# Iridium-Catalyzed Asymmetric Hydrogenation:
# A: Studies on the Synthesis of Pyrazine-Based P,N Ligands
# B: Diastereoselective Hydrogenation of Chiral Cyclohexenes

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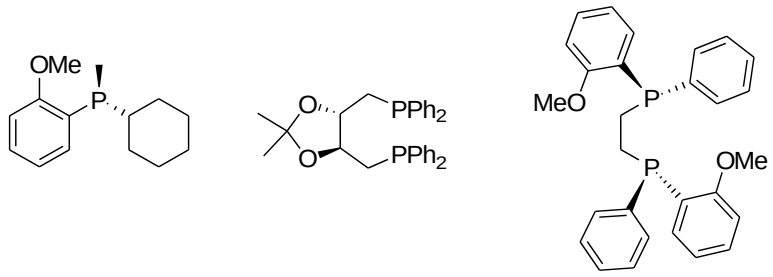
# 1 Introduction

## 1.1 Transition metal-catalyzed asymmetric hydrogenation

Nowadays, the synthesis of chiral compounds is one of the major tasks in organic synthesis and among all the developed asymmetric catalytic methods[1] hydrogenation of double bonds became one of the most powerful tools.[2] Normally, high conversions and excellent enantioselectivities can be obtained at low catalyst loadings, together with a perfect atom economy which guarantee that the asymmetric hydrogenation is also applied in industrial processes.[3] After Wilkinson's and Coffey's pioneering work on phosphine based rhodium catalysts for the homogeneous hydrogenation of alkenes and alkynes[4] the first asymmetric versions were reported two years later[5], but only poor enantioselectivities were achieved. Further ligand development led to the introduction of $C_2$-symmetric bidentate bisphosphine ligands which showed better selectivities compared to monodentate ligands like (*S*)-CAMP.[6] In 1971, Kagan published the first example of rhodium-catalyzed asymmetric hydrogenation using a bidentate ligand (DIOP).[6a] Some years later Knowles introduced the bisphosphine ligand DIPAMP for the asymmetric reduction of dehydroamino acids yielding the corresponding products in high selectivities.[6c] Due to its high efficiency for this substrate class it was employed in the industrial synthesis of L-DOPA.[7]

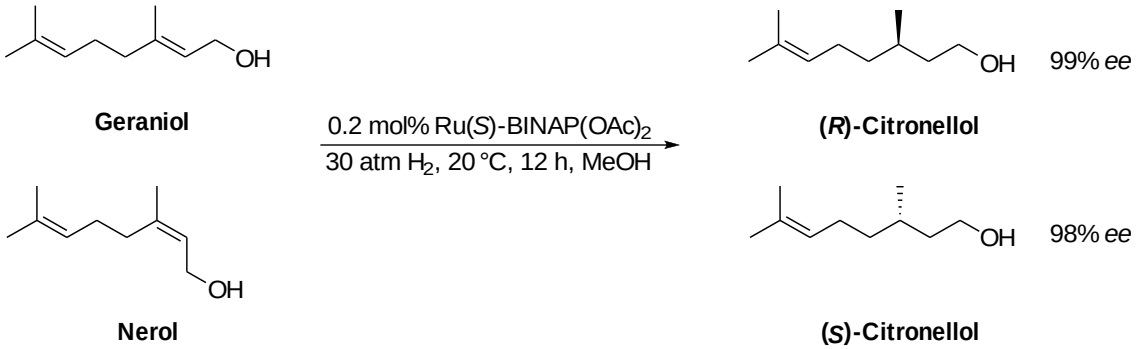



**(*S*)-CAMP** **(*S*,*S*)-DIOP** **(*S*,*S*)-DIPAMP**

***Figure 1***: Structure of the first phosphine and bisphosphine ligands used in rhodium-catalyzed asymmetric hydrogenation reactions.

However, research was mainly focused on rhodium catalyzed hydrogenation and the substrate scope was limited to dehydroamino acids.[8] In 1988, Noyori discovered that ruthenium can also be

applied for asymmetric hydrogenation.[9] In his catalytic system a biaryl phosphine ligand (BINAP) was used to successfully reduce different types of alkenes and thereby broadened the scope of this reaction. For example in the synthesis of citronellol both enantiomers can be obtained by asymmetric ruthenium-catalyzed hydrogenation of geraniol or nerol, respectively (*Scheme 1*).[10] The double bond close to the hydroxy group is reduced by the catalyst while the remote double bond remains untouched.




***Scheme 1***: Ruthenium-catalyzed hydrogenation of geraniol and nerol.

Furthermore, he could not only reduce carbon carbon double bonds but also ketones which allowed the synthesis of numerous chiral alcohols. For their pioneering work in the field of asymmetric hydrogenation Knowles and Noyori were awarded the Nobel Prize in 2001.

In the 1990's many more ligands were developed so that the scope for rhodium-catalyzed hydrogenation could also be improved.[11] Both, rhodium- and ruthenium-catalysts usually need a coordinating group in the substrate like an alcohol, amine or carbonyl group. This requirement limits the scope as only a few examples of hydrogenations of unfunctionalized olefins are known.[12]

To reduce unfunctionalized olefins other transition metals like platinum[13], titanium[14], zirconium[15] or iridium[2a,e,f,16] are normally employed. Pioneering work in this field was done by Kagan who used a titanium cyclopentadienyl complex to reduce 2-phenyl-1-butene in an asymmetric fashion, albeit with low selectivity.[17] More than ten years later Buchwald reported the reduction of unfunctionalized olefins and enamines by a titanium cyclopentadienyl complex with high *ee*'s.[14a] However, this catalyst is very air- and moisture-sensitive and a strong base like *n*-butyl lithium is necessary to activate the precatalyst. Today, iridium complexes are mostly used for the reduction of unfunctionalized olefins.

## 1.2 Iridium-catalyzed asymmetric hydrogenation

In 1977, Crabtree reported the first application of iridium catalysts in the hydrogenation of double bonds.[18] Before, rhodium was the metal of choice since the iridium analogs showed lower reactivity. Crabtree assumed that this low activity was due to the strong binding affinity of iridium to coordinating solvents. He proposed that this strong interaction avoids the dissociation of a solvent molecule which prevents coordination of the substrate to the metal center. To inhibit deactivation of the catalyst he investigated the reactivity of $[Ir(COD)L_2]PF_6$ complexes in various non-coordinating solvents and observed high activity in chloroform and methylene chloride. He found that $[Ir(COD)PCy_3(py)]PF_6$, the so called Crabtree catalyst, gave the best results for the hydrogenation of unfunctionalized olefins. This catalyst even allowed the reduction of tetrasubstituted double bonds which could not be reduced by rhodium complexes.
However, conversions were often low even though he observed high initial turnover frequency (TOF). The high reactivity also resulted in destabilization of the catalyst. The lack of a coordinating solvent which could stabilize the complex means that only the substrate can stabilize it. When most of the substrate is consumed or the olefin is weakly coordinating the metal complex forms a stable inactive trinuclear iridium complex (*Figure 2*).

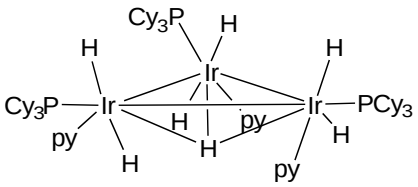
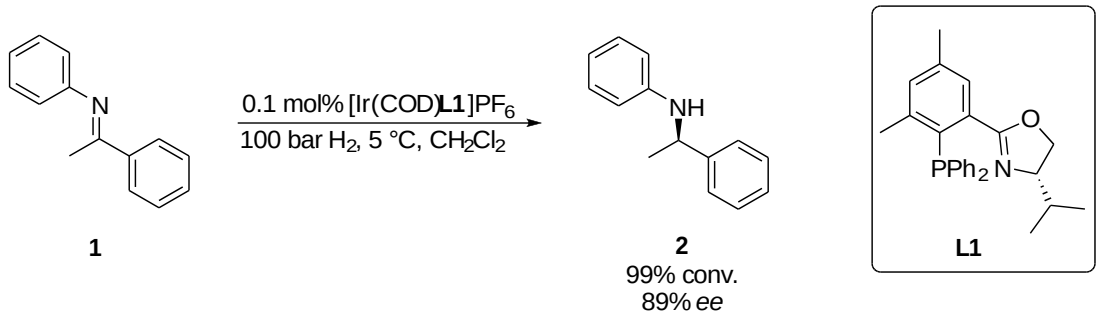



***Figure 2***: Structure of inactive iridium trimer formed during the hydrogenation with Crabtree's catalyst.[19]

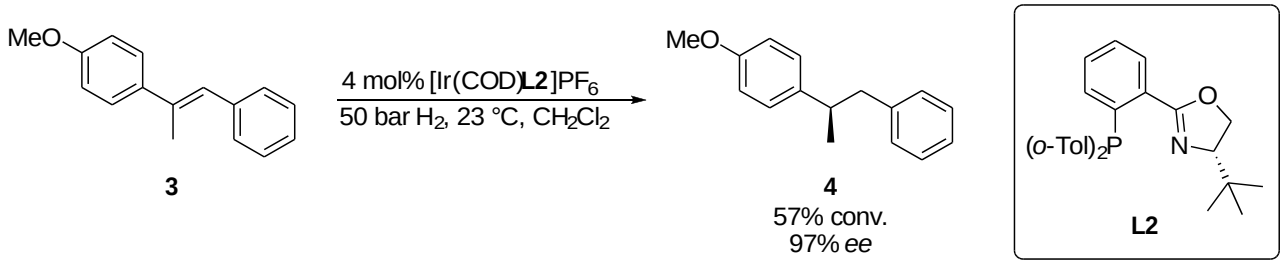
In 1997, the first asymmetric iridium-catalyzed hydrogenation was published by our group. In our approach, chiral phosphinooxazoline (PHOX) ligand **L1** was used for the iridium-catalyzed hydrogenation of imine **1** to yield the corresponding chiral amine **2** with high enantioselectivity (*Scheme 2*).[20]




***Scheme 2***: First example of asymmetric iridium-catalyzed hydrogenation.

The ligand employed consists of a tertiary phosphine and a chiral oxazoline moiety derived from an amino acid, which form a coordination sphere similar to that of Crabtree's catalyst. The catalyst showed good results for substrates with an aryl group attached to the newly formed stereogenic center but low *ee*'s for imines with two alkyl groups.

