point was the hydrogenation of a β-ketoester as was shown by Coutable *et al.*.[25]

4.1.2 Mechanism of the hydrogenation of β-ketoesters

The catalytic cycle of the hydrogenation of β-ketoesters[26;27] (Figure 5) starts off from the ruthenium mono hydride complex (**I**), which is formed with the dichloride precursor by heterolytic splitting of a hydrogen molecule. The substrate is bound to the ruthenium in a bidentate fashion via both carbonyls (**II**), replacing one or more solvent molecules. The binding of the ester carbonyl group is vital for the reaction to proceed.
To make sure the substrate stays in close proximity of the Ru-center long enough for the reaction to take place it needs an anchoring group in addition to the carbonyl that is to be reduced. The carbonyl group of the ester acts as such an anchoring group ensuring the reaction is able to proceed.

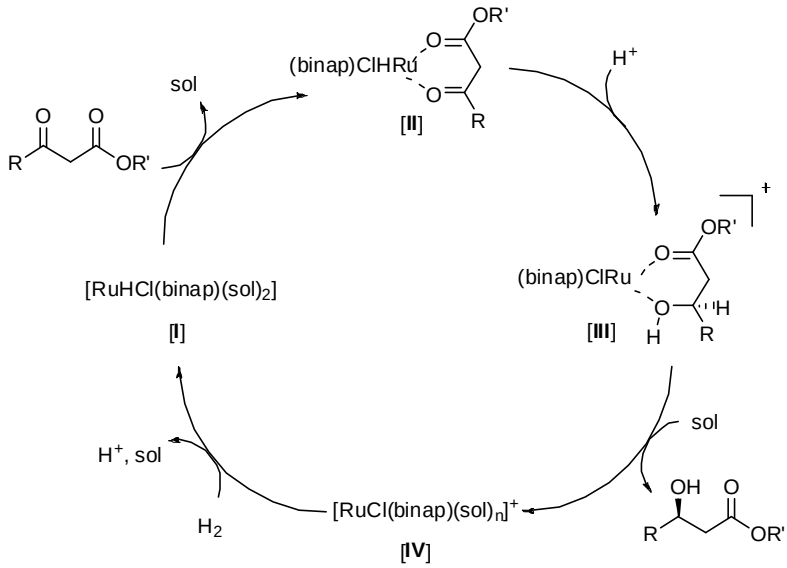
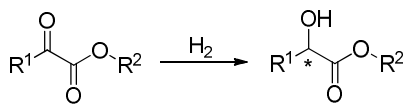


Figure 5: Mechanism of the β-ketoester hydrogenation.

After the hydride transfer from the Ru-center to the keto carbonyl, protonation with a proton from the solution completes the reduction (**III**) and the product is released from the metal where one or more solvent molecules take its place (**IV**). Another heterolytic splitting of a hydrogen molecule completes the cycle by forming again the ruthenium mono hydride complex (**I**).[28]

4.1.3 Introduction into α-ketoester hydrogenation



In comparison with the β-ketoesters a lot less examples are known, in which asymmetric hydrogenation is used for the reduction of α-ketoesters, with good results.[29] There are a few examples by Boaz *et al.*[30] who used the ferrocenyl ligand **4.9** in the rhodium catalyzed hydrogenation of pyruvate and obtained up to 88% ee and up to 97% ee when **4.8** was used as substrate. Mortreux et al. used the phosphinite **4.6**[31] and the chromium complexed aminophosphine **4.7**[32;33] in

the rhodium catalyzed asymmetric hydrogenation of pyruvate in 86% and 89% respectively. When **4.7** was used in the rhodium catalyzed hydrogenation of **4.8** ee's up to 99% were obtained. Mashima *et al.*[34] used a cationic ruthenium-binap catalyst and were able to reach up to 93% ee in the α-ketoester hydrogenation.

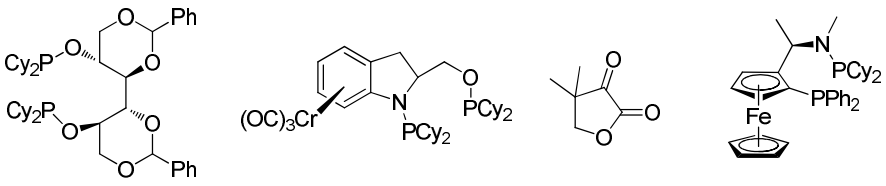


Figure 6: Ligands used in the alpha-ketoester hydrogenation.

But for the best results in this type of transformation mostly a biochemical route is followed using whole cells[35;36] or isolated enzymes.[37;38]

In 2005, Sun *et al.* described the positive influence of the addition of $CeCl_3 \cdot 7H_2O$ on the outcome of the hydrogenation of α-ketoesters. A significant increase in ee was observed (in some cases of even 36 percent points going from 40 to 76% ee) when using this salt as an additive in the reaction. They contribute this to a coordination of the ester to the cerium as shown in Figure 7. This coordination makes that the ester has a more constrained conformation leading to the increase in ee.[39;40]

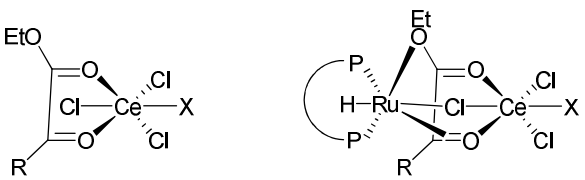


Figure 7: Complexes formed during hydrogenation of α-ketoesters in the presence of a cerium salt (X = Cl, H_2O or solvent).

Also the hydrogenation of α-ketoesters has been used in the synthesis of natural compounds. In 2009 Tone *et al.*[41] reported the first synthesis of Gymnangiamide. This total synthesis starts with the asymmetric hydrogenation of an α-ketoester. By synthesizing the molecule, the authors *en passant*

disproved the absolute stereochemistry that was proposed earlier for the C-34 center of the serine residue by Gustafson *et al*..[42] Gustafson proposed that this C-34 residue came from a L-serine giving the 34*S* stereoisomer. Tone, however, showed that the molecule as the 34*R* stereoisomer, coming from D-serine, displayed a biological activity closer to the natural product than when the 34*S* isomer was tested.

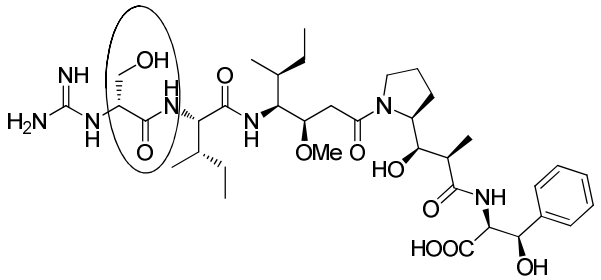


Figure 8: Structure of Gymnangiamide with the C-34*R* stereogenic center obtained by asymmetric hydrogenation of an α-ketoester.

In the synthesis of Amphidinolide Y, which is an interesting cytotoxic compound isolated from the marine species *Amphidinium* sp., the ruthenium-binap catalyzed asymmetric hydrogenation of an α-ketoester is used as one of the key steps in the synthesis.[43]

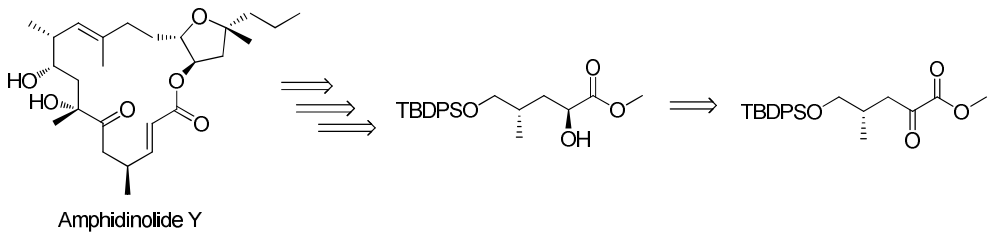


Figure 9: Amphidinolide X and Y; utilizing an asymmetric hydrogenation of an α-ketoester as one of the key steps for introducing chirality.

4.2 Goal

With the good results obtained in the asymmetric hydrogenation of aromatic ketones using phosphoramidite ligands in hand, we decided to focus our attention on a different type of ketones. In DSM some attempts had been made in the asymmetric hydrogenation of α- and β-ketoesters using phosphoramidite ligands. The results there obtained were not very good. In no case a significant ee was found and conversions were mostly poor. But with the experience of the acetophenone type ketones in hand we decided to have another look at these substrate classes. Using the ruthenium type catalyst as described by Noyori[1] replacing the bidentate binap ligand by two monodentate phosphoramidites.
In this chapter the development of an effective ruthenium catalyst containing monodentate phosphoramidite ligands for the asymmetric hydrogenation of α- and β-ketoester will be discussed.

4.3 Results

4.3.1 β -Ketoester results

At DSM the best result in the asymmetric hydrogenation of β-ketoesters was obtained with a Rh-based catalyst in combination with a phosphoramidite ligand (up to a maximum of 41% ee). The reactions with the ruthenium type catalysts were reported to have a lot of side products, nevertheless we decided, based on the good results reported in the literature, to start with a ruthenium based catalyst.

4.3.1.1 The complex

The catalysts for all the reactions as described in this chapter were synthesized starting from the ruthenium precursor $[RuCl_2(cymene)]_2$. To this precursor four equivalents of the appropriate monodentate, or two equivalents of a bidentate ligand were added in DMF. This mixture was heated at 90 ^oC in a Schlenk tube under nitrogen for two hours. In order to obtain the catalyst the DMF was

evaporated *in vacuo*, the residue was immediately used, without purification, in a hydrogenation reaction.

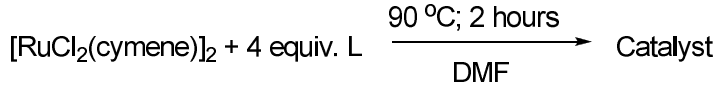
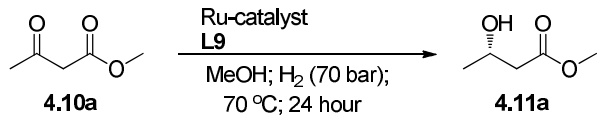


Figure 10: Schematic representation of complex formation when using monodentate phosphoramidite ligands.

The ^{31}P-NMR of the complex obtained with **L9** showed only one very broad peak between 160-150 ppm. Since we knew from the attempts to isolate and indentify the complex that was formed for the acetophenone hydrogenation (see chapter 2), that the phosphoramidite ligands can be easily removed from the ruthenium when in solution, we did not pursue the purification any further.

To investigate the influence of more or less ligand present in the reaction mixture we decided to vary the amount of ligand in the reaction.

Table 1: Ligand : Metal ratio screening.



4.10a **4.11a**

L:M	Conversion[a] (%)	ee[a] (%)
1:1	100	65
2:1	100	99
3:1	85	85
4:1	55	86

All reactions were done in MeOH on a 2 mmol scale in a total volume of 4 mL at 70 °C and 70 bar H_2 for 24h. Substrate/Ru/**L9**: 400/1/2. The catalysts were prepared in the same way described in 4.3.1.1. a) Conversions and ee's were determined via chiral GC.

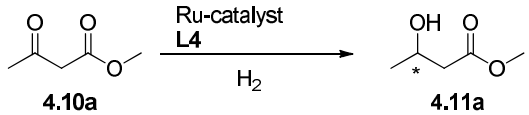
As can be seen in Table 1, the best results are obtained when using a 2:1 ligand to metal ratio. Going below that ratio the reaction still went to full conversion but with a much lower ee. Adding more ligands per metal center resulted in a slower reaction and also in a somewhat decreased ee. This indicates that two

ligands per metal center are needed for a good enantiomeric excess; increasing this ratio however leads to overcrowding at the metal which leads to a much slower and less selective reaction.

4.3.1.2 Screening of reaction conditions

For the screenings towards the most optimal reaction conditions we used 0.25 mol% of the complexes described above in reactions on 2 mmol scale. The screenings started with a small solvent screening in the hydrogenation of methyl acetoacetate (**4.10a**) (Table 2) that showed that the use of an alcohol was needed to reach good conversions and ee's. DCM as a solvent also gave a good result in terms of ee, but the reaction did not go to completion in the 24 hours it was allowed to run. For this reason, and the fact that an alcohol would give us a broader temperature range to work at because of their higher boiling points, we decided to use an alcoholic solvent in all further experiments. Further screening showed that the optimal pressure and temperature for this reaction was 70 bars of hydrogen pressure at a temperature of 70 ^{o}C. Using DiMePip (**L4**, see ligands under Table 3) under these conditions we were able to reach full conversion and 95% ee in the hydrogenation of methyl acetoacetate towards the corresponding β-hydroxy ester within 24 hours. Changing the solvent from MeOH to toluene or DCM did not result in a further improvement of the results. In toluene no reaction took place at all whereas in DCM the reaction resulted in more or less the same ee as when the reaction was done in MeOH but the conversion was not complete after 24 hours.

Table 2: Condition screening.



4.10a 4.11a

	Solvent	P (bar)	T (^{o}C)	Conversion (%)	Ee[a] (%)
1	MeOH	60	50	90	95
2	MeOH	70	70	100	95
3	MeOH	80	70	100	95
4	Toluene	70	70	0	-
5	DCM	70	70	65	94

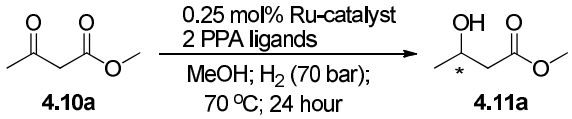
Reactions were done on a 2 mmol scale in a total reaction volume of 4 mL in a small vial, containing a stir bar, which was placed inside an autoclave, for 24 h.. Substrate/Ru/**L4**: 400/1/2. The catalysts were prepared in the same way described in 4.3.1.1. a) Ee's where determined via chiral-GC on a GTA-column.

4.3.1.3 Ligand screening

After determining the optimal reaction conditions we set out to find the best performing phosphoramidite ligand for this reaction. This screening of ligands (Table 3) showed that the presence of a group on the 3 and 3' position of the binol backbone had a positive influence on the ee of the product (**L4**, **L5**, **L6** and **L9** vs. **L2** and **L8**). Since it doesn't seem to matter what kind of substituent is present at this position it suggests to us that the increase in ee can purely be attributed to the increase in bulkiness of the ligand. Also switching from normal PipPhos (**L2**) to the partially saturated, and sterically bulkier, 8H-PipPhos (**L8**) gave a drastic increase in ee going from 51% to 74%.

Since introduction of methyl groups at the 3,3' positions of the binol-backbone also led to a much higher ee we decided to combine the two backbone variations and examine 8H-DiMePip (**L9**) as a ligand. This proved to be the key to success in this case, as the catalyst based on this ligand led to full conversion in 24 hours and 99% ee in the hydrogenation of **4.10a**.

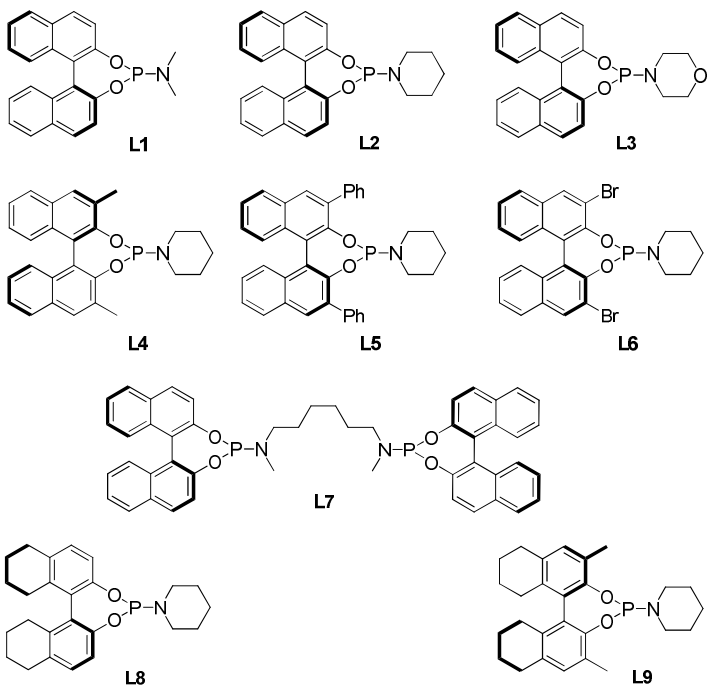
Table 3: Ligand screening in the asymmetric hydrogenation of β-ketoesters.



4.10a **4.11a**

	Ligand	Conversion (%)	Ee[a] (%)
1	**(*S*)-L1**	98	45 (*R*)
2	**(*S*)-L2**	94	51 (*R*)
3	**(*S*)-L3**	92	73 (*R*)
4	**(*R*)-L4**	100	95 (*S*)
5	**(*S*)-L5**	95	97 (*R*)
6	**(*S*)-L6**	92	97 (*R*)
7	**(*S*)-L7[b]**	98	74 (*R*)
8	**(*S*)-L8**	86	74 (*R*)
9	**(*R*)-L9**	**100**	**99 (*S*)**

All reactions were done in MeOH on a 2 mmol scale in a total volume of 4 mL at 70 °C and 70 bar H_2 for 24h. Substrate/Ru/L: 400/1/2. The catalysts were prepared in the same way described in 4.3.1.1 a) ee's were determined via chiral GC b) Substrate/Ru/L: 400/1/1.

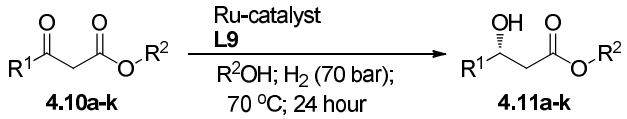


From these screening reactions it became clear that the best results in the hydrogenations of methyl acetoacetate (**4.10a**) are obtained when ligand **L9** is used as a ligand to a ruthenium based catalyst. When the reaction was run for 24 hours at 70 bar of hydrogen pressure and at 70 ^{o}C we were able to obtain the product, methyl 3-hydroxybutanoate (**4.11a**), in full conversion and up to 99% ee.

4.3.1.4 Substrate scope

Having found the optimal conditions and ligand (**L9**) for this hydrogenation we started the investigation towards the substrate scope for the reaction (Table 4). The performance of the catalyst showed good tolerance towards varying the alkyl groups in both the ester part of the substrate (**4.10a, 4.10b)** as well as in the 4-position (**4.10a, 4.10c-e**). Although switching to a more bulky substrate like **4.10d** gave somewhat lower conversion and ee (89 and 91%, respectively) still the results were good. Also a few aryl β-ketoesters were tested (**4.10g-k**) showing excellent conversions and high ee's. Only the 3-(4-pyridyl) (**4.10i**) and the 3-chloro (**4.10f**) substituted substrates showed no or significantly lower conversions and ee. The lack of conversion that was seen with the pyridyl substrate was attributed to a co-coordination of the pyridine ring to the catalyst. This extra coordination to the catalyst could have made it impossible for the substrate to be hydrogenated or for the product to be easily released from the complex, blocking access to the complex for further substrate molecules.

Table 4: Substrate scope of the β-ketoester hydrogenation.



	Substrate	R_1	R_2	Conversion (%)	Ee[a] (%)
1	**4.10a**	Me	Me	100	99 (*S*)
2	**4.10b**	Me	Et	100	98 (*S*)
3	**4.10c**	n-Pr	Et	100	97 (*S*)
4	**4.10d**	i-Pr	Et	89	91 (*S*)
5	**4.10e**	Et	Me	100	98 (*S*)
6	**4.10f**	CH_2Cl	Me	90	44 (*R*)[b]
7	**4.10g**	Ph	Et	100	96 (*R*)[b]
8	**4.10h**	*m*-Cl-Ph	Me	95	94 (*R*)[b]
9	**4.10i**	4-Pyridyl	Me	0	Nd
10	**4.10k**	2-furyl	Et	100	85 (*R*)[b]

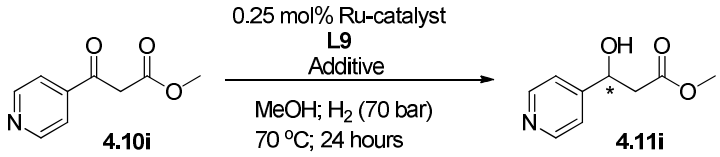
All reactions were done in R_2OH on a 2 mmol scale in a total volume of 4 mL at 70 °C and 70 bar H_2 for 24h. Substrate/Ru/**L9**: 400/1/2. The catalyst was prepared in the same way described in 4.3.1.1 a) ee's were determined via chiral GC. b) Change of configuration due to change in priority of the side groups.

Since compounds containing heterocycles are often of great interest for pharmacological research[44;45] getting the hydrogenation of compound **4.10i** working may serve as a starting point in the development of new active compounds.

In an attempt to get the hydrogenation of substrate **4.10i** working, the reaction was repeated using several additives (Table 5). The idea, to prevent coordination of the pyridyl group to the metal center by protonating the substrate by adding 1 equivalent of sulphuric or acetic acid, proved not to work. Also performing the reaction in neat acetic acid gave no conversion of the substrate.

Adding coordinating salts like lithium chloride or titanium isopropoxide in various equivalents also proved not sufficient to get the reaction going.

Table 5: Additive screening for the hydrogenation of **4.10i**.

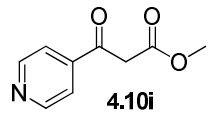


	Additives (wrt 4.6i)	conversion
1	-	none
2	1.0 equiv. HOAc	none
3	HOAc as solvent	none
4	1.0 equiv H_2SO_4	none
5	1.0 equiv LiCl	<10%
6	1.5 equiv LiCl	<10%
7	2.0 equiv LiCl	none
8	0.5 equiv $Ti(OiPr)_4$	none
9	1.0 equiv $Ti(OiPr)_4$	none
10	1.5 equiv $Ti(OiPr)_4$	none

All reactions were performed in MeOH on a 1 mmol scale in a total volume of 2 mL at 70 °C and 70 bar H_2 for 24h. Substrate/Ru/**L9**: 400/1/2. The catalysts were prepared as described in 4.3.1.1. Conversions were determined via GC.

To get more insight in the reaction we tried to hydrogenate methyl acetoacetate (**4.10a**) in the presence of different amounts of **4.10i**. As can be seen in Table 6, adding more of **4.10i** with respect to methyl acetoacetate resulted in a lower conversion of the substrate into the β-hydroxyester all the way to complete blocking of the conversion when a one to one mixture was used. In none of the cases the product of the hydrogenation of **4.10i** was found.

Table 6: Inhibition experiment with substrate **4.10i**.



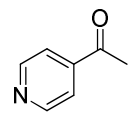
4.10i

Amount of 6i (% wrt 6a)	Conversion of 6a (%)
0	100
0.25	99
2.5	83
10	74
50	35
100	0

All reactions were done in MeOH on a 1 mmol scale in a total volume of 2 mL at 70 ^{o}C and 70 bar H_2 for 24h. Substrate/Ru/**L9**: 400/1/2. **4.10i** was added to the reaction vials in indicated amounts. Conversions were determined via GC.

A structurally equivalent compound (acetyl pyridine **4.12**) proved to be an even more efficient inhibitor of the hydrogenation of methyl acetoacetate as can be seen in Table 7.

Table 7: Inhibition of the hydrogenation of **4.10a** by **4.12**.



4.12

Amount of 4.8 (% wrt 4.6a)	Conversion of 4.6a (%)
0	100
2.5	<5
12.5	<5
25	<5

All reactions were done in MeOH on a 1 mmol scale in a total volume of 2 mL at 70 ^{o}C and 70 bar H_2 for 24h. Substrate/Ru/**L9**: 400/1/2. **4.12** was added to the reaction vials in indicated amounts. Conversions were determined via GC.

These results suggest that the pyridyl ring in some way inactivates the catalyst in this reaction completely. These observations would also explain the lack of

literature data on the reduction of these pyridyl substrates to their β-hydroxyesters. To the best of our knowledge only one patent describes the reduction of this type of substrates by means of asymmetric transfer hydrogenation[46] and one by means of biochemical reduction.[47]

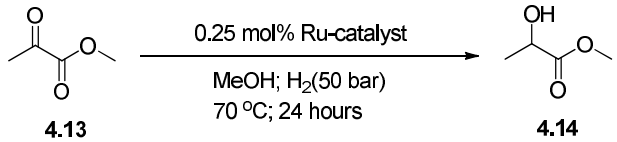
4.3.1.5 Conclusion on the hydrogenation of β-ketoesters

From the results described above it can be concluded that we have developed a ruthenium based catalyst, containing monodentate phosphoramidite ligands, which is able to hydrogenate a range of beta-ketoesters in good yields and with excellent enantioselectivities. The best performing ligand proved to be the partly saturated and methyl substituted phosphoramidite **L9.** When used in a 2 :1 ligand to metal ratio the complex can be used with a 0.25 mol% loading at 70 ^{o}C and at 70 bars of hydrogen pressure the reactions are usually complete within 24 hours.

4.3.2 Results of the α –ketoester hydrogenation

In an attempt to find a good system for the asymmetric hydrogenation of α-ketoesters we tested a few ligands in the hydrogenation of methyl pyruvate (**4.13**). The reactions were performed in MeOH while applying 50 bar of hydrogen pressure at 70 ^{o}C for 24 hours. 0.25 mol% Of a ruthenium catalyst was used in combination with the different ligands. In first instance all reactions were done without the presence of $CeCl_3 \cdot 7H_2O$.

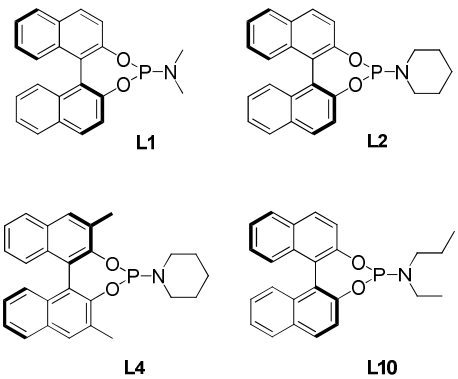
Table 8: α-ketoester hydrogenation results.



4.13 4.14

	Without $CeCl_3 \cdot 7H_2O$		With $CeCl_3 \cdot 7H_2O$	
Ligand	**Conversion[a] (%)**	**ee[a] (%)**	**Conversion[a] (%)**	**ee[a] (%)**
L1	60	<5	60	<5
L2	75	<5	55	<5
L4	80	<5	60	<5
L10	60	<5	50	<5

All reactions were done in MeOH on a 2 mmol scale in a total volume of 4 mL at room temperature and 70 bar H_2 for 24h. Substrate/Ru/L/$CeCl_3 \cdot H_2O$: 400/1/2/0 or 5. Ru-catalyst was prepared as described in 4.3.1.1. a) Conversions and ee's were determined via chiral GC.



As in none of the reactions full conversion was reached or any significant ee was obtained, we decided to add 1.25 mol% cerium salt to the reaction as was described by Sun *et al.*.[40] Sadly also this proved not to lead to any ee or full conversions in the reaction.

4.4 Conclusions

In this chapter it is shown that it is possible to use monodentate phosphoramidites as ligands in the hydrogenation of β-ketoesters. The performance of the ligands in this reaction seems to be determined more by the structure of the backbone than of the amine part of the ligand. Making the backbone more sterically demanding by placing side groups on the 3 and 3' position in combination with the saturation of the outer rings of the naphthyl group, results in ee's up to 99% with full conversion. These are the best results obtained in the asymmetric hydrogenation of β-ketoesters when using monodentate ligands in the catalyst. We showed that this ruthenium catalyst containing the sterically large phosphoramidite ligand is able to hydrogenate a range of β-ketoesters and performs best when two phosphoramidite ligands per ruthenium center are present in the reaction mixture.
The hydrogenation of α-ketoesters with the same type of catalyst led to incomplete conversions and racemic products. Also the addition of an additive ($CeCl_3 \cdot 7H_2O$), known to work very well in another case, gave no improvement of the results.

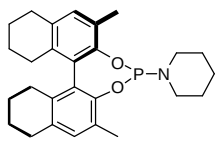
4.5 Experimental

Starting materials were purchased from Aldrich, Alfa Aesar or Acros and used as received unless stated otherwise. $[RuCl_2(cymene)]_2$ was bought from Strem and used as received. Substrates **4.10h**, **4.10i** and (*R*)-3,3'-dimethyl bis-β-naphthol were kindly provided by DSM. All solvents were reagent grade and, if necessary, dried and distilled prior to use. Column chromatography was performed on silica gel (Aldrich 60, 230-400 mesh). TLC was performed on silica gel 60/Kieselguhr $F_{254.}$ ^{1}H and ^{13}C NMR spectra were recorded on a Varian AMX400 (399.93 MHz for ^{1}H, 100.59 MHz for ^{13}C and 161.9 MHz (^{1}H-decoupled) for ^{31}P). Mass spectra (HRMS) were performed on a Jeol JMS-600H. HPLC analysis was performed on a Shimadzu HPLC system equipped with two LC-10AD solvent delivery systems, a DGU-14A degasser, a SIL-10AD *vp* auto injector, an SPD-M10A *vp* diode array detector, a CTO-10A *vp* column oven, and an SCL-10A *vp* system controller using the columns indicated for each compound

separately. Optical rotations were measured on a *Schmidt+ Haensch* polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL).

Ligands **L1,**[48] **L2-3**,[11] **L5-6**, **L7**,[49] **L8** and **L10** were described in literature before and used from the general phosphoramidite library present in our labs. The preparation of **L4** is described in Chapter 2.

(*R*)-1-(2,6-dimethyl-8,9,10,11,12,13,14,15-octahydrodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)piperidine; 8H-DiMe-PipPhos (L9)



L9

(*R*)-3,3'-dimethyl-5,6,7,8,5',6',7',8'-octahydro-[1,1']-binaphthal-enyl-2,2'-diol (8H-bis-β-naphtol) (1.6 g, 5 mmol) was dissolved in PCl_3 (5 mL) under nitrogen atmosphere. The mixture was heated under reflux for 16 h, keeping the system under anhydrous conditions using a $CaCl_2$ tube. Excess of PCl_3 was removed by distillation and the residual solid was subjected to azeotropic distillation with toluene (3 × 5 mL). The resulting yellow foam was dissolved in toluene (10 mL). The resulting solution was cooled to 0 °C and Et_3N (2 equiv, 10 mmol, 1.4 mL) was added. This was let to stir for 10 minutes, then piperidine (1.1 equiv, 5.5 mmol, 550 μL) in toluene (5 mL) was added dropwise. After stirring overnight, (allowing the temperature to rise to room temperature) the reaction mixture was diluted with Et_2O and the salts were filtered off. The mixture was concentrated under reduced pressure and the residue purified by flash chromatography (pentane:Et_2O 8:1) to give the pure phosphoramidite as a white solid still contaminated with some toluene. Stripping with acetone furnished 1.2 g (2.8 mmol, 56%) of the phosphoramidite as foamy solid. Mp 97.9 - 98.2 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.93 (s, 1H), 6.87 (s, 1H), 2.68-2.96 (m, 8H), 2.50-2.66 (m, 2H), 2.12-2.38 (m, 8H), 1.63-1.81 (m, 6H), 1.48-1.62 (m, 4H), 1.30-1.46 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 147, 147, 135, 135, 133, 132, 130, 130, 129, 128, 127, 126, 44.8, 44.6, 29.1, 29.0, 27.6, 27.4, 27.1, 27.0, 25.0, 23.0, 22.9, 22.7, 22.5, 16.4, 16.2. ^{31}P-NMR (162 MHz, $CDCl_3$) δ (ppm) 137.0. HRMS calcd for $C_{27}H_{34}NO_2P$ (M^+): 435.2327; found: 435.2295.

General procedure for hydrogenation of β-ketoesters

2.5 μmol of $[RuCl_2(cymene)]_2$ and 10 μmol (4 equivalents) phosphoramidite were dissolved in 1.5 ml DMF. This mixture was stirred while heated for two hours at 90 °C. After two hours the mixture was let to cool down to room temperature after which the DMF was removed *in vacuo*. The residue was dissolved in 4 ml of MeOH in case of a methylester and EtOH in case of an ethylester. This solution was added to 2 mmol of

substrate in an 8 ml glass vial. The vial was capped with a septum which was pierced by a hyperdermic needle and put into an autoclave. The autoclave was closed, purged three times with 5 bar of N_2 and three times with 8 bar of H_2 before brought up to the working pressure of 70 bar H_2. The autoclave was heated till 70 ^oC and kept stirring for 24 hours. After the reaction time the autoclave was allowed to cool down to room temperature before the hydrogen pressure was carefully released. The solvent was evaporated and of the remains a small volume was run over a short silica plug in order to make a GC sample for the determination of conversion and ee.

(*S*)-Methyl 3-hydroxybutyrate[2] **(4.11a)** Was obtained as a yellow oil (full conversion, 99% ee), ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 4.28-4.13 (m, 1H), 3.47 (bs, 1H), 3.23 (s, 3H), 2.57-2.36 (m, 2H), 1.23 (d, 3H, *J* = 6.3 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 170.1, 64.2, 42.5, 51.7, 22.4. $[\alpha]_D$ = 23.9 (c 0.99, $CHCl_3$). Ee determination was performed on a GTA-column. $T_{inlet} = T_{det} = 250\ ^oC$; $T_{isotherm} = 110\ ^oC$ (15 min) T_R = 10.9 min. T_S = 11.2 min.

(*S*)-Ethyl 3-hydroxybutyrate[50] **(4.11b)** was obtained as a light brown oil (full conversion, 98% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 4.28-4.12 (m, 3H), 2.56-2.34 (m, 2H), 1.29-1.13 (m, 6H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 172.9, 64.2, 60.6, 42.7, 22.4, 14.2. $[\alpha]_D$ = 40.3 (c 0.92, $CHCl_3$). Ee determination was performed on a Chiralsil DEX CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 50\ ^oC$ (5 min) – (1 ^oC / min) → 170 ^oC T_R = 23.1 min. T_S = 23.5 min.

(*S*)-Ethyl 3-hydroxyhexanoate[51] **(4.11c)** was obtained as a yellow oil (full conversion, 97% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 4.21 (q, 2H, *J* = 7.1 Hz), 4.08-3.96 (m, 1H), 3.43 (s, 1H), 2.56-2.37 (m, 2H), 1.75-1.36 (m, 4H), 1.28 (t, 3H, *J* = 7.2 Hz), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 173.1, 67.7, 60.6, 41.3, 38.6, 18.6, 14.2, 13.9. $[\alpha]_D$ = 15.3 (c 1.02, $CHCl_3$). Ee determination was performed on a Chiralsil DEX CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 50\ ^oC$ (5 min) – (1 ^oC / min) → 170 ^oC T_R = 38.1 min. T_S = 40.0 min.