One year later our group showed that this ligand class also gives excellent results in the asymmetric reduction of unfunctionalized olefins (*Scheme 3*).[21]

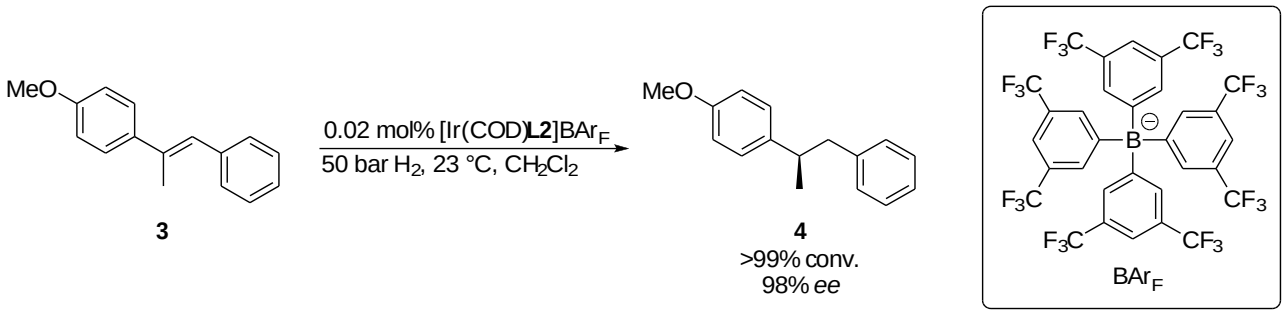



***Scheme 3***: Asymmetric hydrogenation of unfunctionalized olefin **3** with an Ir-PHOX complex.

Several alkenes could be reduced using oxazoline **L2** as chiral ligand for the reduction with very good enantioselectivities. However, high catalyst loading was necessary to obtain good conversions. Even though the catalyst showed high initial TOF, it was deactivated within short time. The reason for the deactivation is that the complex forms, like in the case of Crabtree's catalyst, a stable trinuclear species which cannot be converted back to an active complex .[22]

### 1.2.1 *Effect of the counterion*

Numerous conditions were screened to improve the stability of the catalyst during the reaction but none was successful. The use of coordinating solvents or additives such as amines inhibited the reaction. However, when the counterion was exchanged for $BAr_F$ the stability could be increased tremendously and much lower catalyst loadings were necessary (*Scheme 4*).[23]




***Scheme 4***: Asymmetric hydrogenation of olefin **3** with BArF as counterion.

With only 0.02 mol% catalyst loading full conversion was observed with slightly better *ee*. Numerous other alkenes could be reduced with full conversion as well.[21] Iridium catalysts with $BAr_F$ as anion give not only better conversions but they are also more stable towards air and moisture than the $PF_6$ analogs. The bulky $BAr_F$ anion is only weakly coordinating which facilitates coordination of the substrate to the metal center so that the hydrogenation pathway is favored over deactivation.[24] Today, most cationic iridium catalysts for hydrogenation use the $BAr_F$ anion as counterion of choice.

### 1.2.2 *N,P-Ligands for asymmetric hydrogenation*

Although PHOX ligands showed excellent results in asymmetric hydrogenation reactions the substrate scope was only limited. Therefore, much work was invested to find other ligands to broaden the scope. In the following years, many other N,P-ligands with similar structures were developed in our group which allowed the selective reduction of various other substrates. The most successful ligands are shown below (*Figure 3*).

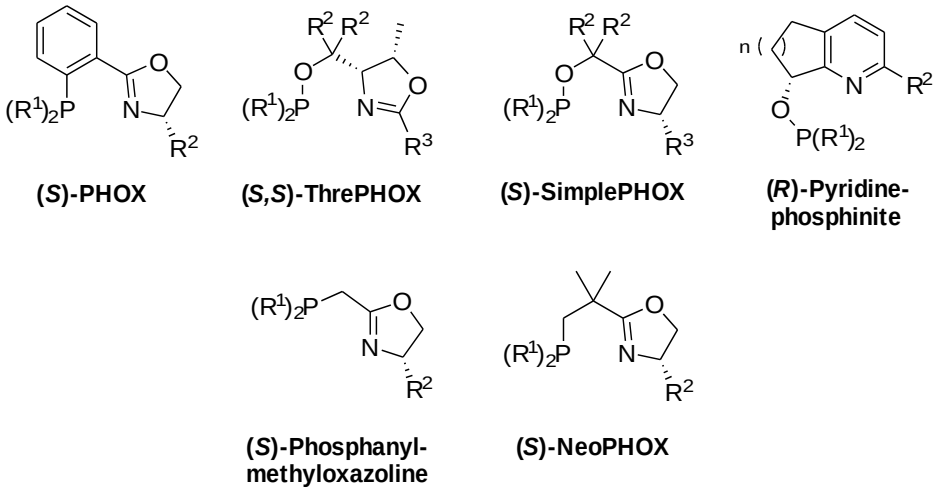



***Figure 3***: Selected N,P-ligands developed in the Pfaltz group.

Starting from the methyl ester of threonine the ThrePHOX ligands can be synthesized in a few steps.[25] Different substituents at the phosphorus atom, the backbone or the oxazoline moiety can simply be introduced by using different acid derivatives, Grignard reagents or phosphine chlorides during the synthesis which gives access to a wide library of ligands and allows fine tuning for different substrates. This ligand class has two stereogenic centers of which one is at the backbone. Furthermore, it consists of a phosphinite moiety instead of a phosphine which changes the electronic properties of the ligand. The ThrePHOX ligands allowed the hydrogenation of 2-aryl-2-butenes with high enantioselectivities for the first time.[26] In addition, excellent *ee*'s could be observed for the asymmetric reduction of terminal alkenes and flavene **5** (*Figure 4*).

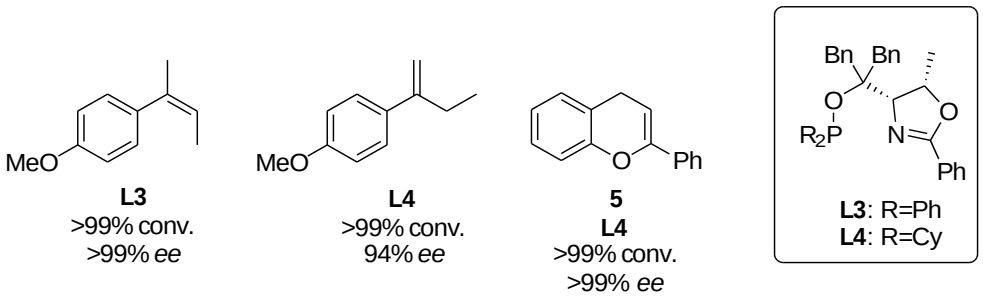
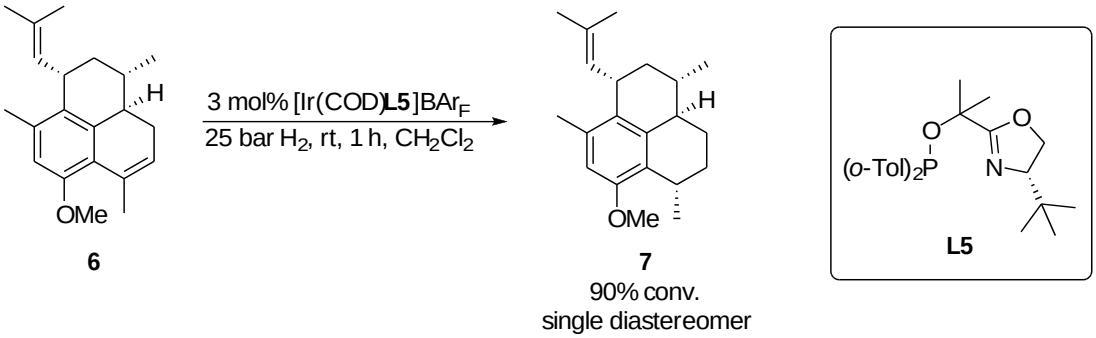



***Figure 4***: Selection of substrates that can be reduced with ThrePHOX ligands.

Another easily accessible class are the SimplePHOX ligands which can be synthesized from chiral α-amino alcohols in two steps.[27] It showed lower selectivities for unfunctionalized olefins than the ThrePHOX ligands but gave excellent results for acrylic esters and allylic alcohols. In addition, this

ligand class was very effective for cyclic substrates. Harmata and Hong used SimplePHOX ligand **L5** in the synthesis of antibiotic pseudopteroxazole.[28] They reduced the tricyclic intermediate **6** with perfect stereocontrol and obtained the reduced product **7** in 90% yield together with some over-hydrogenated product (*Scheme 5*). The reason that the exocyclic double bond does not react is explained by the methyl group attached to the phenyl ring which blocks the side of the double bond from where the catalyst would preferentially attack in an unhindered system.




***Scheme 5***: Regioselective asymmetric hydrogenation in the synthesis of pseudopteraxole.

A ligand class with a different structural motif are the bicyclic pyridine-phosphinite ligands. Instead of an oxazoline moiety they have a pyridine ring which mimics the coordination sphere of Crabtree's catalyst. These ligands have a very rigid structure and turned out to be one of the most powerful ligands for the asymmetric iridium-catalyzed hydrogenation. The pyridine-phosphinite ligands can be used to reduce a broad range of substrates with full conversion and excellent enantioselectivities. Not only unfunctionalized olefins[29] can be hydrogenated, but also α,β-unsaturated esters, vinyl borates[30] and even heteroaromatic compounds like furans[29a,31] which are normally tough substrates due to the aromaticity (*Figure 5*).

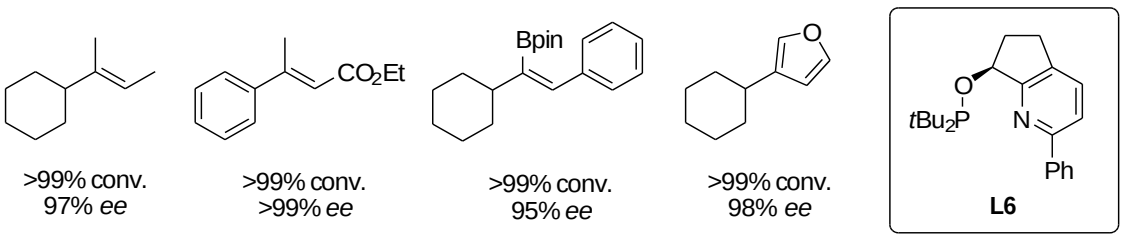
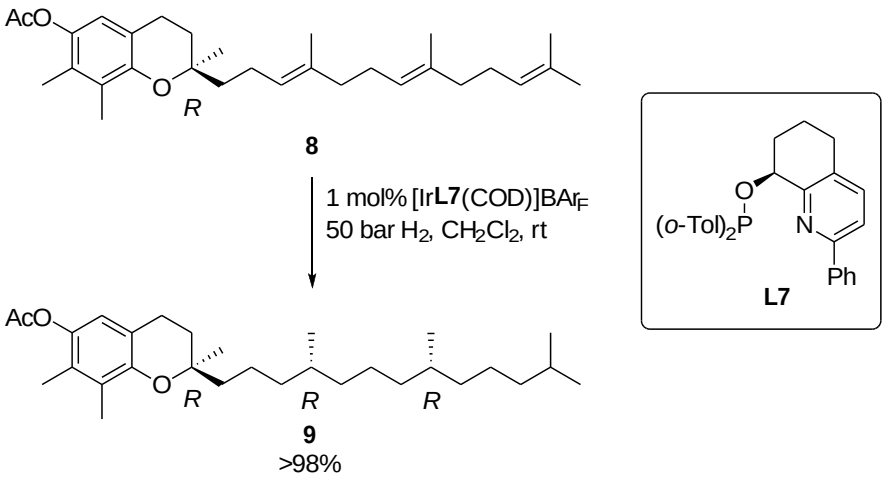



***Figure 5***: Selection of substrates that can be reduced with pyridine-phosphinite ligands.

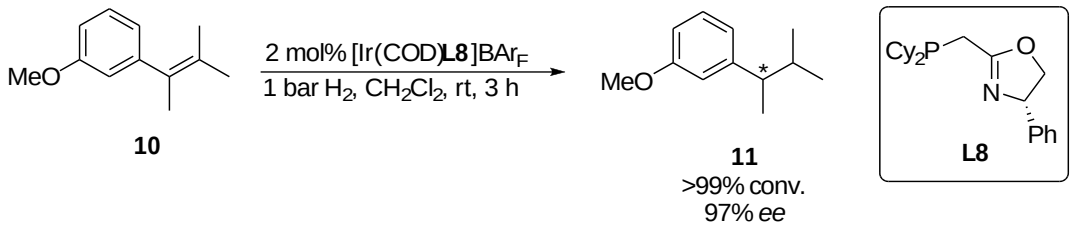
Due to its broad substrate scope, this ligand class found application in the synthesis of many natural

products.[29b,31,32] A nice example for the utility of this ligand class is the synthesis of a tocopherol derivative. One of the key steps is the hydrogenation of γ-tocotrienyl acetate (**8**) where three double bonds are reduced in one step and two new stereogenic centers are created to form γ-tocopheryl acetate (**9**) (*Scheme 6*).[29b] Among the four possible isomers the desired *R,R,R*-isomer is formed with more than 98%. Before, the side chain had to be synthesized stepwise by sequential elongation-hydrogenation protocols.[33]




***Scheme 6***: Asymmetric hydrogenation in the synthesis of γ-tocopherol derivative.

For the hydrogenation of tetrasubstituted olefins phosphanyl-methyloxazoline ligands proved to be the most effective.[34] This ligand class was originally reported by Helmchen and Sprinz and was initially applied in asymmetric allylic substitution.[35] Unlike the ligand classes described above, theses ligands form only a five-membered chelate ring with the metal and not a six-membered ring. The phosphanyl-methyloxazoline ligands allowed the asymmetric hydrogenation of several substrates with low to moderate catalyst loading and hydrogen pressure within short reaction times (*Scheme 7*). Noteworthy, it was observed in some cases that reducing hydrogen pressure results in better selectivity while Buchwald described the opposite trend for his zirconocene catalyst.[15c]




***Scheme 7***: Hydrogenation of a tetrasubstituted olefin with a phosphanyl-methyloxazoline ligand.

Other groups as well developed many different N,P-ligands which also give excellent results in iridium-catalyzed asymmetric hydrogenation. Zhou synthesized pyridine-phosphinite ligands very similar to ours which reduced functionalized and unfunctionalized olefins efficiently.[36] Anderson reported the use of phosphinite oxazole, phosphine thiazole and 2-azanorbornane-oxazoline ligands to hydrogenate successfully various substrate classes among vinylsilanes[37], fluorinated olefins[38] and phosphinates.[39]

Two other efficient ligand classes for the iridium-catalyzed hydrogenation were developed by Ding (SpinPHOX)[40] and Zhou (SiPHOX).[41] The scope of these phosphine oxazoline ligands with a spirocyclic backbone is largely complementary to that of the P,N ligands described above (*Figure 6*).

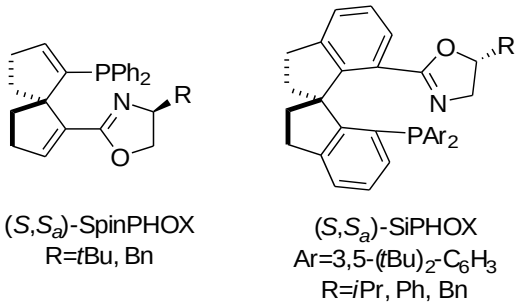
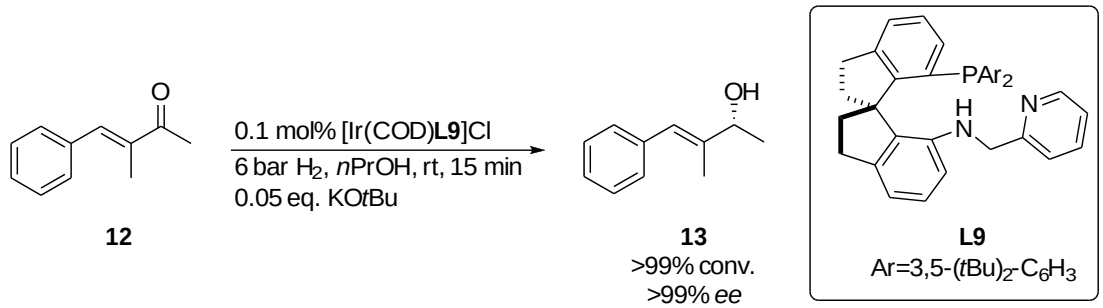



***Figure 6***: General structure of spirocyclic SpinPHOX and SiPHOX ligands.

α,β-Unsaturated carboxylic acids were reduced with these ligands with high enantiomeric excess.[41,42] Furthermore, the reduction of imines could be performed with excellent *ee*'s.[40] A structurally related spirocyclic phosphine amino pyridine ligand was used for the reduction of C=O bonds[43] which are normally hard to reduce efficiently. Interestingly, with ligand **L9** this methodology can be used to reduce chemoselectively the carbonyl group of α,β-unsaturated ketone **12** while the olefinic double bond remains untouched (*Scheme 8*).[44]




***Scheme 8***: Chemoselective reduction of a carbonyl group in presence of a C=C double bond.

Even though there are numerous of different ligands which give excellent results for the asymmetric hydrogenation of various substrate classes, there is still a need for further improvement of catalyst efficiency. It is highly desirable to develop catalytic systems which allow to decrease catalyst loadings to make hydrogenation reactions more attractive for industrial applications. Furthermore, new catalysts have to be found to broaden the scope so that even challenging substrates can be reduced with good conversions and high enantiomeric excess.

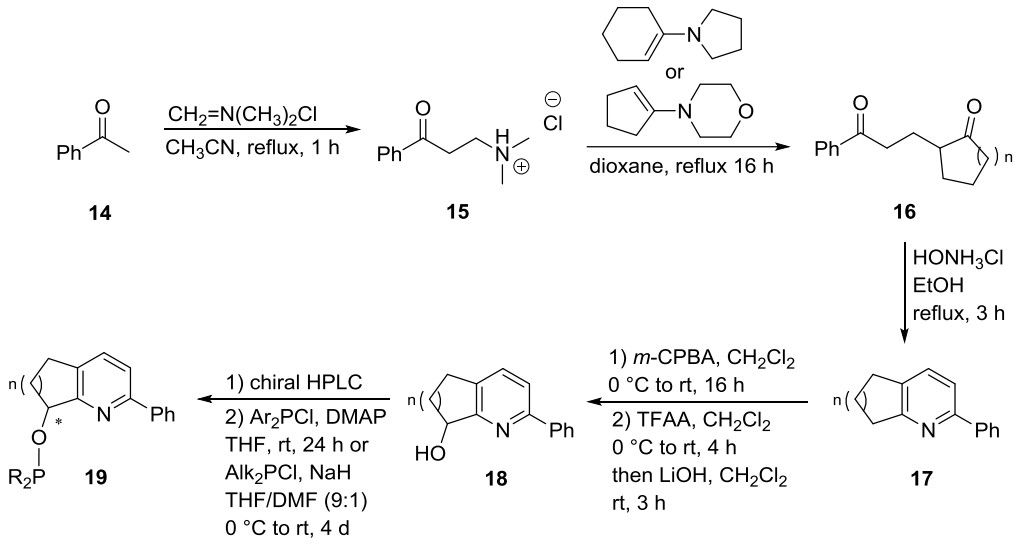
## 1.3 Aim of this work

Chapter 2 deals with the development of a new ligand class based on the pyridine-phosphinite ligands which can complex two iridium atoms to form dimeric complexes. These catalysts should be tested in the asymmetric hydrogenation of different substrates. The third chapter discusses the synthesis of several chiral cyclohexenes by enantioselective Diels-Alder reactions. These cyclohexenes and derivatives thereof were tested in the diastereoselective reduction by a chiral iridium catalyst. In Chapter 4, some results of enantioselective palladium-catalyzed allylic substitution reactions and asymmetric iridium-catalyzed hydrogenation with different NeoPHOX ligands are presented.