(*S*)-Ethyl 3-hydroxy 4-methylpentanoate[6] **(4.11d)** was obtained as a yellow oil (89% conversion, 91% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 4.22 (q, 2H, *J* = 7.0 Hz), 3.98-3.93 (m, 1H), 2.59-2.37 (m, 2H), 1.99-1.86 (m, 1H), 1.28 (t, 3H, *J* = 7.1 Hz), 0.89 (d, 6H, *J* = 6.8 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 173.6, 73.9, 61.2, 37.9, 35.6, 17.5, 14.1. $[\alpha]_D$ = 19.3 (c 0.89, $CHCl_3$). Ee determination was performed on a Chiralsil

DEX CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 50\ ^oC$ (5 min) – (1 ^oC / min) → 170 ^oC T_R = 31.2 min. T_S = 31.9 min.

(*S*)-Methyl 3-hydroxypentanoate[52] **(4.11e)** was obtained as a colorless oil (full conversion, 98% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 4.00-3.88 (m, 1H), 3.72 (s, 3H), 3.69, (bs, 1H), 2.55-2.19 (m, 2H), 1.61-1.45 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 167.7 69.3, 51.7, 40.6, 29.4, 9.8. $[\alpha]_D$ = 35.1 (c 0.92, $CHCl_3$). Ee determination was performed on a Chiralsil DEX CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 50\ ^oC$ (5 min) – (1 ^oC / min) → 170 ^oC T_R = 17.4 min. T_S = 17.9 min.

(*R*)-Methyl 3-hydroxy 4-chlorobutyrate[53] **(4.11f)** was obtained as a yellow oil (full conversion, 44% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 4.32-4.21 (m, 1H), 3.79-3.60 (m, 6H), 2.72-2.63 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 172.1, 67.9, 52.0, 51.8, 38.2. $[\alpha]_D$ = 9.6 (c 0.87, $CHCl_3$). Ee determination was performed on a Chiralsil DEX CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 50\ ^oC$ (5 min) – (1 ^oC / min) → 170 ^oC T_S = 18.6 min. T_R = 18.9 min.

(*R*)-Ethyl 3-hydroxy 3-phenylpropionate[3] **(4.11g)** was obtained as a yellow oil (full conversion, 96% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.97-7.35 (m, 5H), 5.14 (dd, 1H, *J* = 5.0 Hz, *J* = 7.9 Hz), 4.27 (q, 2H, *J* = 7.0 Hz), 2.84-2.61 (m, 2H), 1.26 (t, 3H, *J* = 7.1 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 172.4, 142.5, 128.7, 128.5, 128.5, 70.3, 61.5, 43.3, 14.1. $[\alpha]_D$ = –50.3 (c 1.08, $CHCl_3$). Ee determination was performed on a Chiralsil DEX CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 50\ ^oC$ (5 min) – (1 ^oC / min) → 170 ^oC T_S = 90.1 min. T_R = 90.8 min.

(*R*)-Methyl 3-hydroxy 3-(3-chlorophenyl)-propionate (4.11h) was obtained as a pale yellow oil (95% conversion, 94% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.83-7.31 (m, 4H), 5.11 (t, 1H, *J* = 6.3 Hz), 3.76 (s, 3H), 3.73 (s, 1H), 2.74-2.70 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 169.5, 137.4, 135.2, 131.2, 127.9, 126.3, 125.9, 69.6, 52.6, 42.9. $[\alpha]_D$ = –49.2 (c 0.79, $CHCl_3$). Ee determination was performed on a Chiralsil DEX CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 50\ ^oC$ (5 min) – (1 ^oC / min) → 170 ^oC T_S = 92.5 min. T_R = 92.8 min.

(*R*)-Ethyl 3-hydroxy 3-(2-furyl)-propionate[54] **(4.11k)** was obtained as a brown oil (full conversion, 85% ee). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.62 (d, 1H, *J* = 1.5 Hz), 7.28 (d, 1H, *J* = 3.1 Hz), 6.57 (dd, 1H, *J* = 1.7 Hz, *J* = 3.6 Hz) 4.21 (q, 2H, *J* = 7.1 Hz), 2.72-2.55 (m, 2H), 1.26 (t, 3H, *J* = 7.1 Hz) ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 171.9,

152.0, 142.1, 110.9, 105.9, 65.0, 61.5, 41.5, 14.1. $[\alpha]_D$ = 16.3 (c 1.09, $CHCl_3$). Ee determination was performed on a Chiralsil DEX CB column $T_{inlet} = T_{det}$ = 250 ^oC; T_{start} = 50 ^oC (5 min) – (1 ^oC / min) → 170 ^oC T_S = 65.1 min. T_R = 65.3 min.

Procedure for hydrogenation of methyl pyruvate (4.13) in the prescense of $CeCl_3 \cdot 7H_2O$.

2.5 μmol of $[RuCl_2(cymene)]_2$ and 10 μmol (4 eq.) phosphoramidite were dissolved in 1.5 ml DMF. This mixture was stirred while heated for two hours at 90 ^oC. After two hours the mixture was let to cool down to room temperature after which the DMF was removed *in vacuo*. The residue was dissolved in 4 ml of methanol. This solution was added to 204 mg methyl pyruvate (2 mmol) in an 8 ml glass vial. To this 9.3 mg $CeCl_3 \cdot 7H_2O$ (25 μmol) was added. The vial was capped with a septum which was pierced by a hypodermic needle and put into an autoclave. The autoclave was closed, purged three times with 5 bar of N_2 and three times with 8 bar of H_2 before it was brought up to the working pressure of 50 bar H_2. The autoclave was heated till 70 ^oC and kept stirring for 24 hours. After the reaction time the autoclave was allowed to cool down to room temperature before the hydrogen pressure was carefully released. The solvent was evaporated and of the remains a small volume was run over a short silica plug in order to make a GC sample. Conversion and ee of the product were determined via chiral GC. GTA column, $T_{inlet} = T_{det}$ = 250 ^oC; $T_{isotherm}$ = 80 ^oC (50 min) T_1 = 15.2 min. T_2 = 16.4 min.

4.6 References

[1.] M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J.Am.Chem.Soc.* **1988,** *110* 629-631.

[2.] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J.Am.Chem.Soc.* **1987,** *109* 5856-5858.

[3.] V. Ratovelomanana-Vidal, C. G. R. Touati, J. P. Tranchier, B. ben Hassine, J.-P. Genêt, *Adv.Synth.Catal.* **2003,** *345* 261-274.

[4.] T. Sturm, W. Weissensteiner, F. Spindler, *Adv.Synth.Catal.* **2003,** *345* 160-164.

[5.] T. Yamano, N. Taya, H. Kawada, T. Huang, T. Imamoto, *Tetrahedron Lett.* **1999,** *40* 2577-2580.

[6.] T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem.Eur.J.* **2002,** *8* 843-852.

[7.] Y. G. Zhou, W. Tang, W. B. Wang, W. Li, X. Zhang, *J.Am.Chem.Soc.* **2002,** *124* 4952-4953.

[8.] M. T. Reetz, X. Li, *Adv.Synth.Catal.* **2006,** *348* 1157-1160.

[9.] W. Tang, X. Zhang, *Chem.Rev.* **2003,** *103* 3029-3069.

[10.] Y. H. Sun, X. B. Wan, M. J. Guo, D. H. Wang, X. C. Dong, Y. Pan, Z. G. Zhang, *Tetrahedron: Asymmetry* **2004,** *15* 2185-2188.

[11.] H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J.Org.Chem* **2005,** *70* 943-951.

[12.] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew.Chem.Int.Ed.* **2005,** *44* 4209-4212.

[13.] A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc.Chem.Res.* **2007,** *40* 1267-1277.

[14.] M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J.Am.Chem.Soc.* **2000,** *122* 11539-11540.

[15.] N. Mršic, L. Lefort, J. A. F. Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv.Synth.Catal.* **2008,** *350* 1081-1089.

[16.] N. Mršic, T. Jerphagnon, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv.Synth.Catal.* **2009,** *351* 2549-2552.

[17.] Q. Jing, X. Zhang, J. Sun, K. Ding, *Adv.Synth.Catal.* **2005,** *347* 1193-1197.

[18.] Y. Xu, G. C. Clarkson, G. Docherty, C. L. North, G. Woodward, M. Wills, *J.Org.Chem.* **2005,** *70* 8079-8087.

[19.] B. Hagemann, K. Junge, S. Enthaler, M. Michalik, T. Riermeier, A. Monsees, M. Beller, *Adv.Synth.Catal.* **2005,** *347* 1978-1986.

[20.] K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew.Chem.Int.Ed.* **2004,** *43* 5066-5069.

[21.] N. Andrushko, V. Andrushko, G. Köning, A. Spannenberg, A. Börner, *Eur.J.Org.Chem* **2008,** 847-853.

[22.] A. Korostylev, V. Andrushko, N. Andrushko, V. I. Tararov, G. Köning, A. Börner, *Eur.J.Org.Chem* **2008,** 840-846.

[23.] V. I. Tararov, G. Köning, A. Börner, *Adv.Synth.Catal.* **2006,** *348* 2633-2644.

[24.] J. P. Genêt, *Acc.Chem.Res.* **2003,** *36* 908-918.

[25.] L. Coutable, K. Adil, C. Saluzzo, *Tetrahedron* **2008,** *64* 11296-11303.

[26.] R. Noyori, T. Ohkuma, *Angew.Chem.Int.Ed.* **2001,** *40* 40-73.

[27.] R. Noyori, *Adv.Synth.Catal.* **2003,** *345* 15-32.

[28.] T. Ohkuma, R. Noyori, in *Handbook of Homogeneous Hydrogenation* ,*Vol. III*, (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 1105-1163.

[29.] A. Mortreux, A. Karim, in *Handbook of homogeneous hydrogenation*Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**, p. pp. 1165-1191.

[30.] N. W. Boaz, E. B. Mackenzie, S. D. Debenham, S. E. Large, J. A. Ponasik, *J.Org.Chem* **2005,** *70* 1872-1880.

[31.] S. Naili, I. Suisse, A. Mortreux, F. Agbossou, M. Ait Ali, A. Karim, *Tetrahedron Lett.* **2000,** *41* 2867-2870.

[32.] C. Pasquier, S. Naili, A. Mortreux, F. Agbossou, L. Pélinski, J. Brocard, J. Eilers, I. Reiners, V. Peper, J. Martens, *Organometallics* **2000,** *19* 5723-5732.

[33.] C. Pasquier, L. Pélinski, J. Brocard, A. Mortreux, F. Agbossou-Niedercorn, *Tetrahedron Lett.* **2001,** *42* 2809-2812.

[34.] K. Mashima, K. h. Kusano, N. Sato, Y. i. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, *J.Org.Chem.* **2002,** *59* 3064-3076.

[35.] Y. Chen, J. Xu, X. Xu, Y. Xia, H. Lin, S. Xia, L. Wang, *Tetrahedron: Asymmetry* **2007,** *18* 2537-2540.

[36.] W. Yang, J. H. Xu, Y. Xie, Y. Xu, G. Zhao, G. Q. Lin, *Tetrahedron: Asymmetry* **2006,** *17* 1769-1774.

[37.] D. Zhu, J. E. Stearns, M. Ramirez, L. Hua, *Tetrahedron* **2006,** *62* 4535-4539.

[38.] D. M. Zhu, Y. Yang, J. D. Buynak, L. Hua, *Org.Biomol.Chem.* **2006,** *4* 2690-2695.

[39.] Q. Meng, Y. Sun, V. Ratovelomanana-Vidal, P. Jean, Z. Zhang, *J.Org.Chem.* **2008,** *73* 3842-3847.

[40.] Y. Sun, X. Wan, J. Wang, Q. Meng, H. Zhang, L. Jiang, Z. Zhang, *Org.Lett.* **2005,** *7* 5425-5427.

[41.] H. Tone, M. Buchotte, C. Mordant, E. Guittet, T. Ayad, V. Ratovelomanana-Vidal, *Org.Lett.* **2009,** *11* 1995-1997.

[42.] D. J. Milanowski, K. R. Gustafson, M. A. Rashid, L. K. Pannell, J. B. McMahon, M. R. Boyd, *J.Org.Chem.* **2004,** *69* 3036-3042.

[43.] A. Fürstner, E. Kattnig, O. Lepage, *J.Am.Chem.Soc.* **2006,** *128* 9194-9204.

[44.] *Topics in Heterocyclic Chemistry*, (Ed.: N. Motohashi) Springer GmbH, Berlin **2009**.

[45.] T. Eicher, E. Hauptmann, R. Besenbruch, *The chemistry of heterocycles: structure, reactions, synthesis and applications*, Thieme, New York **1995**.

[46.] Bosch, B. E., Eckert, M., Militzer, H.-C., and Dreisbach, C. Process for the reduction of 3-heteroaryl-3-oxo-propanoic acid derivatives. Bayer

AG. [EP1340746]. 2003.
Ref Type: Patent

[47.] Reddy, K. R. and Erion, M. D. Novel 2'-C-methyl nucleoside derivatives. Janofsky & Walker LLP. [US 2005182252]. 2005.
Ref Type: Patent

[48.] R. Hulst, N. K. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1994,** *5* 699-708.

[49.] M. T. Reetz, G. Mehler, O. Bondarev, *Chem.Commun* **2006,** 2292-2294.

[50.] J. F. Bower, T. Riis-Johannessen, P. Szeto, A. J. Whitehead, T. Gallagher, *Chem.Commun.* **2007,** 728-730.

[51.] S. Rodríguez, M. M. Kayser, J. D. Stewart, *J.Am.Chem.Soc.* **2001,** *123* 1547-1555.

[52.] J.-P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, L. Bischoff, M. C. C. Deandrade, S. Darses, C. Galopin, J. A. Laffitte, *Tetrahedron-Asymmetry* **1994,** *5* 675-690.

[53.] C. W. Bradshaw, H. Fu, G. J. Shen, C. H. Wong, *J.Org.Chem.* **1992,** *57* 1526-1532.

[54.] K. Kurumaya, K. Takatori, R. Isii, M. Kajiwara, *Heterocycles* **1990,** *30* 745-748.

Chapter 5

Asymmetric Hydrogenation under DKR Conditions.

Abstract

In this chapter the attempts to perform an asymmetric hydrogenation on α-substituted β-ketoesters and α-aryl aldehydes are described. In the hydrogenation of the α-substituted β-ketoesters no syn/anti selectivity was obtained when using a ruthenium based catalyst containing phosphoramidite ligands. For the α-aryl aldehydes full conversions and selectivities of up to 83% ee were obtained when using a ruthenium phosphoramidite catalyst.

5.1 Introduction

As discussed in Chapter 1, kinetic resolution is one of the methods to obtain an enantiopure compound. In a kinetic resolution, a reaction is performed in which one of the two enantiomers of the substrate reacts (much) faster than the other. In this way one of the enantiomers is reacted away and the other enantiomer is left in enantioenriched form. The major drawback of this method for making an enantiopure compound is the fact that the maximum yield for these reactions is only 50%, since only half of the substrate will react.

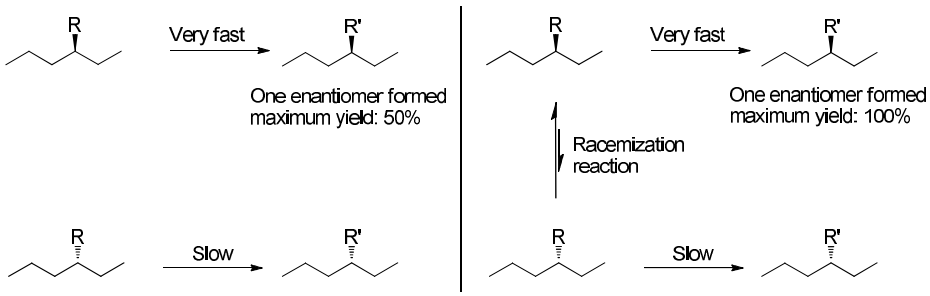
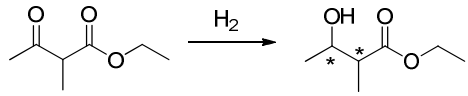


Figure 1: Kinetic resolution *vs.* dynamic kinetic resolution

If it would be possible to transform the other, non reacting, enantiomer into the reacting enantiomer while the resolution is taking place, it would be possible to obtain a yield higher than 50% and even go to full conversion. This process, in which the non-reactive enantiomer is transformed via, for instance, a racemization reaction into the reactive enantiomer during the resolution, is called a dynamic kinetic resolution (DKR).[1]

5.1.1 Dynamic kinetic resolution of α-substituted β-ketoesters



A class of substrates on which a DKR can readily be performed comprizes the α-substituted β-ketoesters because of their rapid racemization which occurs even at room temperature. The hydrogenation of these compounds has been an area of interest for quite some years. Since, if done correctly, one is able to control the formation of two stereogenic centers in one reaction step. A lot of work has been carried out on this subject by the group of Noyori after their discovery of the ruthenium-binap system.[2] They have proven to be able to hydrogenate methyl 2-(benzamidomethyl)-3-oxobutanoate (**5.1**) with excellent de and ee.[3]

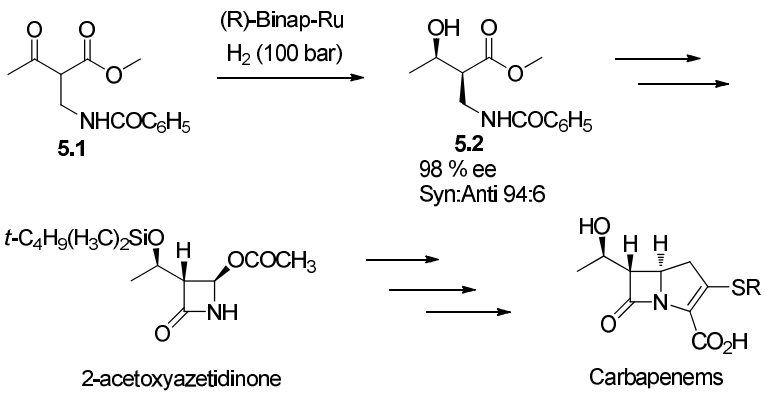


Figure 2: Industrial synthesis of a carbapenem intermediate via an enantioselective hydrogenation under DKR conditions.