# 2 Development of pyrazine-phosphinite ligands and formation of their iridium complexes

## 2.1 Introduction

Among the N,P-ligand classes developed in our research group, the pyridine-phosphinite ligand class proved to be the most efficient (see *Figure 5*).[29-32] Their structure can be easily modified by the introduction of different substitutents at the phosphorus unit or the pyridine ring. Furthermore, either a five- or a six-membered carbocycle in the backbone can be introduced giving access to a broad library of ligands which allows the selective reduction of many substrates. However, the synthesis for ligands with a substituent at the pyridine ring includes many steps which make the formation of these compounds expensive (*Scheme 9*).[29a]




***Scheme 9***: Synthesis of phenyl subtstituted pyridine-phosphinite ligands.

For ligands with a phenyl moiety on the pyridine ring, the synthesis starts from acetophenone (**14**). In the first step, ammonium chloride **15** is formed by a Mannich reaction. Next, the ammonium species reacts with the corresponding enamine to give diketone **16** with either a five- or a six-membered carbocycle. After treatment with hydroxyl ammonium chloride, bicyclic pyridine **17** is formed which can be converted to pyridyl alcohol **18** after formation of the *N*-oxide followed by

Boekelheide rearrangement. In the last step, phosphinite **19** can be obtained by nucleophilic substitution with a phosphine chloride. For ligands with no substituent on the pyridine ring the synthesis can be started with the formation of the *N*-oxide from the corresponding commercially available bicyclic pyridine.

Since ligands with a phenyl moiety on the pyridne ring usually gave the best results in the asymmetric hydrogenation the synthesis was optimized for this type of ligands. Therefore, pyridyl alcohol **18** and other aryl derivatives were synthesized by a Suzuki-coupling of the chloride precursor with the corresponding boronic acid.[45] The pyridyl chlorides are mostly commercially available which reduces the necessary number of steps for the formation of the ligands.

One possibility to improve the efficiency of the synthesis of ligands of this type could be the introduction of a second N,P-functionalization into the molecule which would allow the complexation of two iridium atoms (*Figure 7*). Assuming that the iridium complexes of this novel ligand class show the same activity and selectivity as the monomeric complexes, the necessary amount of catalyst for the hydrogenation could be cut in half.

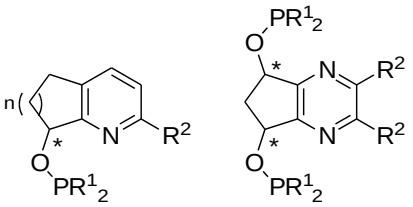
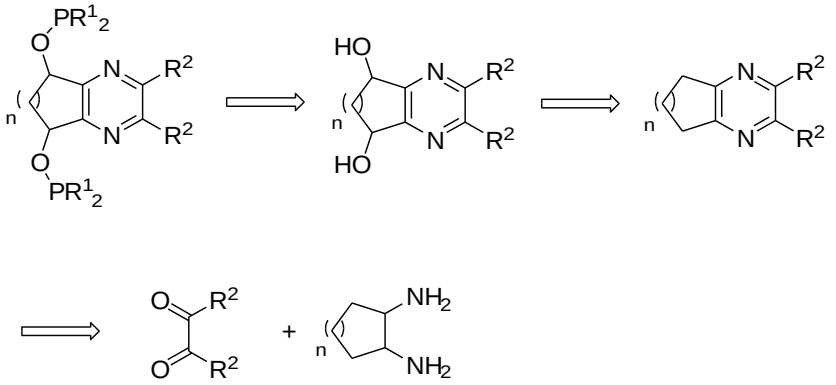



***Figure 7***: Structure of pyridine-phosphinite ligands (left) and new target pyrazine-diphosphinite ligands (right).

The proposed new ligand class consists of a pyrazine ring instead of a pyridine ring and a carbocycle with two phosphinite moieties instead of only one. Due to the $C_2$-symmetry it should be possible to introduce the functional groups on both sides in the same reaction which avoids the need of additional steps. The retrosynthetic strategy is based on the synthesis of the pyridine-phosphinite ligands and is identical for the last steps (*Scheme 10*).



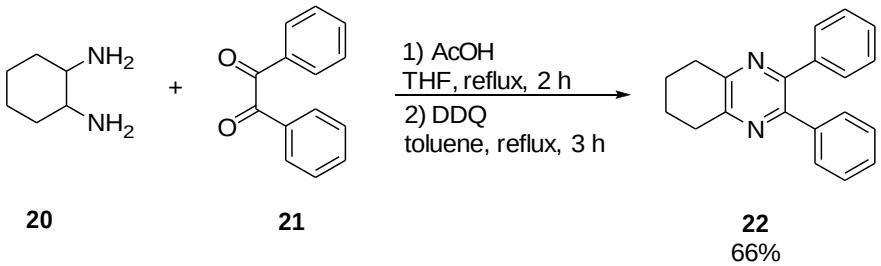
***Scheme 10***: Retrosynthetic analysis for pyrazine-diphosphinite ligands.

Condensation of a cyclic diamine with a diketone followed by oxidation should give the bicyclic pyrazine. Next, the pyrazine can be oxidized to the bis *N*-oxide followed by Boekelheide rearrangement as before to form the pyridyl diol. In the last step the phosphinite is formed by a nucleophilic substitution reaction between the hydroxy group and a phosphine chloride to form the desired ligand.

## 2.2 Synthesis of complexes with a six-membered carbocycle

### 2.2.1 *Synthesis of pyrazine diols via Boekelheide rearrangement*

First, we tried to synthesize several tetrahydroquinoxalines with different substituents at the pyrazine ring. We started with the synthesis of tetrahydroquinoxaline **22** with two phenyl groups (*Scheme 11*).



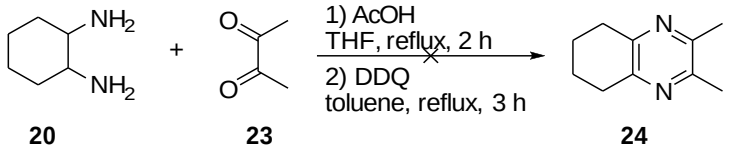

**20** **21** **22**
66%

***Scheme 11***: Synthesis of tetrahydroquinoxaline **22**.

1,2-Cyclohexanediamin (**20**) was treated with benzil (**21**) in THF under acidic conditions to form the diimine precursor. After purification by recrystalization, the diimine was oxidized using DDQ to

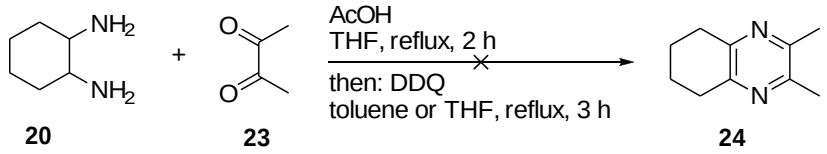
give pyrazine **22** in 66% yield over two steps.

Next, we wanted to synthesize tetrahydroquinoxaline **24** with two methyl groups at the pyrazine ring (*Scheme 12*).




***Scheme 12***: Attempted synthesis of tetrahydroquinoxaline **24**.

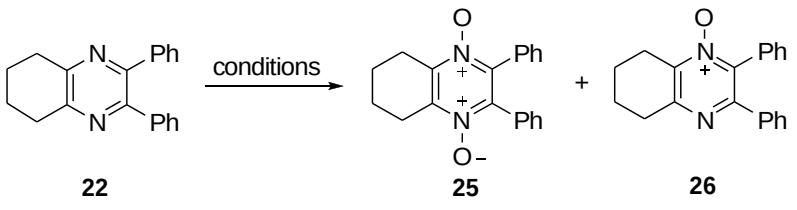
Therefore, 1,2-Cyclohexanediamin (**20**) was treated with 2,3-butanedione (**23**) under the same conditions as before to form the diimine. After two hours complete product formation was observed by GCMS. However, after recrystalization the desired product could not be isolated. Purification by column chromatography only gave low yield of the hexahydroquinoxaline. We assume that the diimine might be unstable and decomposes during purification. Therefore, we tried to oxidize it to pyrazine **24** immediately after formation of the diimine without any purification of the diimine (*Scheme 13*).




***Scheme 13***: Attempted synthesis of tetrahydroquinoxaline **24** without purification of the diimine.

Unfortunately, this new synthetic procedure was not successful either and the final product was not isolated. Since the residue turned black during removal of the solvent after the first step, which might be an indication for decomposition of the diimine, we also tried a one pot procedure without change of solvent. Unfortunately, still no pyrazine formation was observed. We do not know why the oxidation did not work but decided to put no more effort into the synthesis of pyrazine **24**. Next, we investigated the oxidation of commercially available unsubstituted pyrazine **22** to its bis-*N*-oxide **25** (*Table 1*).

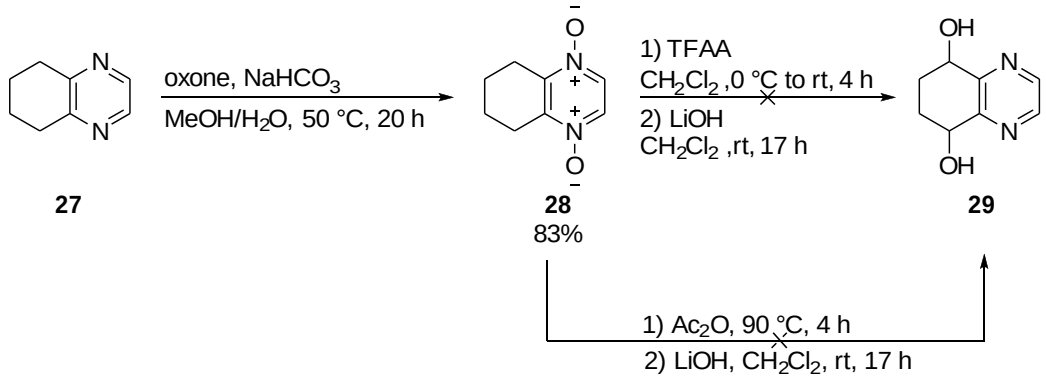
***Table 1***: Screening of conditions for the oxidation of pyrazine **22** to bis-*N*-oxide 2**5**.



| Entry | Solvent | Oxidant (eq.) | Additive (eq.) | Observed Product |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | $H_2O_2$ (4.0) | MTO (0.04) | Monooxide |
| 2 | AcOH | $H_2O_2$ (4.0) | No additive | Monooxide |
| 3 | $CHCl_3$ | *m*-CPBA (2.3) | $NaHCO_3$ (20.0) | No reaction |
| 4 | $CHCl_3$ | *m*-CPBA (4.6) | No additive | No reaction |
| 5 | EtOAc | *m*-CPBA (2.2) | No additive | Monooxide |
| 6 | MeOH | Oxone (2.3) | $NaHCO_3$ (5.0) | No reaction |
| 7 | $CH_2Cl_2$ | Oxone (2.3) | $NaHCO_3$ (5.0) | No reaction |

First, we tried to oxidize the pyrazine using conditions for the synthesis of the pyridine-phosphinite ligands described by Kaiser .[29a] Methyltrioxorhenium (MTO) was employed as a catalyst and aqueous hydrogen peroxide solution as oxidant (entry 1). However, we only observed formation of the mono-*N*-oxide **26** and no bis-*N*-oxide **25**. After an extended literature search we tested further oxidation methods for the synthesis of pyrazine-bis-*N*-oxides[46] but none of them worked. When the reaction was performed in acetic acid with hydrogen peroxide as oxidant only the monooxide was detected again (entry 2). By switching to chloroform as solvent and *m*-CPBA as oxidant the reactivity was totally inhibited even if sodium bicarbonate was added as additive (entry 3 and 4). Using ethyl acetate instead of chloroform led only to the formation of mono-*N*-oxide **26** (entry 5). Last, we tried oxone as oxidant together with sodium bicarbonate as additive in methanol or methylene chloride (entry 6 and 7). However, both procedures failed and no conversion was observed.

We decided to change the substrate to see if the phenyl moieties are the reason for the inhibited reactivity and investigated the oxidation of unsubstituted tetrahydroquinoxaline **27** (*Scheme 14*).



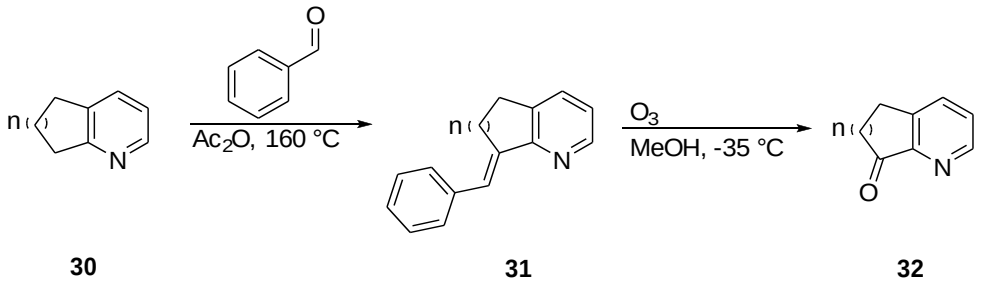

***Scheme 14***: Attempted synthesis of **29** by Boekelheide rearrangement.

Pyrazine **27** was treated with an excess of oxone and sodium bicarbonate in a 2:1 methanol/water mixture to yield the desired bis-*N*-oxide **28** in 83%. Under related conditions no reaction was observed for the phenyl substituted pyrazine (*Table 1*, entry 6) which indicates that the phenyl rings inhibit the reactivity. A similar behavior was observed in the synthesis of the pyridine-phosphinite ligands in which the oxidation of substituted pyridines was more difficult.[29a]

Next, we investigated the Boekelheide rearrangement of bis-*N*-oxide **28** to diol **29**. An excess of trifluoroacetic anhydride was added to the oxide followed by *in situ* hydrolysis with lithium hydroxide but only decomposition of the intermediate could be observed. Alternatively, a milder protocol in acetic anhydride was tested but it did not lead to product formation either.

### 2.2.2 *Synthesis of pyrazine diols via condensation reaction*

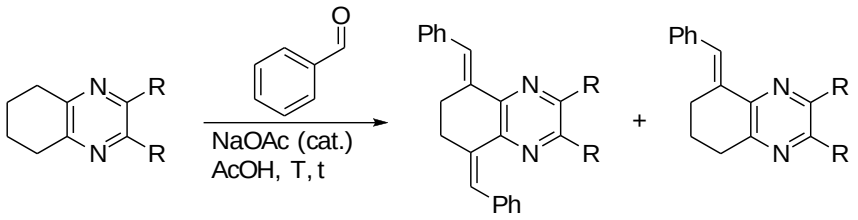
Since the strategy involving a Boekelheide rearrangement did not succeed we decided to try another synthetic route which was previously applied in our group for the synthesis of N,P ligands (*Scheme 15*).[47]




***Scheme 15***: Synthesis of pyridyl ketones by A. Ganic for the development of N,P-ligands.

A condensation between bicyclic pyridines **30** and benzaldehyde led to formation of olefins **31**. These products were transformed to ketones **32** by ozonolysis. We thought that the same strategy should be applicable to our system using quinoxaline **27** or **22** as starting material. Reduction of the formed ketone or reductive workup after ozonolysis should give the desired diol.

***Table 2***: Condensation reaction of pyrazines **22** and **27** with benzaldehyde.




**27**: R = H
**22**: R = Ph

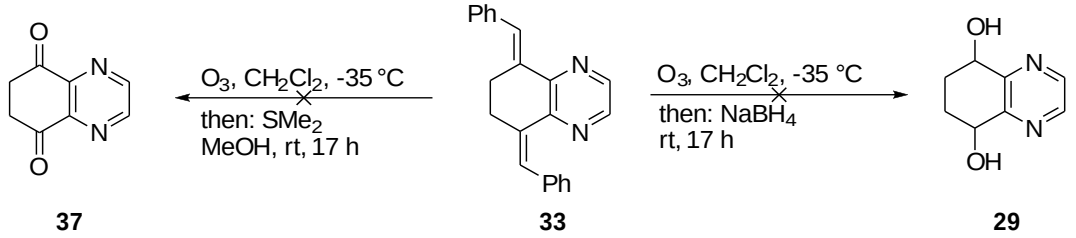
**33**: R = H
**34**: R = Ph

**35**: R = H
**36**: R = Ph

| Entry | R | T (°C) | t (days) | Yield mono (%) | Yield di (%) |
|---|---|---|---|---|---|
| 1 | H | 120 | 1 | 42 | 0 |
| 2 | H | 180 | 5 | 34 | 63 |
| 3 | Ph | 120 | 1 | 0 | 0 |

We used a modified protocol published by Jahng[48] for the condensation between the pyrazines and benzaldehyde. However, treatment of tetrahydroquinoxaline **27** with an excess of benzaldehyde under these conditions led only to the monoolefin **35** (entry 1). Very high temperature (180 °C) and a long reaction time (5 days) were necessary to obtain the diolefin **33** in good yield (63%) together with the monoolefin (entry 2). After five days the reaction was stopped since no more product generation could be observed. Because pyrazine **22** with two phenyl groups at the pyrazine ring turned out to be even less reactive, no diolefin **34** or monoolefin **36** was formed under standard conditions. Since not even the monoolefin was observed we decided not to test the synthesis at higher temperature.

With diolefin **33** in hand we investigated the ozonolysis step next (*Scheme 16*).



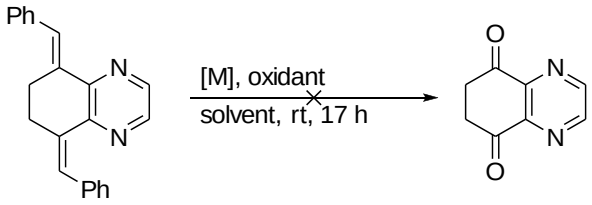

**37** **33** **29**

***Scheme 16***: Attempted ozonolysis of diolefin **33**.

First, we tried to synthesize diketone **37** by reductive workup with dimethyl sulfide but the desired product could not be isolated and only an unidentifiable mixture was obtained. Also changing the solvent for the ozonolysis from methylene chloride to methanol did not result in product formation. We tried to form diol **29** directly by adding sodium borohydride after ozonolysis but again, the desired product could not be detected.

Because diol **29** was not accessible by ozonolysis we tried to synthesize diketone **37** by transition metal catalyzed oxidative cleavage and tested various procedures (*Table 3*).[49,50]

***Table 3***: Attempted synthesis of diketone **37** by oxidative cleavage of diolefin **33**.



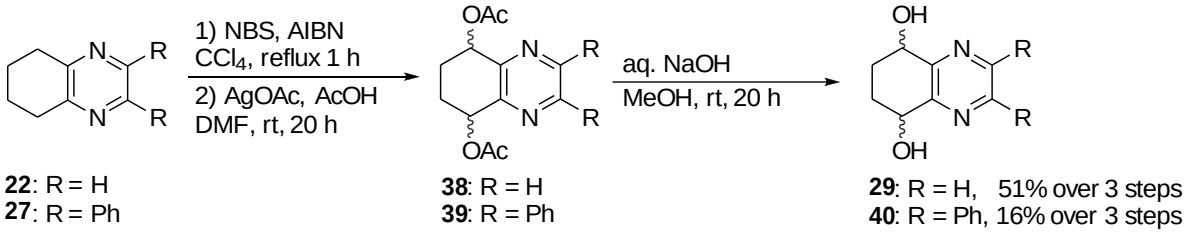

**33** **37**

| Entry | [M] | Oxidant | Additive | Solvent |
|---|---|---|---|---|
| 1 | $OsO_4$ | Oxone | $NaHCO_3$ | DMF |
| 2 | $OsO_4$ | $NaIO_4$ | $NaHCO_3$ | DMF |
| 3 | $RuCl_3$ | Oxone | $NaHCO_3$ | Dichloroethane/$H_2O$ |
| 4 | $RuCl_3$ | $NaIO_4$ | No additive | Dichloroethane/$H_2O$ |

Unfortunately, none of the procedures yielded in product formation. Using osmium tetroxide with either oxone or sodium periodate as oxidant resulted in an unidentifiable mixture. When ruthenium chloride was used as catalyst in combination with oxone only starting material could be obtained, whereas ruthenium chloride with sodium perioadate led to an complex mixture. Since the synthesis of diol **29** failed by this strategy we searched the literature for an alternative route.