This selective hydrogenation led to the development of an industrial scale process for the synthesis of an intermediate in the production of carbapenems (see Figure 2); an important class of antibiotics.

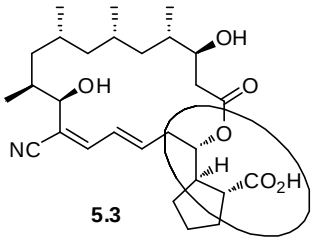


Figure 3: The structure of the natural product borrelidin (**5.3**) with, indicated by the ellipse, the part of the molecule which could be constructed using a DKR hydrogenation on a β-ketoester

Being able to control two stereocenters in one reaction step makes the synthesis of molecules containing multiple stereocenters a lot easier since it reduces the number of chirality introducing steps. In our group the natural antibiotic borrelidin (**5.3**)[4] (Figure 3) is being synthesized. This molecule contains a part which has been synthesized via asymmetric hydrogenation and DKR.

5.1.2 Enantioselective hydrogenation of aldehydes

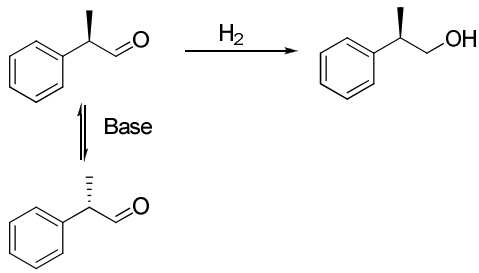


Figure 4: Hydrogenation of α-aryl aldehydes under DKR conditions.

Another class of substrates that can be interesting for hydrogenation under DKR conditions consists of α-aryl aldehydes. The stereogenic center of this type of aldehydes is known to racemize easily under basic conditions, due to the keto-enol tautomerism the aldehydes are, continuously, undergoing. By choosing the reaction conditions correctly it has been shown that it is possible to hydrogenate these aldehydes into enantiomerically enriched primary β-aryl alcohols.
So far, two examples are known of the enantioselective hydrogenation of aryl aldehydes. One by the group of List[5], who used a ruthenium catalyst containing

binap and DPEN as ligands, and the other one, reported by Zhou[6], who used a catalyst containing their SDP ligand (**5.4a-e**, Figure 5) in combination with a 1,2-diamine. Both systems have shown to be able to hydrogenate the aldehyde substrates in excellent yields and up to 99% ee.

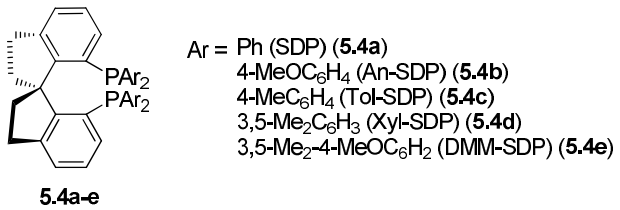


Figure 5: The different SDP ligands (**5.4a-e**) as used by the group of Zhou in the asymmetric hydrogenation of aldehydes.[6;7]

The products of these hydrogenations can be used in the synthesis of several biologically interesting compounds. As shown by the group of List it is possible to synthesize Ibuprofen® in two steps from the 2-(4-(*sec*-butyl)phenyl)-propionaldehyde. After the hydrogenation, $KMnO_4$ is used for the oxidation of the alcohol to the desired acid, keeping the stereogenic center in tact (still 92% ee after oxidation).[8]

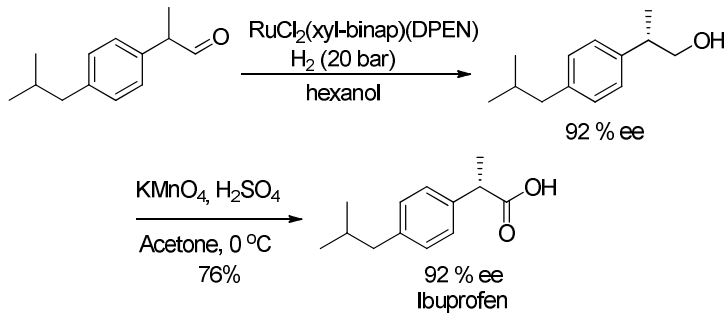


Figure 6: Synthesis of Ibuprofen as proposed by Li and List.[5]

In the synthesis of the pesticide Fenvalerate and the lipoxygenase inhibitor BAY x 1005[9] the hydrogenation of an α-aryl aldehyde can also be used as key step for the introduction of chirality.

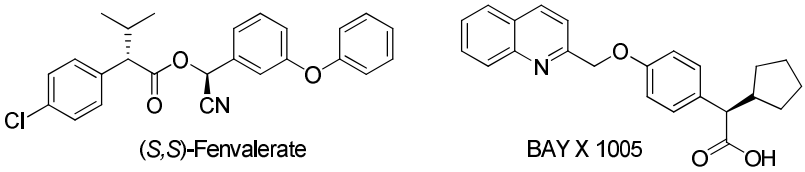


Figure 7: Structures of Fenvalerate and BAY X 1005 made by hydrogenation of an α-aryl aldehyde.[6]

Besides the α-aryl aldehydes, the group of Zhou also reported the asymmetric hydrogenation of α-aryloxy aldehydes[7] (Figure 8) under the same conditions.

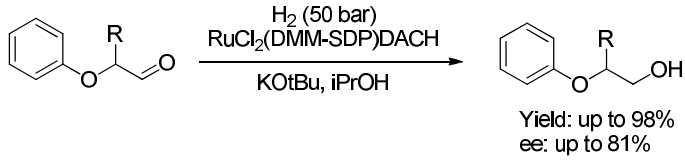


Figure 8: The α-aryloxy aldehydes which can also undergo asymmetric hydrogenation under DKR conditions.

They were able to reach excellent yields, up to 98%, and moderate to good ee's, up to 81% using a ruthenium catalyst containing their DMM-SDP (**5.4e**) ligand (see Figure 5) in combination with the diamine DACH.

In this chapter the results will be discussed of the hydrogenation of ethyl 2-methylacetoacetate (**5.5**) using a ruthenium catalyst based on phosphoramidite ligands. In the second part of the chapter, the synthesis of several α-arylaldehydes will be described. Also the search for a good, ruthenium based, hydrogenation catalyst for these aldehydes, using phosphoramidite ligands, will be discussed.

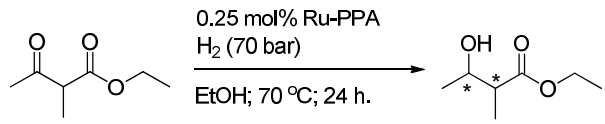
5.2 Results

The good results we obtained in the asymmetric hydrogenation of acetophenones and β-ketoesters as described in chapters 2 and 4, respectively, prompted us to also try the phosphoramidite ligands in hydrogenations under DKR conditions.

5.2.1 Hydrogenation results of α-substituted β-ketoesters

The asymmetric hydrogenation of ethyl 2-methyl-acetoacetate (**5.5**) was tested with the same catalyst that was used for the hydrogenation of β-ketoesters as described in chapter 4, thus a ruthenium catalyst in combination with two monodentate phosphoramidite ligands.

Table 1: Ligand screening in the hydrogenation of **5.5** under DKR conditions.

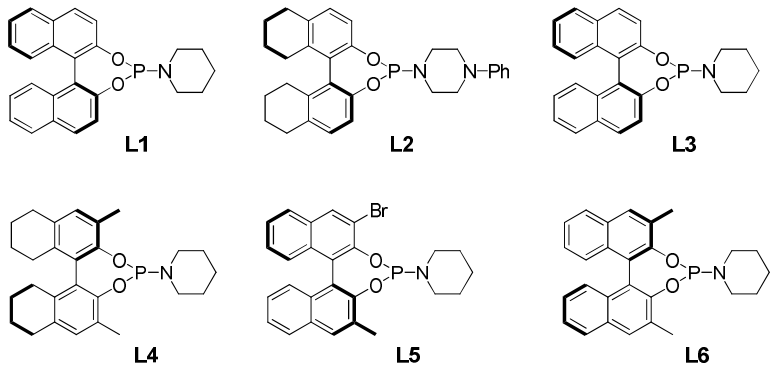


5.5 **5.6**

Ligand	Conversion (%)	syn:anti	ee syn (%)	ee anti (%)
(*S*)-**L1**	35	7:9	71	33
(*S*)-**L1**[a]	76	5:9	71	33
(*S*)-**L1**[b]	48	1:1	0	0
(*S*)-**L1**[c]	49	2:3	71	29
(*S*)-**L2**	15	8:9	31	19
(*S*)-**L3**	21	1:1	32	11
(*R*)-**L4**	18	1:1	28	15
(*S*)-**L5**	20	1:1	25	8
(*R*)-**L6**	10	1:1	-19	-9

Unless stated otherwise, reactions were carried out on 2 mmol of **5.5** catalyzed by 0.25 mol% ruthenium-phosphoramidite catalyst in 4 mL MeOH, 70 bar H_2 at 70 °C for 24 h. Catalysts where made as described in chapter 4. Substrate/Ru/L 400/1/4. a) Reaction time: 48 h. b) 5% KO*t*Bu added to the reaction mixture c) 0.5 mol% catalyst used.

Conversion, syn:anti-ratio and ee's were determined via chiral GC using a Chiralsil Dex-CB column isothermal (110 ^{o}C) conditions.



As can be seen in Table 1, the hydrogenation of **5.5** is much slower compared to β-ketoesters that do not have a substitution on the α-position. It was not possible to get the reaction to go to full completion within 24 hours. Also we were not able to achieve good selectivity for the *syn* or the *anti* product. The best selectivity we were able to get was a 3:2 ratio in favor of the anti product when we used 0.5 mol% of the catalyst which has the **L1** ligand. Disappointing also was the fact that of the two products it was the *syn* that displayed the higher ee; 71% in comparison to 29% for the more abundant *anti* product!

Another substrate tested in the asymmetric hydrogenation under DKR conditions was methyl 2-oxocyclopentanecarboxylate (**5.7**). The product of this hydrogenation is of great interest for our research group since it could be used as one of the precursors in the synthesis of borrelidin. The selective hydrogenation of this substrate can be achieved using a Ru binap type catalyst.[3] The interest within our group for the product of this hydrogenation prompted us to attempt it using a Ru-phosphoramidite catalyst.

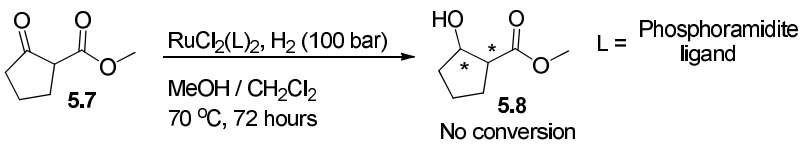


Figure 9: Asymmetric hydrogenation of methyl 2-oxocyclopentane carboxylate (**5.7**) in which no conversion was observed when a phosphoramidite ligand as used.

Sadly, in none of hydrogenation reactions of **5.7** in which a phosphoramidite ligand was used any conversion was observed. Also a switch in solvent from methanol to DCM did not get the reaction started.
With these disappointing results in hand we decided to try a different class of substrates which could also undergo asymmetric hydrogenation under DKR conditions.

5.3 Synthesis of α-arylaldehydes

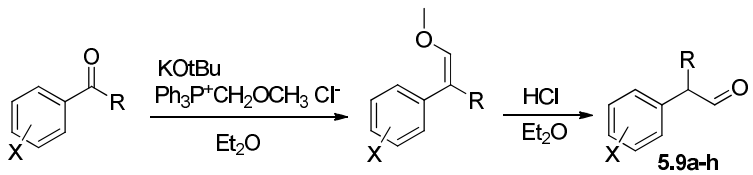


Figure 10: Synthesis of the α-branched arylaldehydes.

The various α-substituted arylaldehydes were synthesized as previously described by Xie *et al.*[6] and Yamazaki *et al.*[10] starting from the corresponding ketones. On these substrates a Wittig methoxymethylenation was performed using (methoxymethyl)triphenylphosphonium chloride with KO*t*Bu as a base. This resulted in the corresponding enol-methyl ethers. An acid catalyzed hydrolysis, using hydrochloric acid, gave the various arylaldehydes (**5.9b-h**) in moderate to good yields (51-72%), over two steps, as shown in Figure 11.

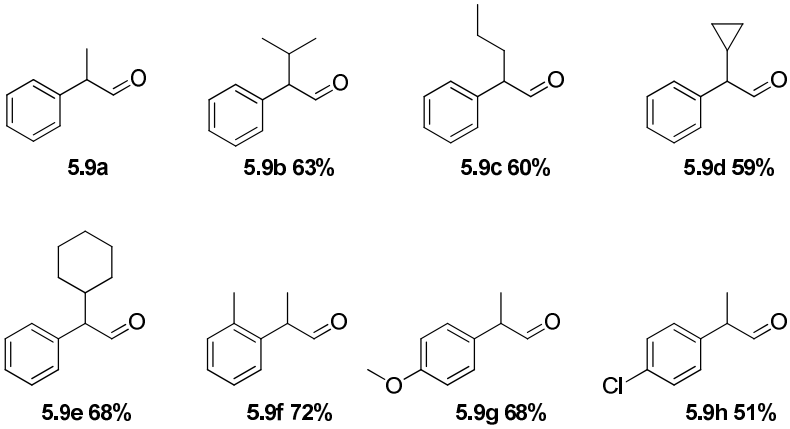


Figure 11: The α-alkylated phenyl acetaldehydes with the yields over two steps. Aldehyde **5.9a** is commercially available.

5.4 Results of the asymmetric hydrogenation of α-arylaldehydes

In order to get good results in the asymmetric hydrogenation of aryl aldehydes we had to make sure that the base induced racemization of the starting material was faster than the rate of hydrogenation. If this would not be the case the catalyst would eventually have no choice but to start hydrogenation the non-preferred enantiomer of the starting material.

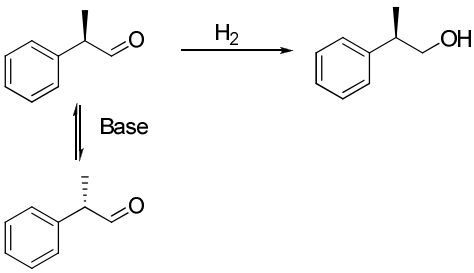
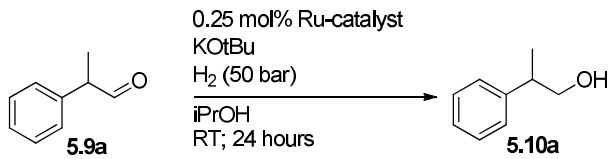


Figure 12: Base induced racemization during dynamic kinetic resolution in the hydrogenation of aldehydes.

By stopping the hydrogenation reaction at different times before full completion we were able to check the ee of the starting material.

In all cases, chiral-GC analysis of the reaction mixture showed that the starting material remained a racemic mixture. This was proof that the racemization was fast enough to keep up with the actual DKR hydrogenation experiments.
In the hydrogenation of hydratropaldehyde (**5.9a**) we started with the catalyst that performed best in the hydrogenation of simple aryl ketones. Using **(*R*)-L1**, different combinations with diamines were tested as well as different amounts of base to get the right combinations for this type of hydrogenation. As can be seen in Table 2 the best results in this type of hydrogenations are obtained when using a diamine of opposite configuration as the phosphoramidite.

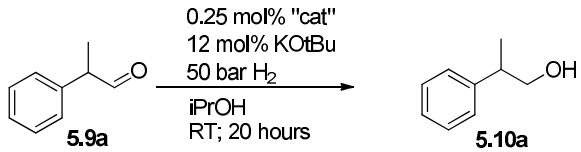
Table 2: Results of ligand diamine combinations



Entry	Ligand	Diamine	Base (mol%)	Conversion[a] (%)	ee[b] (%)
1	(*R*)-**L6**	(*R*,*R*)-DACH	12	85	−62
2	(*R*)-**L6**	(*S*,*S*)-DACH	12	full (85)	83
3	(*R*)-**L6**	(*R*,*R*)-DACH	24	full (93)	−33
4	(*R*)-**L6**	(*S*,*S*)-DPEN	12	full (90)	32
5	(*R*)-**L6**	(*S*,*S*)-DPEN	24	full (90)	29

All reactions were carried out on 2 mmol of **5.9a** with 0.25 mol% Ru-catalyst, which was made the same way as described in chapter 2, in a total volume of 4 mL while applying 50 bar H_2 pressure at room temperature for 24 hours. Substrate/Ru/PPA/Diamine 400/1/2/1. a) Number in parentheses is the isolated yield of the product. b) Ee's were determined via chiral GC using a Chiralsil Dex-CB column.

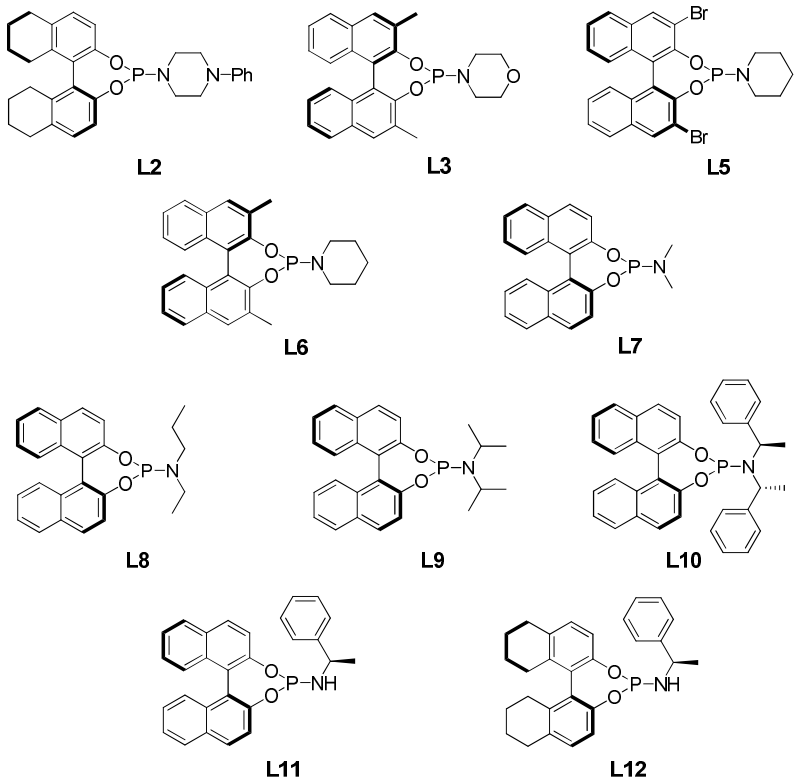
Table 3: Results of the ligand screening in the asymmetric hydrogenation of hydratropaldehyde.



	Ligand	Conversion (%)	ee (%)
1	**(*R*)-L6**	full	83
2	**(*S*)-L7**	70	−14
3	**(*S*)-L8**	40	−28
4	**(*R*)-L3**	full	71
5	**(*S*)-L5**	full	−51
6	**(*S*)-L2**	<10	nd
7	**(*S*)-L9**	<10	nd
8	**(*S*)-L10**	<10	nd
9	**(*S*)-L11**	<10	nd
10	**(*S*)-L12**	<10	nd

Unless stated otherwise all reactions were carried out on 2 mmol **5.9a** with 0.25 mol% ruthenium catalyst bearing the mentioned PPA-ligand in combination with DACH of the opposite absolute configuration.

After finding a catalyst and conditions that led to full conversion but induced an ee that is up for improvement, a small screening of ligands was done. As shown in Table 3 none of the ligands led to a better performing catalyst than the DiMePip ligand **L6** which was used in first instance.

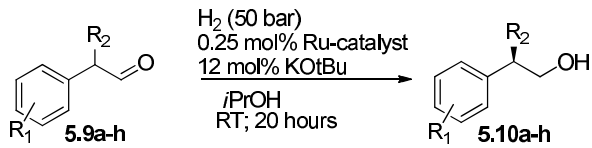


Use of MonoPhos, **L7**, and the somewhat bigger Et-Propyl ligand **L8** did not result in full conversion within 20 hours. Also the ee's reached after the 20 hours of 14% and 28% respectively were nowhere near the level reached when **L6** was used. The even bulkier phosphoramidites, di-isopropyl phosphoramidite **L9** and Leggy ligand **L10**, performed even worse, as hardly any conversion and a negligible ee were observed. Also the two NH-ligands **L11** and **L12** and the very bulky 8H-Ph-piperazine **L2** did not result in conversion and ee. The only two ligands which allowed us to obtain similar results as with DiMePip were the two ligands that had a substitution on the 3,3'-position of the binol backbone. Both the 3,3'-DiMethyl-Morfphos (**L3**) and the 3,3'-dibromo-Pipphos (**L5**) ligands induced full conversion and 71% and 51% ee, respectively. This indicates again the importance of the extra bulk created at these positions with respect to enhancing the selectivity of the reaction. However, none of these ligands outperformed **L6**.

5.5 Substrate scope

After it was concluded that none of the tested ligands gave a better result in the asymmetric hydrogenation of hydratropaldehyde we decided to explore the substrate scope of the reaction with the catalyst that was used in first instance. This is the ruthenium catalyst which bears the phosphoramidite (*R*)-**L6** in combination with the diamine (*S,S*)-DACH. The results of these reactions can be found in Table 4. It can be seen that also varying the substrate did not lead to a higher ee either.

Table 4: Results of the asymmetric hydrogenation of different α-aryl aldehydes.



	Aldehyde	R1	R2	Conversion[a,b] (%)	ee[a] (%)
1	**5.9a**	H	Me	full (95)	83
2	**5.9b**	H	*i*Pr	full (91)	74
3	**5.9c**	H	*n*Pr	full (96)	71
4	**5.9d**	H	*c*Pr	full (90)	78
5	**5.9e**	H	Cyclohexyl	full (89)	78
6	**5.9f**	*o*-Me	Me	full (92)	69
7	**5.9g**	*p*-OMe	Me	full (89)	62
8	**5.9h**	*p*-Cl	Me	full (87)	63

All reactions were carried out on 1 mmol substrate with 0.25 mol% Ru catalyst bearing two (*R*)-**L6** and (*S,S*)-DACH in the presence of 12 mol% KOtBu in a total volume of 2 mL iPrOH. During the reaction 50 bar H_2 was applied for 20 hours at room temperature. a) Conversion and ee's were determined via chiral-GC using a Chiralsil Dex-CB column. All products are of (*R*)-configuration. b) Number in parentheses denotes isolated yield.

What does become clear from this table is that the substituent on the alpha position or on the phenyl ring does not influence the outcome of the reaction very much. In all cases the reaction goes to full completion and the ee's are all moderate to good (62 – 83%). Selectivity-wise it can be seen that the ee drops a

little bit when a substituent is placed on the phenyl ring (**5.9f-h**), although it does not seem to matter whether these substituents are electron withdrawing (**5.9h**), electron donating (**5.9g**) or a more sterically demanding *o*-methyl group (**5.9f**). In all cases the ee drops about 15-20% compared to the best performing substrate **4a**. Placing different substituents on the alpha position (**5.9b-e**) does not seem to make much difference since in all cases the ee remains about the same. If anything it can be said, it is that the introduction of a cycloalkane (**5.9d-e**) makes the reaction a bit more selective in comparison to the non cyclic side chains (**5.9b-c**).

5.6 Conclusions

It is concluded that the hydrogenation of **5.5** under DKR conditions is possible. Unfortunately, the selectivity in this hydrogenation is not very high. Mostly equimolar mixtures of *syn* and *anti* product are formed with at best a 9:5 ratio in favor of the anti product. The ee's of the major diastereomer are at best moderate. The minor diastereomer displayed better enantioselectivity up to a good 71%. Also it appeared that the reaction proceeded much slower in comparison with that of the unsubstituted β-ketoesters (See Chapter 4), and did not go to full conversion. Apparently the extra substituent on the α-position made the substrate less likely to coordinate to the catalyst. In the case of substrate **5.7** the ring structure made it even impossible for the substrate to be hydrogenated using phosphoramidite ligands in the catalyst.

The α-aryl aldehydes could be fully hydrogenated in most cases, however, the selectivity of the reaction is only moderate. It appears that the phosphoramidite ligands in combination with the chiral 1,2-diamine, in this case, cannot create an environment selective enough to obtain good ee's.

5.7 Experimental

General Experimental

For general experimental remarks see Chapter 2. Substrates **5.5**, **5.7** as well as the ketones used in the aldehyde synthesis were purchased from Aldrich and used as received. The $Ph_3P^+CH_2OCH_3\,Cl^-$ was obtained from Alfa Aesar. Ligands **L4** and **L6** are previously described in this thesis, **L1**,[11] **L2,**[12] **L3,**[11] **L7,**[13] **L8,**[14] **L9-10,**[11] **L11**[15] and **L12**[16] were all described in literature before.

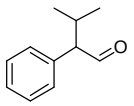
Procedure for the hydrogenation of ethyl 2-methyl-acetoacetate (**5.5)**

In 2 mL DMF 1.5 mg (2.5 μmol) $[RuCl_2(cymene)]_2$ and 4 eq (10 μmol) phosphoramidite were dissolved. The solution was heated at 90 ^oC for two hours while stirring. After two hours the solution was cooled down to room temperature after which the DMF was removed *in vacuo*. The residue was redissolved in 4 mL MeOH. The solution containing the catalyst was transferred to a glass vial loaded with 288 mg (2 mmol) **5.5** and a stirring bar. The vial was closed with a septum cap. The septum was pierced with a hypodermic needle and placed in an autoclave. After the autoclave was closed it was purged three times with 5 bar N_2 and three times with 8 bar H_2. After purging the pressure was set at 70 bar and the autoclave was heated till 70 ^oC for 24 hours. When the reaction time had passed, the autoclave was let to cool down to room temperature and the hydrogen pressure was carefully released. After evaporation of the solvent the residue was passed over a small silica column. Ethyl 2-methyl-3-hydroxybutanoate (**5.6**) was obtained as a mixture of four products **(*R,S*)-5.6**, **(*R,R*)-5.6**, **(*S,R*)-5.6** and **(*S,S*)-5.6.** ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 4.38-4.01 (m, 6H), 2.56-2.41 (m, 2H), 1.37-1.17 (m, 18H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 170.5, 67.9, 61.3, 45.4, 21.8, 14.0, 12.7. Ee's and *syn / anti* ratios were determined via chiral GC[17], Chiralsil Dex-CB $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (50 min) – (10 ^oC / min) → 180 ^oC. $T_{S,S} = 33.45$ min, $T_{R,S} = 34.19$ min, $T_{S,R} = 34.47$ min, $T_{R,R} = 35.37$ min.

General procedure for the aldehyde synthesis: A suspension of 5.1 gram $Ph_3P^+CH_2OCH_3\,Cl^-$ (15 mmol) in 40 mL ether was cooled to 0 ^oC and 2.0 gram KO*t*-Bu (17.5 mmol, 1.2 equiv.) was added in portions to give a dark red solution. After stirring this mixture for 30 minutes, a solution of 0.66 eq of ketone (10 mmol) in 10 mL ether was added dropwise to the solution containing the Wittig reagent. The resulting mixture was stirred at 0 ^oC for 30 minutes, after which it was allowed to warm up to room temperature and kept stirring until the reaction was finished (TLC monitor). When the

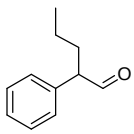
reaction was completed, the mixture was poured into 75 mL of water. The layers were separated and the aqueous layer was extracted twice with EtOAc (30 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified on a silica gel column with a ether/pentane (1 : 20) mixture as eluent to afford the enol-methyl ether.

This enol-methyl ether was dissolved in Et_2O (30 mL) and to this solution was slowly added a 70% aqueous solution of $HClO_4$ (~3 mL). After stirring for several hours (TLC monitor) at room temperature the mixture was added slowly to a saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated and the aqueous layer was extracted twice with 30 mL Et_2O. The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified on a silica gel column with a ether/pentane (1 : 20) mixture as eluent to afford the corresponding α-aryl aldehyde as an oil in reasonable to good yields.



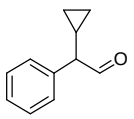
2-phenyl-3-methylbutanal[6] **(5.9b)**

The product was obtained as a colorless oil after column chromatography, 1.02 gram (6.31 mmol 63%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 9.70 (d, *J* = 3.2 Hz, 1H), 7.37-7.16 (m, 5H), 3.18 (dd, *J* = 3.2 Hz, *J* = 9.4 Hz, 1H), 2.47-2.33 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 201.1, 134.9, 129.3, 128.9, 127.4, 66.8, 28.8, 21.2, 20.0. HRMS (EI) calcd for $C_{11}H_{14}O$ (M^+) 162.1045 found 162.1051.



2-phenylpentanal[18] **(5.9c)**

The product was obtained as a colorless oil after column chromatography, 0.98 gram (6.02 mmol, 60%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 9.66 (d, *J* = 1.9 Hz, 1H), 7.38-7.17 (m, 5H), 3.51 (dt, *J* = 2.0 Hz, *J* = 3.5 Hz, 1H), 1.83-1.60 (m, 2H), 1.32-1.22 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 201.1, 134.8, 129.0, 128.8, 127.5, 58.4, 31.8, 20.3, 13.9. HRMS (EI) calcd for $C_{11}H_{14}O$ (M^+) 162.1045 found 162.1049.

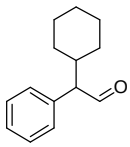


2-cyclopropyl-2-phenylacetaldehyde[19] **(5.9d)**

The product was obtained as a colorless oil after column chromatography, 0.94 gram (5.89 mmol, 59%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 9.75 (d, *J* = 3.4 Hz, 1H), 7.39-7.24 (m, 5H), 2.80 (dd, *J* = 2.5 Hz, *J* = 9.5 Hz,

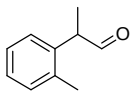
1H), 1.41-1.23 (m, 1H), 0.82-0.55 (m, 2H), 0.44-0.17 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 197.0, 132.9, 125.5, 125.2, 124.2, 59.9, 7.5, 1.1, 0.0. HRMS (EI) calcd for $C_{11}H_{12}O$ (M^+) 160.0888 found 160.0877.

2-cyclohexyl-2-phenylacetaldehyde[20] **(5.9e)**



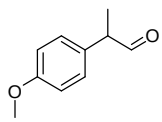
The product was obtained as a colorless oil after column chromatography, 1.38 gram (6.84 mmol, 68%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 9.69 (d, *J* = 3.6 Hz, 1H), 7.40-7.14 (m, 5H), 3.25 (dd, *J* = 3.5 Hz, *J* = 9.7 Hz, 1H), 2.20-2.01 (m, 1H), 1.87-1.62 (m, 4H), 1.44-0.95 (m, 4H), 0.90-0.70 (m, 2H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 201.2, 135.2, 129.3, 128.9, 127.4, 65.8, 38.2, 31.8, 30.2, 26.2, 26.0. HRMS (EI) calcd for $C_{14}H_{18}O$ (M^+) 202.1358 found 202.1351.

2-(2-methylphenyl)-propanal[21] **(5.9f).**



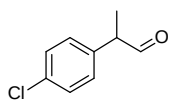
The product was obtained as a colorless oil after column chromatography 1.06 gram (7.16 mmol, 72%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 9.66, (d, *J* = 1.5 Hz, 1H), 7.28-7.16 (m, 2H), 7.09-7.02 (m, 2H), 3.84 (dq, *J* = 1.3 Hz, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 201.1, 136.3, 130.9, 127.5, 127.4, 126.7, 49.3, 19.6, 14.3. HRMS (EI) calcd for $C_{10}H_{12}O$ (M^+) 148.0888 found 148.0892.

2-(4-metoxyphenyl)-propanal[22] **(5.9g)**



The product was obtained as a colorless oil after column chromatography, 1.12 gram (6.83 mmol, 68%) ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 9.65 (d, *J* = 1.4 Hz, 1H), 7.15-7.09 (m, 2H), 6.95-6.88 (m, 2H), 3.81 (s, 3H), 3.60-3.56 (m, 1H), 1.41 (d, *J* = 7.1 Hz, 3H) ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 201.2, 159.0, 129.6, 129.3, 114.5, 66.3, 52.1, 14.7. HRMS (EI) calcd for $C_{10}H_{12}O_2$ (M^+) 164.0837 found 164.0849.

2-(4-chlorophenyl)-propanal[22] **(5.9h)**



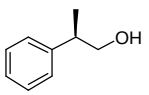
The product was obtained as a yellow oil after column chromatography, 0.85 gram (5.06 mmol, 51%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 9.66 (d, *J* = 1.2 Hz, 1H), 7.47-7.08 (m, 4H), 3.48 (q, *J* = 7.0 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 200.2,

136.2, 133.1, 129.6, 129.2, 65.8, 14.6. HRMS (EI) calcd for C_9H_9ClO (M^+) 168.0342 found 168.0337.

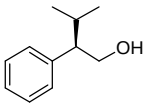
General procedure for the hydrogenation of the aldehydes: In 2 mL DMF were dissolved 1.5 mg (2.5 μmol) $[RuCl_2(cymene)]_2$ and 10 μmol (4 equiv) phosphoramidite ligand. The solution was heated at 90 °C for two hours while stirring. Subsequently, the solution was cooled down to room temperature after which 5 μmol (2 equiv.) of diamine were added and the solution was stirred for an additional 16 hours. After overnight stirring the DMF was removed *in vacuo* and the residue was stripped twice with toluene and washed once with hexane. The now remaining powder was redissolved in 2 mL *i*PrOH. The solution containing the catalyst was transferred to a glass vial loaded with 1 mmol of the aldehyde substrate and a stirring bar. Just prior to placing the vial in the autoclave 0.12 mL of a 1.0M KO*t*Bu solution was added to the solution. The vial was closed with a septum cap. The septum was pierced with a hypodermic needle and placed in an autoclave. After the autoclave was closed it was purged three times with 5 bar N_2 and three times with 8 bar H_2. After purging the pressure was set to 50 bar and the autoclave was placed on a stirring plate and stirred at room temperature for 24 hours. The hydrogen pressure was carefully released. After evaporation of the solvent a small sample of the residue was passed over a silica plug in order to obtain a GC sample. Conversion and ee were determined via ^{1}H-NMR and chiral GC respectively.