### 2.2.3 *Final synthesis of pyrazine diols*

An intensive search for routes to similar molecules revealed a three step synthesis for tetrahydronaphthalenediol starting from tetrahydronaphthalene[51] which we thought should be adaptable to our system (*Scheme 17*).

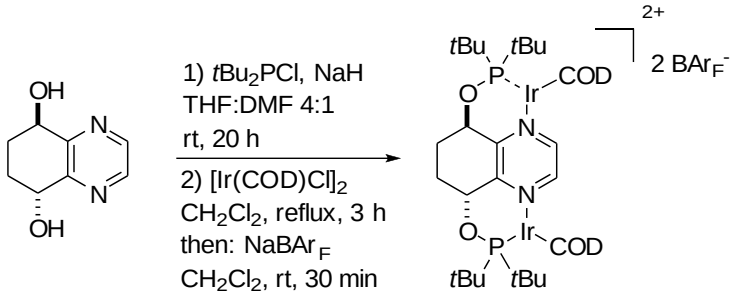



***Scheme 17***: Synthesis of diols **29** and **40**.

First, we invesigated the synthesis of diol **29**. Starting with a radical benzylic bromination of pyrazine **22** using *N*-bromosuccinimide gave the dibromide followed by conversion to the diacetate **38** using silver acetate. The corresponding diacetate was obtained as a 2:1 mixture of the diastereomers in favor of the desired *trans*-diacetate. The mixture was used without separation of the diastereomers in the next step. Hydrolysis of the acetate using 2 M NaOH in methanol resulted in diol **29** in an overall yield of 51%. The diastereomers were separated by column chromatography to give *trans*-**29** in an overall yield of 34% and *cis*-**29** in 17%. The synthesis of phenyl substituted diol **40** started from the corresponding pyrazine **27** and was less efficient. The diol could be isolated in only 16% after the three steps. Again, it was obtained as a 2:1 mixture in favor of the *trans*-isomer which was separated by column chromatography.

### 2.2.4 *Ligand formation and complexation*

With the diols in hand we tried to synthesize the ligands by nucleophilic substitution with phosphine chlorides followed by *in situ* complexation with iridium and counterion exchange according to the standard procedure for the pyridine-phosphinite ligands (*Scheme 18*).[29a,45]




**29** **C1**

***Scheme 18***: Synthesis of catalyst **C1**.

The reaction progress was controlled by $^{31}$P-NMR analysis and measured chemical shifts were compared with the value for the corresponding pyridine-phosphinite ligand. After stirring overnight phosphinite formation could be observed together with some decomposition of the phosphorus reagent. A shift of the signal in $^{31}$P-NMR after addition of bis(1,5-cyclooctadiene)diiridium dichloride showed that the complexation worked but when $NaBAr_F$ was added the reaction solution turned from red to green which normally indicates oxidation of the phosphorus atom. Nevertheless, the corresponding product was identified by $^{31}$P-NMR analysis of the crude mixture. After column chromatography, one fraction was obtained which showed several spots in TLC. In $^{31}$P-NMR, several peaks around 140 ppm could be observed (*Figure 8*), in the region where the signal for the catalyst is expected since the signal for the analogous pyridine-phosphinite complex comes at 135 ppm. The signal at 30 ppm belongs to an oxidized phosphorus atom. However, the $^{1}$H-NMR revealed that the desired complex **C1** was not present in the mixture. The two singlets in the aromatic range should belong to the $BAr_F$ anion but the signal for the protons at the pyrazine ring at 8.5 ppm was not observed. Furthermore, there were no signals for the olefinic protons of the cycloocatdiene.

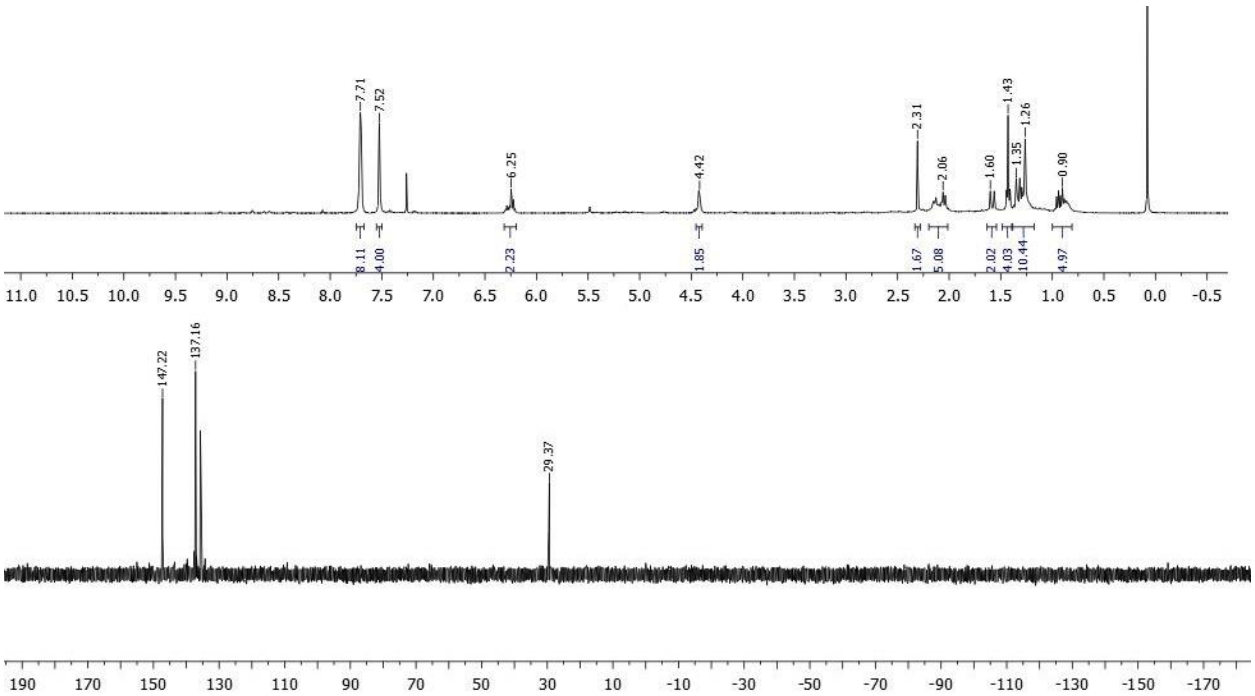
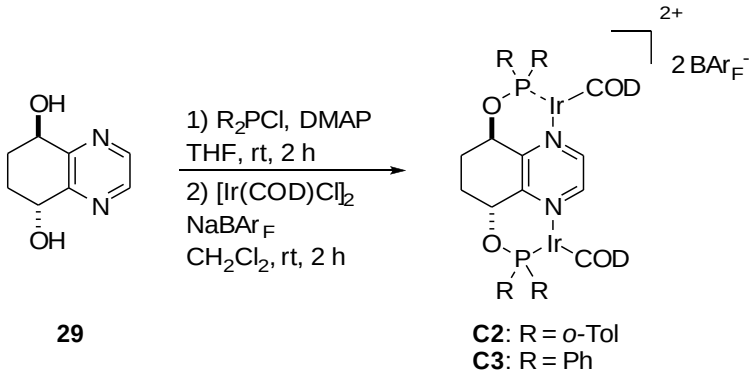



***Figure 8***: $^{1}$H- (top) and $^{31}$P-NMR spectrum (bottom) after column chromatography of attempted synthesis of **C1**.

Since oxidation at the phosphorus atom was an issue and alkyl phosphines are more sensitive towards oxidation we decided to continue our investigations with aryl phosphines. They are easier to handle and we thought that the corresponding iridium complexes are more stable simplifying the isolation. Therefore, we attempted to synthesize *ortho*-tolyl substituted catalyst **C3** and iridium complex **C2** bearing two phenyl groups at the phosphinite residue (*Scheme 19*).




**29**

**C2**: R = *o*-Tol
**C3**: R = Ph

***Scheme 19***: Attempted synthesis of aryl substituted iridium complexes.

Unfortunately, the outcome was similar to the alkyl substituted phosphine. According to phosphorus NMR phosphinite formation and complexation worked fine but after addition of $NaBAr_F$ the

reaction mixture turned green in both cases. However, the NMR spectra of the crude products looked promising and did not show any oxidized species and after column chromatography a red foam was obtained. However, the $^{1}$H-NMR spectrum revealed that the desired complex **C2** was not present. Although the signal for the pyrazine ring at 8.58 ppm could be observed for the *ortho*-tolyl substituted compound (*Figure 9*), the signals for the olefinic protons of the cyclooctadiene were missing. A broad signal at about 3.80 ppm could not be assigned. Furthermore, there were too many signals in the aliphatic region. The proton spectrum from the attempted synthesis of complex **C3** looked similar.

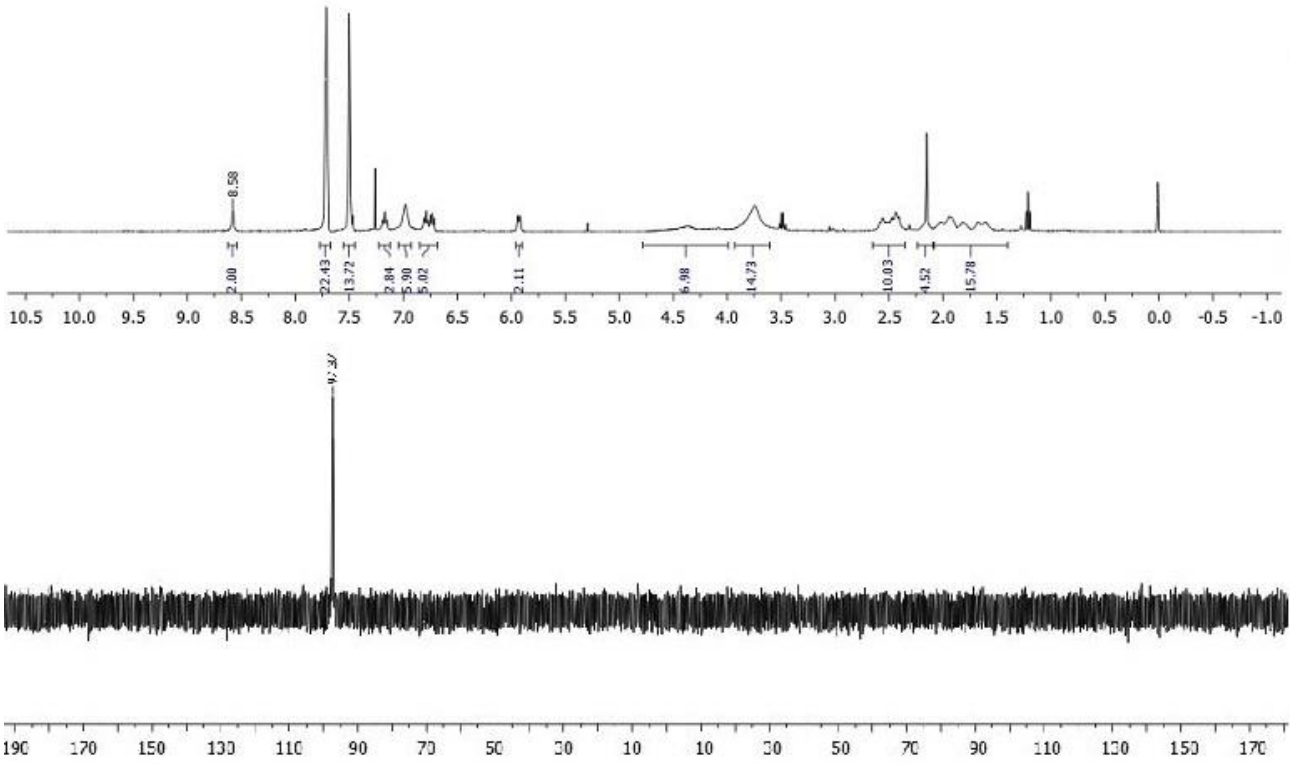
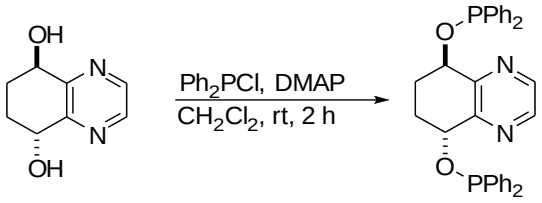



***Figure 9***: $^{1}$H- (top) and $^{31}$P-NMR spectrum (bottom) of attempted synthesis of **C2**.

Because the synthesis of the iridium catalysts was unsuccessful by this procedure we investigated other strategies. First, we wanted to know whether the formation of the phosphinite was the problem or the complexation. Therefore, we tried to isolate ligand **L10** (*Scheme 20*).




**29** **L10**

***Scheme 20***: Synthesis of ligand **L10**.

We stopped the reaction after phosphinite formation was complete according to phosphorus NMR and after workup we checked the $^{1}$H-NMR spectrum of the crude product to see if the ligand was formed (*Figure 10*). We were delighted to see that the synthesis worked and ligand **L10** was isolated. The $^{31}$P-NMR spectrum showed only one signal and also the $^{1}$H-NMR spectrum was clean showing that there was no starting material left and no side products were formed.

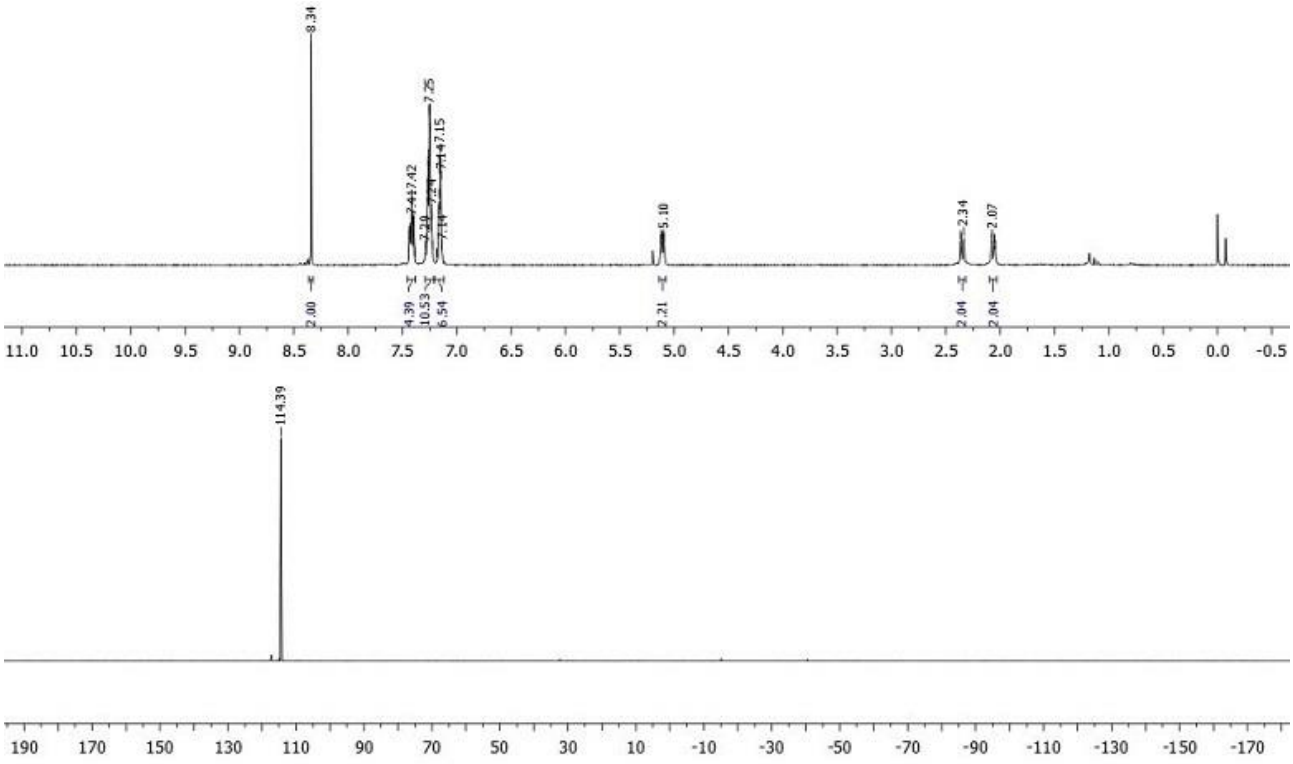
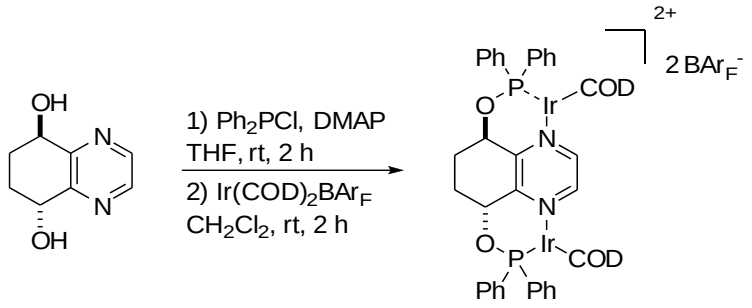



***Figure 10***: $^{1}$H- (top) and $^{31}$P-NMR spectrum (bottom) of ligand **L10**.

Since phospinite formation was not the problem we concentrated on further investigating the complexation with iridium. As the reaction mixture always turned green after addition of $NaBAr_F$ we thought that the counterion exchange might be the critical step and we decided to try another

iridium source (*Scheme 21*).



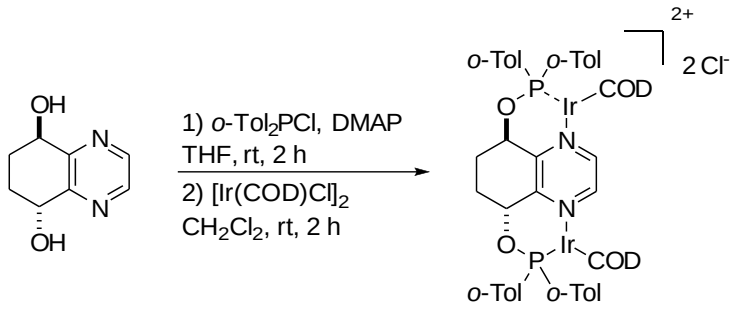

**29** **C3**

***Scheme 21***: Attempted complex formation with $Ir(COD)_2BAr_F$.

Instead of $[Ir(COD)Cl]_2$, bis(cyclooctadiene)iridium(I) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate was used which would directly lead to catalyst **C3** so that counterion exchange was not necessary anymore. However, the iridium complex was not isolated even though $^{31}$P-NMR analysis indicated product formation. The $^{1}$H-NMR spectrum showed mainly signals belonging to the iridium source together with some signals in the aliphatic range.

Next, we tried to purify the crude product by column chromatography on AlOx because we thought that the complexes might decompose on silica gel but this procedure was not successful either. Another problem of column chromatography could be that a methanol/methylene chloride mixture was necessary as eluent due to the high polarity of the iridium complexes. Methanol might lead to a ligand exchange and could be the reason why not all the expected signals could be observed in proton NMR. Attempts to use less coordinating solvents such as THF were not successful.