All alcohols were made via the hydrogenation using (*R*)-DimethylPipPhos (**L6**) and (*S*,*S*)-DACH.

(*R*)-2-phenylpropan-1-ol[6] **(5.10a)**

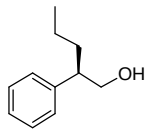


The product was obtained as a colorless oil in 95% yield. $[\alpha]_D$ = 13.3 (c 1.19, $CHCl_3$), 83% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.42-7.01 (m, 5H), 3.70 (d, *J* = 6.8 Hz, 2H), 3.03-2.86 (m, 1H) 1.28 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 143.6, 128.6, 137.5, 126.7, 68.7, 42.4, 17.6. Ee determination was carried out on Chiralsil Dex-CB column $T_{inlet} = T_{det}$ = 250 °C; T_{start} = 100 °C (35 min) – (10 °C / min) → 180 °C. T_S = 34.80 min; T_R = 35.48 min.



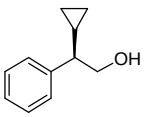
(*R*)-2-phenyl-3-methyl-butan-1-ol[6] **(5.10b)**

The product was obtained as a colorless oil in 91% yield. $[\alpha]_D$ = −9.9 (c 1.14, $CHCl_3$), 74% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.37-7.20 (m, 5H), 4.01-3.77 (m, 2H), 2.56-2.45 (m, 1H), 1.94-1.84 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 141.7, 128.7, 128.5, 126.7, 65.2, 55.8, 30.1, 21.0. Ee determination was carried out on Chiralsil Dex-CB column $T_{inlet} = T_{det}$ = 250 °C; T_{start} = 100 °C (30 min) – (10 °C / min) → 180 °C. T_S = 26.86 min; T_R = 26.93 min.



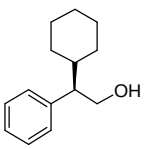
(*R*)-2-phenylpentan-1-ol[23] **(5.10c)**

The product was obtained as a colorless oil in 96% yield. $[\alpha]_D$ = −8.3 (c 1.05, $CHCl_3$), 71% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.36-7.20 (m, 5H), 3.80-3.65 (m, 2H), 2.81-2.78 (m, 1H), 1.71-1.50 (m, 2H), 1.34 (bs, 1H), 1.25-1.22 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 142.5, 128.6, 128.1, 126.8, 67.7, 48.4, 34.2, 20.5, 14.1. Ee determination was carried out on Chiralsil Dex-CB column $T_{inlet} = T_{det}$ = 250 °C; T_{start} = 110 °C (3 min) – (1 °C / min) → 180 °C. T_S = 52.85 min; T_R = 53.05 min.



(*R*)-2-cyclopropyl-2-phenylethanol[24] **(5.10d)**

The product was obtained as a colorless oil in 90% yield. $[\alpha]_D$ = −8.5 (c 0.93, $CHCl_3$), 78% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.40-7.20 (m, 5H), 3.89-3.86 (m, 2H), 2.09-1.98 (m, 1H), 1.45 (bs, 1H), 1.11-0.93 (m, 1H), 0.71-0.58 (m, 1H), 0.51-0.26 (m, 2H), 0.16-0.04 (m, 1H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 139.3, 125.5, 124.9, 123.7, 64.5, 50.3, 10.2, 2.0, 0.0. Ee determination was carried out on Chiralsil Dex-CB column $T_{inlet} = T_{det}$ = 250 °C; T_{start} = 110 °C (3 min) – (1 °C / min) → 180 °C. T_R = 47.59 min; T_S = 49.59 min.

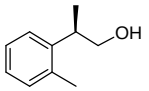


(*R*)-2-cyclohexyl-2-phenylethanol[6] **(5.10e)**

The product was obtained as a white solid, M_p = 48-50 °C, in 89% yield. $[\alpha]_D$ = −4.7 (c 0.95, $CHCl_3$), 78% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.37-7.16 (m, 5H), 4.04-3.77 (m, 2H), 2.62-2.51 (m, 1H), 1.91-0.76 (m, 11H) ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 141.7, 128.8, 128.5, 126.6, 64.8, 54.8, 39.7, 31.3, 31.2, 26.4, 26.3, 26.3. Ee determination was carried out on

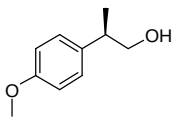
Chiralsil Dex-CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (3 min) – (1 ^oC / min) → 180 ^oC. $T_S = 69.16$ min; $T_R = 69.44$ min.

(*R*)-2-(2-methylphenyl)-propan-1-ol[25] **(5.10f)**



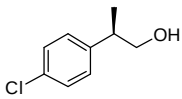
The product was obtained as a colorless oil in 92% yield. $[\alpha]_D = 10.1$ (c 1.16, $CHCl_3$), 69% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.22-7.07 (m, 4H), 3.80-3.63 (m, 2H), 3.27-3.17 (m, 1H), 2.36 (s, 3H), 1.41 (bs, 1H), 1.24 (d, *J* = 6.9 Hz, 3H) ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 141.7, 136.4, 130.5, 126.3, 126.3, 125.4, 68.0, 37.2, 19.6, 17.5. Ee determination was carried out on Chiralsil Dex-CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 100\ ^oC$ (30 min) – (10 ^oC / min) → 180 ^oC. T_S = 24.80 min; $T_R = 24.91$ min.

(*R*)-2-(4-methoxyphenyl)-propan-1-ol[23] **(5.10g)**



The product was obtained as a colorless oil in 89% yield. $[\alpha]_D = 9.6$ (c 1.11, $CHCl_3$), 62% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.19-7.13 (m, 2H), 6.91-6.84 (m, 2H), 3.79 (s, 3H), 3.66 (d, *J* = 7.0 Hz, 2H), 2.92-2.82 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 158.3, 135.6, 128.4, 114.0, 68.8, 55.3, 41.6, 17.7. Ee determination was carried out on Chiralsil Dex-CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 110\ ^oC$ (3 min) – (1 ^oC / min) → 180 ^oC. $T_S = 31.65$ min; $T_R = 33.21$ min.

(*R*)-2-(4-chlorophenyl)-propan-1-ol[26] **(5.10h)**



The product was obtained as a colorless oil in 87% yield. $[\alpha]_D = 5.3$ (c 0.98, $CHCl_3$), 63% ee. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm) 7.33-7.27 (m, 2H), 7.20-7.15 (m, 2H), 3.71-3.62 (m, 2H), 2.95-2.86 (m, 1H), 1.52 (bs, 1H), 1.24 (d, *J* = 6.9 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 142.2, 132.4, 128.9, 128.7, 68.5, 41.7, 17.5. Ee determination was carried out on Chiralsil Dex-CB column $T_{inlet} = T_{det} = 250\ ^oC$; $T_{start} = 100\ ^oC$ (30 min) – (10 ^oC / min) → 180 ^oC. T_S = 23.55 min; $T_R = 26.09$ min.

5.8 References

[1.] H. Pellissier, *Tetrahedron* **2008,** *64* 1563-1601.

[2.] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J.Am.Chem.Soc.* **1987,** *109* 5856-5858.

[3.] R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, *J.Am.Chem.Soc.* **1989,** *111* 9134-9135.

[4.] J. Berger, L. M. Jampolsky, M. W. Goldberg, *Arch.Biochem.* **1949,** *22* 476-478.

[5.] X. G. Li, B. List, *Chem.Commun.* **2007,** 1739-1741.

[6.] J.-H. Xie, Z.-T. Zhou, W.-L. Kong, Q.-L. Zhou, *J.Am.Chem.Soc.* **2007,** *129* 1868-1869.

[7.] Z.-T. Zhou, J.-H. Xie, Q.-L. Zhou, *Adv.Synth.Catal.* **2009,** *351* 363-366.

[8.] J. Barluenga, B. Baragana, J. M. Concellon, A. Pinera-Nicolas, M. R. Diaz, S. Garcia-Granda, *J.Org.Chem.* **1999,** *64* 5048-5052.

[9.] A. Hatzelmann, R. Fruchtmann, K. H. Mohrs, S. Raddatz, R. Mullerpeddinghaus, *Biochem.Pharm.* **1993,** *45* 101-111.

[10.] J. Yamazaki, T. Watanabe, K. Tanaka, *Tetrahedron: Asymmetry* **2001,** *12* 669-675.

[11.] L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. de Vries, R. Naasz, B. L. Feringa, *Tetrahedron* **2000,** *56* 2865-2878.

[12.] H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. de Vries, B. L. Feringa, *J.Org.Chem* **2005,** *70* 943-951.

[13.] R. Hulst, N. K. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1994,** *5* 699-708.

[14.] A. Duursma, J. G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J.Org.Chem.* **2004,** *69* 8045-8052.

[15.] D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J.Am.Chem.Soc.* **2002,** *124* 14552-14553.

[16.] X. Li, X. Jia, G. Lu, T. T. L. Au-Yeung, K. H. Lam, T. W. H. Lo, A. S. C. Chan, *Tetrahedron: Asymmetry* **2003,** *14* 2687-2691.

[17.] T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem.Eur.J.* **2002,** *8* 843-852.

[18.] T. Satoh, N. Itoh, K. Gengyo, S. Takada, N. Asakawa, Y. Yamani, K. Yamakawa, *Tetrahedron* **1994,** *50* 11839-11852.

[19.] L. A. Paquette, G. D. Maynard, *J.Org.Chem.* **1989,** *54* 5054-5063.

[20.] M. Stratakis, D. Kalaitzakis, D. Stavroulakis, G. Kosmas, C. Tsangarakis, *Org.Lett.* **2003,** *5* 3471-3474.

[21.] A. I. Meyers, R. D. Walkup, *Tetrahedron* **1985,** *41* 5089-5106.

[22.] T. Bauman, H. Vogt, S. Bräse, *Eur.J.Org.Chem.* **2007,** 266-282.

[23.] D. Strübing, P. Krumlinde, J. Piera, J.-E. Bäckvall, *Adv.Synth.Catal.* **2007,** *349* 1577-1581.

[24.] S. Nishida, T. Fujioka, N. Shimizu, *J.Organomet.Chem.* **1978,** *156* 37-44.

[25.] A. G. Schultz, S. J. Kirincich, *J.Org.Chem.* **1996,** *61* 5631-5634.

[26.] S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt, A. Pfaltz, *Adv.Synth.Catal.* **2005,** *347* 282-288.

Chapter 6
Conclusions and Outlook for Further Research

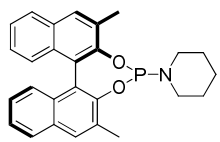
6.1 Introduction

In the year 2000 several groups rediscovered the use of monodentate ligands in asymmetric hydrogenation.[1-3] The search for new methodologies using these monodentate ligands instead of bidentate ligands in several types of asymmetric hydrogenation reactions has been a topic of great interest since then. In our group a number of methods have successfully been developed using monodentate phosphoramidite ligands in the asymmetric hydrogenation of olefinic[4;5] and imine[6] type substrates.[7]
The goal of the research described in this thesis was to develop methodologies for the asymmetric hydrogenation of different types of ketones using monodentate phosphoramidite ligands. Here the conclusions of this research are presented and a brief outlook towards future research is given.

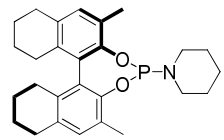
6.2 Conclusions

We have shown that monodentate phosphoramidites are highly versatile chiral ligands in the ruthenium catalyzed asymmetric hydrogenation of several types of carbonyl compounds.
In chapter 2 we showed that a ruthenium catalyst containing a chiral diamine and two bulky phosphoramidite ligands, all with the same absolute configuration, was able to hydrogenate a range of acetophenone type ketones in good yields and enantioselectivities. The best performing combination was found to be the one in which DACH is used in combination with the phosporamidite ligand 3-3'-dimethyl PipPhos (See Figure 1). Reaching ee's of up to 97%, the catalytic experiments show that the selectivity, as well as the substrate scope, of these types of complexes are better or comparable with other catalysts based upon monodentate ligands so far reported in literature.[8-10] This, combined with a turnover number (TON) up to 1000 and the easy ligand synthesis and access to structurally diverse ligands, makes the method, although slower then Noyori's original binap based catalyst and other bidentate ligand based catalysts, a good candidate for possible applications in industry.

Elucidating the structure of the complex proved, however, to be troublesome. From ^{31}P-NMR studies it became clear that, in the pre-catalyst, despite a Ru-ligand ratio of 1:2, only one phosphoramidite ligand is bound per ruthenium as an absorption was found corresponding to the free phosphoramidite ligand. We assume that the pre-catalyst has a dimeric structure in which one phosphoramidite ligand per ruthenium is bound. However all attempts at obtaining further analytical data on this complex failed. From the experimental results, however, we must conclude that in order to get good selectivity in the hydrogenation reactions there need to be two phosphoramidite ligands per metal center present in the reaction mixture.



3-3'-dimethyl PipPhos



(8H)-3-3'-dimethyl PipPhos

Figure 1: The two best performing phosphoramidite ligands in the acetophenone and beta-ketoester hydrogenations.

In chapter 3 we showed that the iridium catalyzed asymmetric hydrogenation of aryl, alkyl-ketones using phosphoramidite ligands works as well. However, the catalyst proved to be less selective compared to the ruthenium based catalyst. Still the obtained ee's of up to 68% are not bad for an iridium based catalyst containing both a phosphorus type ligand and a chiral diamine. We showed that in order to get the best results in terms of selectivity, one phosphoramidite ligand and halve an equivalent of diamine was needed per iridium center. The phenomenon of an iridium catalyst performing very well with only one phosphoramidite has been observed before in the hydrogenation of a dehydroamino acid.[12] The need for just halve an equivalent of diamine per iridium center might point towards a dimeric type complex which is performing the catalysis, although further research on a preformed complex will be needed to prove this indefinitely. So far a TON of <400 is reached which is too low for an iridium based catalyst. If further research into this catalyst also can lead to a faster, and somewhat more selective process, this can become a good alternative for the ruthenium based process in which the presence of a base is necessary in order to get a good result.

The second type of ligand that was tested in the iridium catalyzed hydrogenations was a secondary phosphine oxide ligand. Unfortunately, its use did not lead to very selective reactions. Also in the ruthenium catalyzed hydrogenations, the SPO ligand did not induce selectivities that came anywhere near the ones obtained upon the use of phosphoramidite ligands.

The complex used in the asymmetric hydrogenation of β-ketoesters as described in chapter 4 displayed the difficulties in characterization as the complexes used in chapter 2. Also here no clear absorption was found for a bound phosphoramidite ligand in the ^{31}P NMR of the precatalyst complex that was used in the catalysis. The experimental results showed the presence of two ligands per metal center are necessary in the reaction mixture in order to get good selectivities. We found a metal ligand combination which was able to hydrogenate a range of β-ketoesters with good conversions and excellent ee's (up to 99%). In these types of hydrogenations a phosphoramidite ligand was also found to perform the best when two groups were present on the 3- and 3'-positions as well as a partially saturated backbone; the 8H-3,3'-dimethylPipPhos. This ligand proved to induce the best results in terms of selectivity, creating the catalyst of choice for the asymmetric hydrogenation of β-ketoesters based on monodentate ligands.[11] With a TON of up to 400 the catalyst might be somewhat slower compared to when a bidentate ligand is used, still it might be considered for use in industry because of its high selectivity and again easy ligand preparation, which saves a lot of time in the production process.

Chapter 5 describes the dynamic kinetic resolution of racemic α-substituted aldehydes via hydrogenation to the enantiopure alcohols, using the same catalyst as developed for the asymmetric hydrogenation of aromatic ketones (Chapter 2). Full conversions were achieved. The best enantioselectivity that was obtained never exceeded 85%. This compares poorly with the published results that were obtained wherein binap and SPD ligands were used. In these cases enantioselectivities of up to 99% were obtained.[13;14] Thus, several challenges still remain for the phosphoramidite ligands in the asymmetric hydrogenation research.

6.3 Outlook

The research into asymmetric hydrogenation has come a long way since the first reports in the 1960s. Many substrate classes can be hydrogenated with good conversions and high to excellent selectivities.[15] Also in industry, asymmetric hydrogenations are recognized as a valuable tool for selectively introducing a stereogenic center in a product. However, in the industrial practice the substrates often carry many functional groups that can interfere with the hydrogenation reaction, for instance by binding to the metal centre. Thus far, the best results have been obtained with relatively simple substrates containing none or only non interfering functional groups besides the olefinic double bond

In addition, some substrate classes remain for which no general asymmetric hydrogenation method is available. Especially for compounds containing sulfur or phosphorus functionalities no, or very limited, methods are available for fast and selective hydrogenations.[16;17]

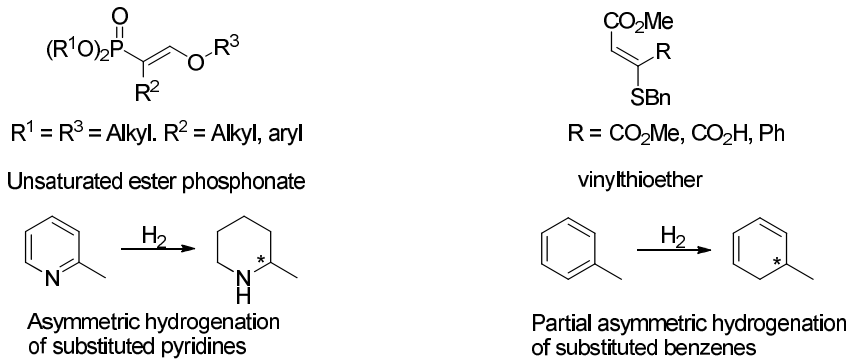


Figure 2: Examples of substrates and reaction types that are (still) difficult to hydrogenate by asymmetric catalysis.

But also in the hydrogenation of aromatic compounds still some major challenges remain. For instance the asymmetric hydrogenation of substituted pyridines, or even more challenging the partial asymmetric hydrogenation of a substituted benzene type substrate. The challenges in asymmetric hydrogenation in academia these days lies with these type of substrates.

Careful screening and further understanding of the mechanisms of the hydrogenations should lead to further insight and development of new ligands

and methods for asymmetric hydrogenation. Monodentate ligands provide a very valuable tool in this research as has been shown in the last ten years. Because of their, often, easy synthesis and high structurally variability they make it easy to screen a large number of ligands in a short amount of time increasing the chances of finding a hit enormously compared to bidentate ligands. A second benefit of using monodentate ligands is the fact that they make it possible to easily use a mixture of different ligands in a mixed ligand approach, this way increasing the amount of possible catalysts when using n ligands to n(n+1)/2.[18-20] Another major challenge that remains in hydrogenation research is replacing the more expensive metals like rhodium, iridium and ruthenium by the cheaper variants like copper, nickel and iron. If efficient and selective catalysts can be created using these types of metals, hydrogenation might become even more interesting for use in industrial processes. Recently, interesting results have been obtained using copper[21] and iron catalysts.[22;23]

To further exploit the use of asymmetric hydrogenation, industry should invest in making the methods, developed by academia, applicable in their processes by working on improving on selectivity and rate for the hydrogenation of their specific substrates. This becomes more and more easy since a lot of ligands are readily available and can be used in high throughput screenings. The monodentate phosphoramidite ligands provide a major advantage in this screening phase since beside the ligands that are commercially available the ones that are not, are very easily synthesized, increasing the chance to find a useful hit.

Asymmetric hydrogenation can become an even more valuable tool in asymmetric synthesis because of the fact the reactions are clean, fast, selective and can usually be performed under relatively mild conditions. Often a catalyst can be chosen in such a way that none of the other functionalities present in the molecule will be affected.

Overall, asymmetric hydrogenation research has come a long way since the first results obtained by the groups of Horner[24] and Knowles[25] but still challenges remain in this field of research for both academia as well as industry.

6.4 References

[1.] C. Claver, E. Fernandez, A. Gillon, K. Heslop, D. J. Hyett, A. Martorell, A. G. Orpen, P. G. Pringle, *Chem.Commun.* **2000,** 961-962.

[2.] M. T. Reetz, G. Mehler, *Angew.Chem.Int.Ed.* **2000,** *39* 3889-3890.

[3.] M. van den Berg, A. J. Minnaard, E. P. Schudde, J. van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J.Am.Chem.Soc.* **2000,** *122* 11539-11540.

[4.] Hoen, R., University of Groningen, **2006**.

[5.] van den Berg, M., University of Groningen, **2006**.

[6.] Mrsic, N., University of Groningen, **2010**.

[7.] A. J. Minnaard, B. L. Feringa, L. Lefort, J. G. de Vries, *Acc.Chem.Res.* **2007,** *40* 1267-1277.

[8.] M. Jahjah, R. Jahjah, S. Pellet-Rostaing, M. Lemaire, *Tetrahedron: Asymmetry* **2007,** *18* 1224-1232.

[9.] Q. Jing, X. Zhang, J. Sun, K. Ding, *Adv.Synth.Catal.* **2005,** *347* 1193-1197.

[10.] Y. Xu, G. C. Clarkson, G. Docherty, C. L. North, G. Woodward, M. Wills, *J.Org.Chem.* **2005,** *70* 8079-8087.

[11.] K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew.Chem.Int.Ed.* **2004,** *43* 5066-5069.

[12.] F. Giacomina, A. Meetsma, L. Panella, L. Lefort, A. H. M. de Vries, J. G. de Vries, *Angew.Chem.Int.Ed.* **2007,** *46* 1497-1500.

[13.] X. G. Li, B. List, *Chem.Commun.* **2007,** 1739-1741.

[14.] J.-H. Xie, Z.-T. Zhou, W.-L. Kong, Q.-L. Zhou, *J.Am.Chem.Soc.* **2007,** *129* 1868-1869.

[15.] *The Handbook of Homogeneous Hydrogenation*, 1 ed. (Eds.: J. G. de Vries, C. J. Elsevier) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2007**.

[16.] Y. Huang, F. Berthiol, B. Stegink, M. M. Pollard, A. J. Minnaard, *Advanced Synthesis & Catalysis* **2009,** *351* 1423-1430.

[17.] A. F. Meindertsma, M. M. Pollard, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Tetrahedron: Asymmetry* **2007,** *18* 2849-2858.

[18.] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew.Chem.Int.Ed.* **2005,** *44* 4209-4212.

[19.] M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew.Chem.Int.Ed.* **2003,** *42* 790-793.

[20.] J. G. de Vries, L. Lefort, *Chem.Eur.J.* **2006,** 4722-4734.

[21.] H. Shimizu, D. Igarashi, W. Kuriyama, Y. Yusa, N. Sayo, T. Saito, *Org.Lett.* **2007,** *9* 1655-1657.

[22.] R. H. Morris, *Chem.Soc.Rev.* **2009,** *38* 2282-2291.

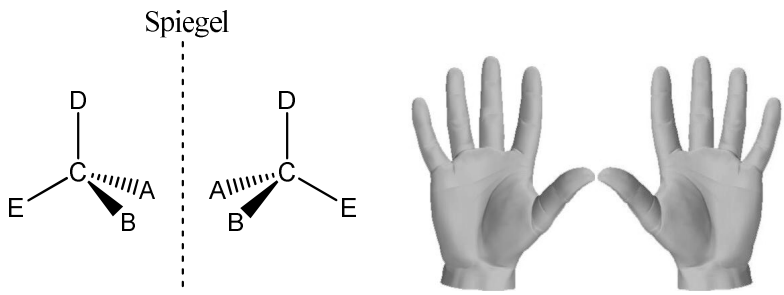
[23.] C. Sui-Seng, F. Freutel, A. J. Lough, R. H. Morris, *Angew.Chem.Int.Ed.* **2008,** *47* 940-943.

[24.] L. Horner, H. Siegel, H. Büthe, *Angew.Chem.Int.Ed.* **1968,** *7* 942.

[25.] W. S. Knowles, M. J. Sabacky, *Chem.Commun.(London)* **1968,** 1445-1446.

Samenvatting

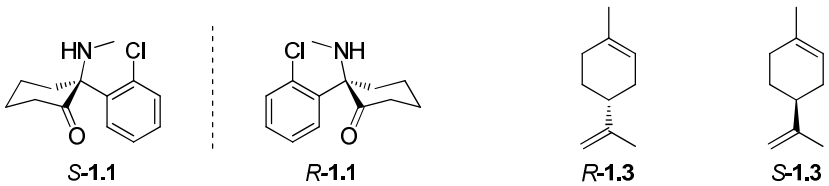
Het in de chemie zo belangrijke begrip chiraliteit komt van het Griekse woord χειρ (“*cheir”*), wat hand betekent. Chirale moleculen spelen een zeer belangrijke rol in de chemie. Een molecuul is chiraal op het moment dat het een asymmetrisch centrum bevat en het spiegelbeeld van dit molecuul op geen manier overlegbaar is op het origineel (zie Figuur 2). Op deze manier zijn ook iemands handen chiraal, links en rechts zijn elkaars spiegelbeeld en niet over elkaar heen te leggen.



Figuur 1: Voorbeeld van een chiraal molecuul met een asymmetrisch centrum (het C-atoom met vier verschillende substituenten) en twee chirale handen.

De twee spiegelbeelden van deze chirale moleculen zijn qua eigenschappen precies gelijk. Het enige, fysische, verschil tussen de twee is het feit dat ze gepolariseerd licht ieder een andere kant op kunnen draaien. Een groot deel van alle in de natuur voorkomende stoffen zijn chiraal, zoals aminozuren, DNA, eiwitten en suikers. Doordat deze stoffen chiraal zijn is vaak het resultaat van een interactie met een ander chiraal molecuul afhankelijk van welk enantiomeer dat is. De consequentie is dat twee verschillende enantiomeren van dezelfde stof een heel ander voorkomen kunnen hebben in biologische systemen. Twee voorbeelden hiervan zijn bijvoorbeeld ketamine en limoneen. In het geval van ketamine is het ene enantiomeer een verdovingsmiddel dat veel gebruikt wordt door dierenartsen en het andere enantiomer een hallucinogeen. Bij limoneen is

het de geur van de enantiomeren die volledig verschillend is. Het ene enantiomeer heeft een typische dennengeur terwijl het andere juist naar sinaasappelschillen ruikt.



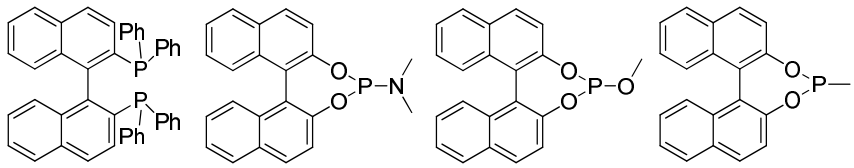
S-**1.1** *R*-**1.1** *R*-**1.3** *S*-**1.3**

Figuur 2: Voorbeelden van enantiomeren die verschillende biologische voorkomens hebben. Ketamine (**1.1**) en limoneen (**1.3**).

De selectieve synthese van deze chirale moleculen is een van de belangrijkste onderzoekstypen binnen de organische synthese.

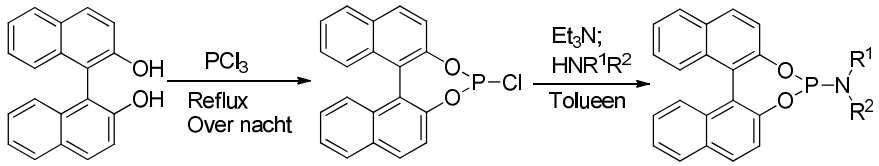
Een van de manieren om selectief een chiraal centrum te creëren is via een asymmetrische hydrogenering. In een asymmetrische hydrogenering reageert een molecuul waterstof met een dubbele binding, meestal met behulp van een katalysator welke is gebaseerd op een overgangsmetaal. Om de hydrogenering selectief te laten verlopen zodat er voornamelijk maar een van de te vormen enantiomeren gemaakt wordt zitten er rondom het overgangsmetaal vaak een of meer chirale liganden.

Tot het jaar 2000 waren deze liganden eigenlijk altijd zogenaamde bidentaten, dat wil zeggen een ligand met twee atomen die kunnen complexeren aan het overgangsmetaal (zie Figuur 3). In dat jaar werd een einde gemaakt aan het idee dat er bidentaat liganden nodig waren om een goede selectiviteit te kunnen bewerkstelligen. Vrijwel tegelijkertijd publiceerden de groepen van Reetz, Pringle en onze eigen het gebruik van monodentaat liganden in de asymmetrische hydrogenering van C=C bindingen.



Figuur 3: Een bidentaat ligand (binap) en de drie monodentaat liganden zoals gebruikt door Reetz, Pringle en onze groep.

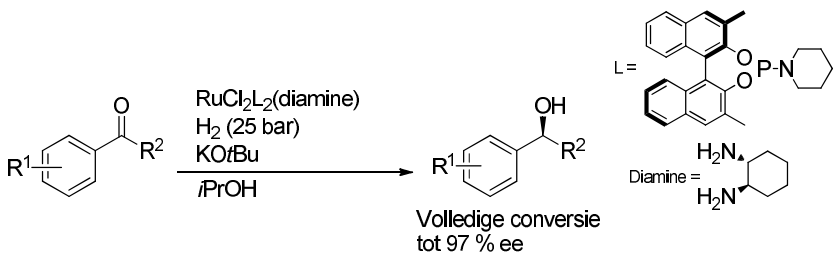
Het grote voordeel van fosforamidieten ten opzichte van de bidentaat liganden is hun synthese. Waar de synthese van bidentaat liganden vaak veel en moeilijke stappen bevat is een fosforamidiet in twee, makkelijke, stappen te synthetiseren zoals te zien is in Figuur 4.



Figuur 4: Synthese van fosforamidiet liganden.

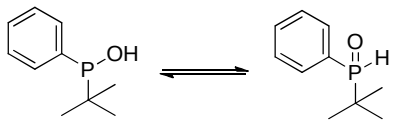
Sinds die eerste publicatie in 2000 heeft onze groep laten zien dat fosforamidieten uitermate geschikt zijn als liganden in verschillende soorten asymmetrische hydrogeneringen.

Het doel van het onderzoek dat in dit proefschrift is beschreven was het ontwikkelen van methodes voor de asymmetrische hydrogenering van carbonylen met behulp van fosforamidieten als liganden.



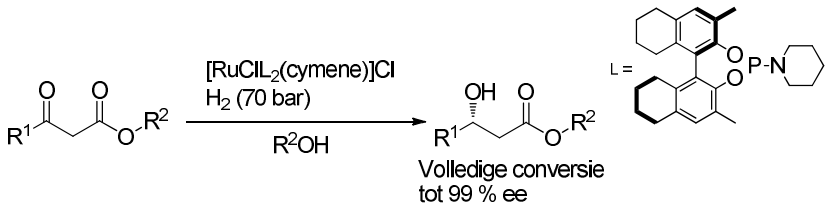
Figuur 5: Asymmetrische hydrogenering van acetofenonen met fosforamidiet liganden.

In hoofdstuk 2 is het onderzoek beschreven naar een op fosforamidieten gebaseerde ruthenium katalysator voor acetofenon achtige ketonen. We hebben ontdekt dat een combinatie van 3,3'-dimethyl PipPhos met DACH de meest selectieve katalysator vormt voor een reeks van acetofenonen (Figuur 5). De pogingen om het complex te karakteriseren dat verantwoordelijk is voor de katalyse leiden, aan de hand van ^{31}P-NMR en massa, tot de conclusie dat het complex dat gevormd word voor de reactie hoogstwaarschijnlijk een dimeer is met slechts één fosforamidiet per metaalatoom. Tijdens de reactie valt dit dimeer uit elkaar en zijn er twee fosforamidieten nodig om de reactie te laten verlopen met goede selectiviteit.



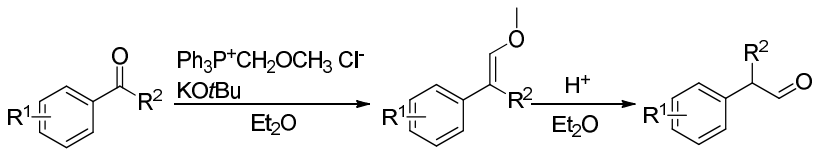
Figuur 6: Het SPO ligand zoals gebruikt in hoofdstuk 3.

In hoofdstuk 3 is er gekeken naar twee dingen. Ten eerste is onderzocht of een secundair fosfine oxide (Figuur 6) gebruikt kan worden in de ruthenium of iridium gekatalyseerde hydrogenering van acetofenon. Dit bleek wel te kunnen, echter bleken de gevormde katalysatoren niet erg selectief te zijn. Ten tweede is er gekeken naar de iridium gekatalyseerde hydrogenering van acetofenon met behulp van fosforamidiet liganden. Ook hier bleek dat dit actieve katalysatoren opleverde maar dat de selectiviteit ervan een stuk minder was ten opzichte van de in hoofdstuk 2 gevonden katalysatoren.



Figuur 7: Ruthenium gekatalyseerde hydrogenering van β-ketoesters met behulp van fosforamidiet 8H-3,3'-dimethyl PipPhos.

In hoofdstuk 4 werd de aandacht verlegd naar een ander type carbonylen, namelijk de α- en β-ketoesters. Gevonden werd dat in de hydrogenering van α-ketoesters geen selectiviteit behaald kon worden met behulp van fosforamidiet liganden. Voor de β-ketoesters bleek dit wel het geval. Een ruthenium complex met twee 8H-3,3'-dimethyl PipPhos liganden bleek in staat meerdere β-ketoesters te hydrogeneren met selectiviteiten to 99 % ee (zie figuur 7).



Figuur 8: Synthese van α-aryl aldehydes.

In hoofdstuk 5 gebruikten we de in hoofdstukken 2 en 4 gevonden katalysatoren in de hydrogeneringen onder DKR condities van α-gesubstitueerde β-ketoesters en α-aryl aldehydes. In de hydrogenering van de gesubstitueerde β-ketoesters waren we helaas niet in staat om een katalysator te vinden die goede enantiomere en diastereomere overmaat gaf.

De aldehydes die gebruikt zijn in de hydrogeneringen werden gesynthetiseerd in twee stappen vanaf het keton zoals te zien is in Figuur 8. Eerst werd er een Wittig methoxymethylenering gedaan en vervolgens werd het gevormde methyl enol ether onder zure condities gehydrolyseerd tot het aldehyde in goede opbrengsten. Voor de gesynthetiseerde aldehydes waren we in staat een

katalysator te vinden die tot volledige conversies leidde, echter was de selectiviteit in geen van de gevallen hoger dan 85 %.

Concluderend kan gezegd worden dat monodentaat fosforamidiet liganden uitermate geschikt zijn als liganden in de asymmetrische hydrogenering van verschillende typen ketonen en een goed alternatief bieden voor de, tot nu toe geprefereerde, bidentaat liganden.

Summary

The in chemistry very important concept chirality stems from the greek word χειρ ("*cheir*"), which means hand. Chiral molecules play a most important role in chemistry. A molecule is called chiral in the case it possesses an asymmetric center and its mirror images are in no way superimposable onto each other. In this way our own hands are chiral as well, they are each other's mirror image but in no way is it possible to position our right hand exactly over our left (see Figure 1).

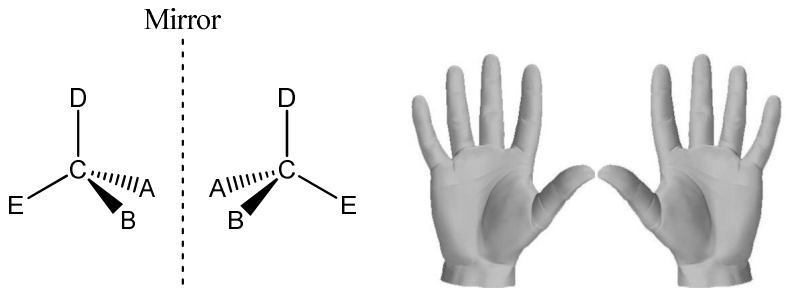


Figure 1: Example of a chiral molecule containing an asymmetric center (the C-atom bearing four different substituents) and two chiral hands.

The two mirror images of chiral molecules have the same physical qualities. The only difference between the two is the fact that they each rotate polarized light in a different direction. Many of the compounds that appear in nature are chiral, such as, DNA, amino acids, proteins and sugars. Because of he fact these compounds are all chiral they can respond differently to interactions with other chiral molecules depending on its enantiomer. A consequence of these different responses to different forms of a substrate is that two enantiomers of the same compound can have a completely different functions or appearances in nature. Two examples of this are for instance the compound ketamine and limonene, which are depicted in Figure 2. One of the forms of ketamine acts as an anesthetic, which is used a lot in veterinarian medicine where the other form is an hallucinogenic substance. For limonene it holds that both enantiomers of the

molecule have a completely different smell. One has a typical pine like odor whereas the other smells like orange peels.

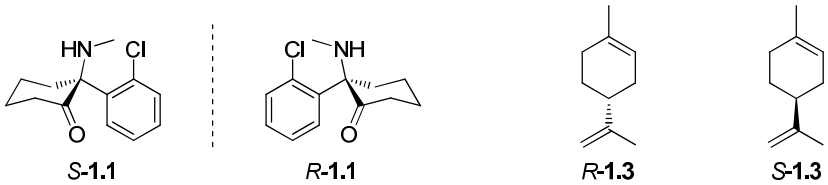


Figure 2: Examples of enantiomers that display completely different behavior. Ketamine (**1.1**) and limonene (**1.3**).

The selective synthesis of chiral molecules is one of the most important research topics within the organic chemistry these days. One of the many ways to selectively make a chiral molecule is via asymmetric hydrogenation. In an asymmetric hydrogenation one molecule of hydrogen reacts with a double bond which is present in the substrate molecule. This usually occurs with the help of a transition metal based catalyst. To make sure the hydrogenation goes in a selective manner and one of the two enantiomers of the product is formed with high preference the transition metal is often surrounded by one or more, so called, chiral ligands.

Until the year 2000 these chiral ligands were almost always bidentate ligands, which means they posses two atoms that can interact with the central metal of the catalyst. In that year three separate groups made an end to the notion that bidentate ligands are necessary in order to get the asymmetric hydrogenations to go with reasonable selectivities. More or less simultaneously three groups, the ones of Pringle, Reetz and our own, published their excellent results obtained in the asymmetric hydrogenation of a C=C double bond using two monodentate ligands instead of one bidentate (see Figure 3).

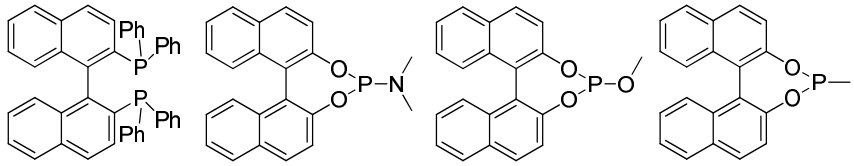


Figure 3: A bidentate ligand (binap) and the three monodentate ligands as used by our group, the group of Reetz and the group of Pringle.

One of the biggest advantages of the use of monodentate ligands instead of bidentates and especially the use of our phosphoramidites lies in their synthesis. Where in the synthesis of bidentate ligands is often long and contains one or more difficult steps the synthesis of a phosphoramidite ligand can be achieved in two quick and easy steps as is depicted in Figure 4.

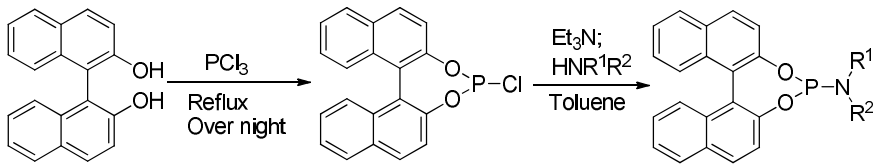


Figure 4: The easy two step synthesis of phosphoramidite ligands.

Since that first publication in 2000 our group has shown that phosphoramidite ligands are very well suited as ligands in a variety of asymmetric hydrogenations. The goal of the research described in this thesis was to develop one or several methods in which these ligands can be used in the asymmetric hydrogenation of carbonyls.

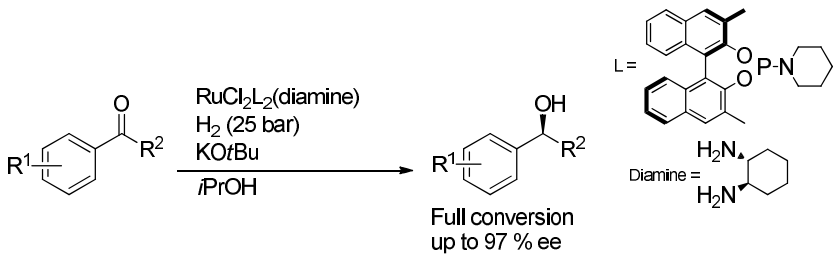


Figure 5: The asymmetric hydrogenations of acetophenone type substrates using a phosporamidite ligand.

In chapter 2 the research towards a ruthenium based catalyst, bearing phosphoramidite ligands, for the asymmetric hydrogenation of acetophenone type substrates is described.

We found a combination of the phosphoramidite 3,3'-dimethyl PipPhos and the chiral diamine DACH produced the most selective catalyst for the asymmetric hydrogenation of a range of acetophenone type substrates (See Figure 5). Attempts to characterize the active complex, with the help of ^{31}P-NMR and mass spectrometry let to inconclusive results. We did conclude that the preformed complex most likely has a dimeric structure containing one phosphoramidite and one diamine molecule per ruthenium center. During the hydrogenation reaction this dimer falls apart and the addition of extra equivalents of phosphoramidite ligand is necessary in order to obtain good selectivity in the reaction.

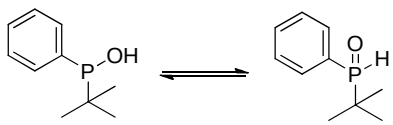


Figure 6: The SPO ligand as used in chapter 3.

In chapter 3 two separate things were investigated. First of all we examined whether an SPO ligand (see Figure 6) could be used as a ligand in the iridium or ruthenium catalyzed asymmetric hydrogenation of acetophenon. As it turned out the SPO ligand could be used to get the reaction going, however, the complex turned out not to be very selective.

Secondly we investigated the iridium catalyzed asymmetric hydrogenation of acetophenones with phosphoramidite ligands. This proofed to work better compared to the use of the SPO ligands but also in this case the selectivities, up to 68% ee, came nowhere near those obtained in chapter 2.

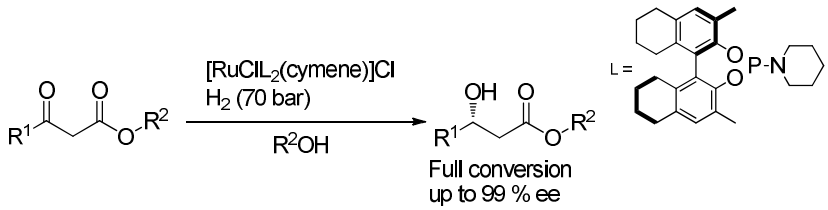


Figure 7: The ruthenium catalyzed asymmetric hydrogenation of β-ketoesters using 8H-3,3'-dimethyl PipPhos as a ligand.

In chapter 4 our attention shifted towards another type of substrates, the α-, and β-ketoesters. We found that the tested phosphoramidite ligands were not able to induce any selectivity in the asymmetric hydrogenation of the α-ketoesters. In the case of the β-ketoester, however, the phosphoramidite ligands proved to be excellent performing ligands. When using the ligand 8H-3,3'-dimethyl PipPhos we were able to achieve selectivities of up to 99% ee in the asymmetric hydrogenation of several β-ketoesters (see figure 7).

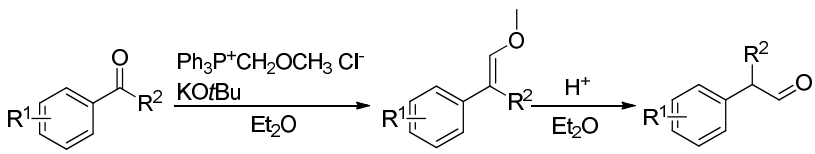


Figure 8: Synthesis of an α-aryl aldehyde.

In chapter 5 we used the types of catalysts found in chapters 2 and 4 to perform asymmetric hydrogenations under DKR conditions. As substrates for these type of hydrogenations we used α-substituted β-ketoesters and α-aryl aldehydes. In the hydrogenations of the first type of substrates we were not able to find a catalyst which was able to induce any good ee or de in the reactions.

In the case of the aldehydes, which were easily synthesized in two steps from their corresponding acetophenons via a Wittig reaction and subsequent hydrolysation (see also figure 8), we were able to find a catalyst which was able

to reduce the substrate to the corresponding alcohol with selectivities of up to 85% ee and full conversions.

In conclusion it can be stated that monodentate phosphoramidite ligands are an excellent choice of ligands in the asymmetric hydrogenations of several carbonyl compounds and they are a good alternative for the, so far mainly used, bidentate ligands.

Dankwoord

Na vijf en een half jaar is het dan zover. Alles is af en het enige dat nog rest is het schrijven van een dankwoord.

Allereerst gaat mijn dank uit naar mijn drie promotoren. Laat mij beginnen jullie alle drie te bedanken voor het geduld en vertrouwen dat jullie in mij hebben gehad. Ik heb momenten gehad dat ik het niet meer zag zitten maar jullie lieten mij altijd weer geloven dat het wel weer goed zou komen, en zie daar; jullie hadden gelijk. Hans, jij was degene die mij uitnodigde in Groningen te komen werken. Een grote, spannende stap maar ik heb er zeker geen spijt van dat ik ja gezegd heb. Dank uiteraard daarvoor, maar ook voor je immere opgewektheid. Na een meeting met jou ging ik eigenlijk altijd weer met vernieuwde moed aan het werk. Ben, als mijn tweede promotor was jij er om mij te blijven prikkelen het beste uit mijzelf te halen. Altijd kritisch en altijd vol nieuwe ideeën. Ik ben er trots op te kunnen zeggen in jouw lab te hebben kunnen werken. Mijn derde promotor was Adri. Als de andere twee er niet waren kon ik altijd met alles bij jou terecht. Ondanks dat je druk was je eigen groep op te zetten bleef je deur altijd open voor hydrogenerings-vragen.

Of course also thanks to the members of my reading committee who took the time to read my manuscript. Professors Vidal, Reek and Harder thank you all for your approval and agreeing to take part in my defense.

Met alleen een onderwerp, promotoren en een lab kun je geen PhD doen. De mensen met wie je dat lab deelt zijn belangrijker dan wat dan ook. Degene met wie ik al die tijd mijn kantoor gedeeld heb is Ebe. Ik vond het altijd erg leuk om ook te zien wat er achter de schermen aan de gang was in de groep en daar had jij vaak mee te maken. Maar ook zaken die speelden buiten het lab waren altijd prima met jou te bespreken. Je wist me altijd weer te verbazen met je onuitputtelijke kennis. Succes en nog veel plezier met je laatste tijd op het lab!
Naast het kantoor waren er de verschillende labs waar ik heb gestaan. Ik ben mijn tijd in Groningen begonnen op 14.240. In mijn eerste twee jaar heb ik dat lab met plezier gedeeld met in eerste instantie Edzard en later Frank.
I ended my time in Groningen on the same lab but with different people. During my "last" experiment(s) in "*The far East"* Wiktor and Alena allowed me to work beside

them in their, already quite full, lab. My biggest thanks for that time goes out to Annick who let me use some of her precious fumehood space. To all of you a big thanks. Sharing the office and labroom with you guys, was made my last months in Groningen much more enjoyable. In die tijd heb ik ook erg genoten van de vele bezoekjes van “Wiktors biochemistry friends”. Christiaan en Alja; het was leuk om af en toe ook eens met “anders denkende” te kunnen kletsen over chemie en te realiseren dat ook in biochemie promoveren niet altijd gesneden koek is.

Tussen mijn twee verblijven in 14.240 heb ik met veel plezier gewerkt op 14.245. Nuria, Kees, Jacqueline, Carolien, Jan Willem, Danny, Yange, Adi, Miriam and Jeffrey, I really enjoyed working together with you guys on the lab. It was great to work in such a lively labroom after spending almost two years in the quiet lab across the hall.

Tussen het werk door kon ik mij tijdens koffie pauzes en lunches altijd probleemloos aansluiten bij de “Ruffles-people” zo goed dat ze me op een gegeven moment maar “geadopteerd” hadden. Een echte groep binnen een groep. Gerard, Arnold, David, Ewold, Nuria, Fiora, Rik, Qian, Lorina, Jeffrey, Jens, Dowine en alle andere studenten (want daar waren er daar nooit te weinig van). Bedankt dat ik van dat groepje deel heb uit mogen maken!
Een andere groep waar ik deel van uit maakte was de HdV-subgroep. Iedere twee weken met soms meer staf dan niet-staf. Bas, Natasa, Robert, Lavinia, Sebastien, Celine, Chris, Adi, Arnaud, Thomas, Nicky, Wiktor, Manuel, Alex en Anne zorgde regelmatig voor interessante discussies en andere kijken op het onderzoek.
Naast de nu genoemde mensen waren er nog veel meer nog niet genoemde die allen in meer of mindere mate hebben bijgedragen aan de plezierige tijden die ik in het lab heb doorgebracht. Bedankt!

Behalve een goede sfeer op het werk is het natuurlijk ook belangrijk een goede tijd buiten het werk te hebben. Naast borrels, feestjes en etentjes was het ook leuk om te ontdekken dat er veel meer mensen houden van het spelen van bordspelletjes. Chris spant daarin natuurlijk de kroon maar de vele avondjes zouden niet compleet geweest zijn zonder ander tegenspelers. Rik, Tim, Danny, Arnold, Dirk, Barbara, Miriam, Derk Jan en alle andere die wel eens aangeschoven zijn, bedankt voor de altijd gezellige avonden.

Naast de collega's was ook mijn familie heel belangrijk voor me tijdens mijn promotie. Al mijn ouders, Janneke, Henk, Caroline en Frans dank dat jullie altijd geïnteresseerd zijn gebleven, ook al konden jullie het lang niet altijd helemaal volgen. Nienke, ondanks dat je er (nog) niets van begrijpt wat ik daar in Groningen allemaal gedaan heb was het altijd weer een lichtpuntje om te zien hoe enthousiast je me altijd weer begroette als je grote broer weer eens langs kwam. Met mijn 'schoonfamilie' heb ik het ook maar getroffen, altijd welkom en altijd een luisterend oor, ook voor de scheikunde, samen met een hapje en een drankje. Maar ook de rest van de Steginks, Schippers, Eversen, Van Goors, Van der Heides, Ernstings en Van Eedens bedankt voor de interesse en de altijd gezellige familie aangelegenheden die mij regelmatig de nodige afleiding gaven van mijn werk.

Rik als paranimf en contactpersoon in Groningen ben je een zeer belangrijke schakel geweest tijdens de laatste regeldingetjes. Heel erg bedankt, niet alleen voor de laatste maanden maar ook voor al die keren koffie, spelletjes en het kwijt kunnen van mijn verhaal in je tussenkamer. Heel veel succes met de rest van je onderzoek en uiteraard jouw en Ellens grote dag volgende maand.
Gijs ook jij bedankt. Niet alleen dat je mijn paranimf wil zijn maar ook voor de vele etentjes de afgelopen jaren. Wie had gedacht dat je zo vaak uit eten kon gaan in Zwolle en het nog steeds leuk zou vinden. Het feit dat ik er altijd weer naar uitkeek lag toch voornamelijk aan jou. De avonden waren altijd uitermate geschikt om weer eens lekker te relativeren en na te denken over andere dingen in het leven. Dat we dat maar veel kunnen blijven doen, ook nadat ik gepromoveerd ben. Hetzij met zijn tweeën, hetzij met Gerda, Hugo en Johanneke erbij.

En dan is de naam Johanneke gevallen. De laatste op het lijstje aan wie ik dank ben verschuldigd. Dank voor het uithouden met mijn eigenwijsheid en het altijd bieden van steun en een luisterend oor ook al ging het bij jezelf ook niet altijd van een leien dakje. Ook jij bent er nu bijna en haalt het zeker! Waarna we nog vele jaren samen met een goed gevoel kunnen terugkijken op de afgelopen tijd.

Met andere woorden: Bedankt iedereen!

Bart