Since the isolation of the $BAr_F$ complexes could not be achieved we tried to synthesize the corresponding iridium complex with a chloride as counterion (*Scheme 22*).




**29** **C4**

***Scheme 22***: Attempted synthesis of complex **C4** with a chloride as counterion.

We stopped the reaction after addition of the iridium source and purified the crude product by column chromatography. A red foam was obtained which showed a signal in the $^{31}$P-NMR spectrum at 92.7 ppm and new signals which had not been observed before at 42 and −42 ppm (*Figure 11*). The latter two signals were interpreted as doublets belonging to two different phosphorus atoms coupled to each other. The proton NMR again showed no signals for the olefinic protons of the cyclooctadiene ligands and was not clean. Therefore, no structural assignments could be made. Attempts to do a counterion exchange with the obtained product failed and only an oxidized phosphorus species could be observed.

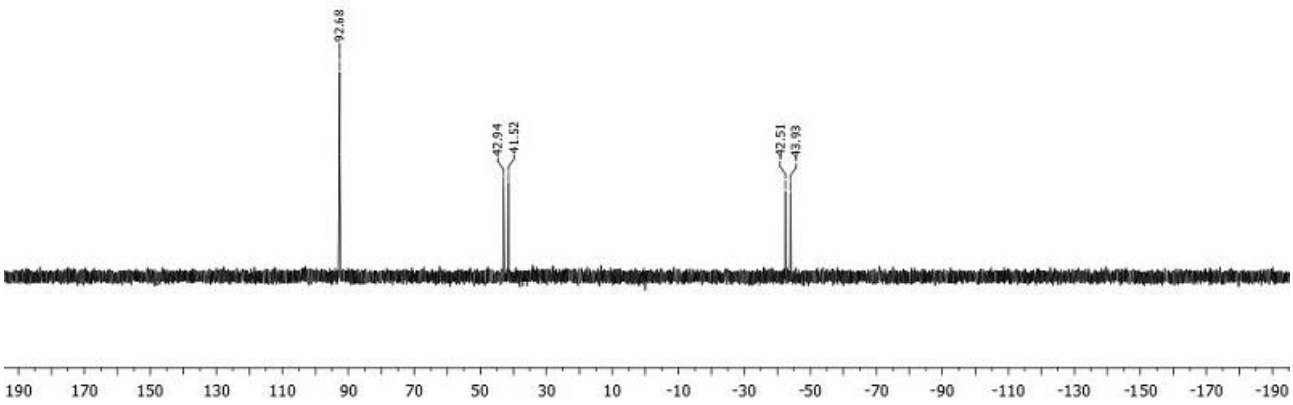
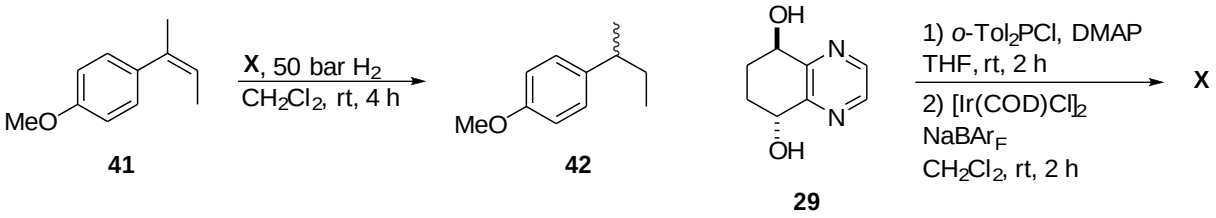



***Figure 11***: $^{31}$P-NMR after column chromatography of synthesis of complex **C4**.

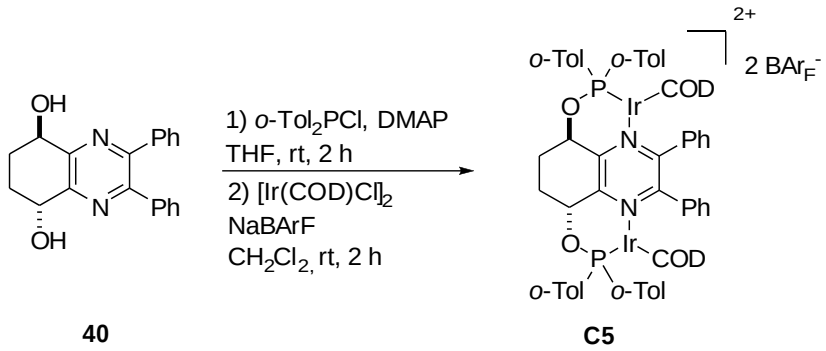
Although all the attempts to isolate a dinuclear iridium complex failed, the phosphorus NMR spectrum indicated that an iridium complex was formed. Therefore, we tested if the formed compound was capable to activate hydrogen and to catalyze hydrogenation. So, we performed the synthesis again and used the crude product directly for the hydrogenation of substrate **41**

(*Scheme 23*).




***Scheme 23***: Test hydrogenation with a crude iridium complex derived from diol **29**.

The reaction was performed with 10 mg of crude **C2** which would correlate to 3.3 mol% if it was a pure catalyst. After four hours reaction time the $^{1}$H-NMR spectrum showed only reduced product **42** and no starting material anymore. We were happy to see that the olefin could be reduced even though the structure of the catalytically active species was not clear. With the aim to prepare a structurally designed catalyst, we investigated the complexation of a ligand with a phenyl substituted pyrazine to see if the corresponding iridium complex is more stable (*Scheme 24*).

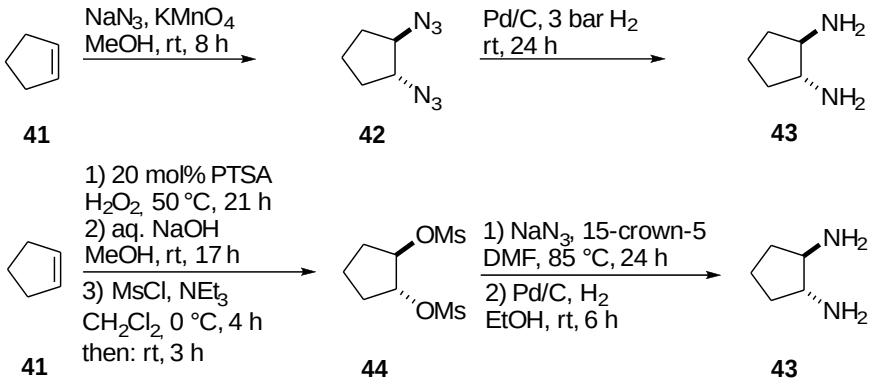



***Scheme 24***: Attempted synthesis of phenyl substituted complex **C5**.

Under the conditions previously used for catalyst preparation from the unsubstituted pyrazine **29** the same problems occurred. Phospinite formation and complexation worked fine according to $^{31}$P-NMR but after addition of $NaBAr_F$ the reaction mixture turned green. In the $^{31}$P-NMR spectrum of the crude product was a signal belonging to a complexed phosphorus atom but after column chromatography this signal disappeared and there was only a peak assigned to an oxidized species. In view of these problems we decided not to do any further studies on the synthesis of these complexes.

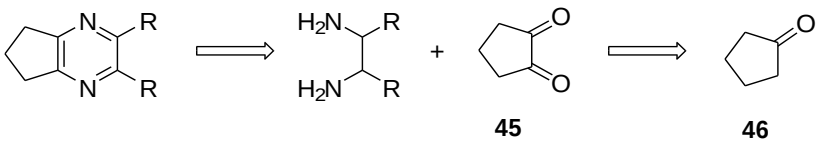
## 2.3 Synthesis of complexes with a five-membered carbocycle

The strategy for the synthesis of complexes with a five-membered carbocycle was the same as for their six-membered analogues (*Scheme 10*). Since 1,2-diaminocyclopentane (**41**) was not commercially available we selected two literature procedures for its synthesis (*Scheme 25*).[52,53]




***Scheme 25***: Synthesis of 1,2-diaminocyclopentane by Gilheany (top)[52] and Deniaud (bottom).[53]

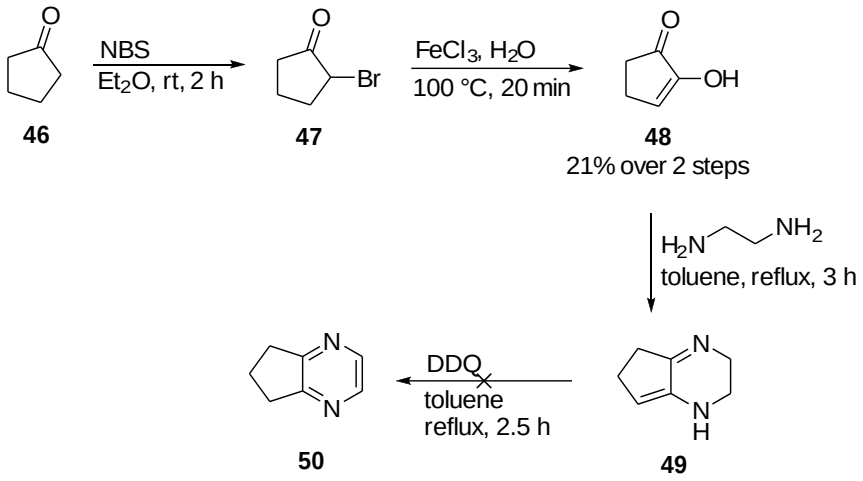
Both syntheses start from cyclopentene (**41**) and include the formation of diazide **42** which is reduced to diamine **43**. Gilheany formed the diazide in one step using sodium azide and potassium permanganate while Deniaud followed a three step procedure to first form dimesylate **44** which is then transformed to diazide **42** and finally reduced. We first explored Gilheany's route since it included less steps. However, direct synthesis of diazide **42** failed and therefore, we tried Deniaud's protocol next. Epoxide formation of cyclopentene worked fine but ring opening with sodium hydroxide failed and the diol could not be obtained. Because of these problems at an early stage of the synthesis and since it included the formation of a diazide which is difficult to handle we chose another strategy.




***Scheme 26***: New retrosynthetic plan for pyrazines with a five-membered carbocycle.

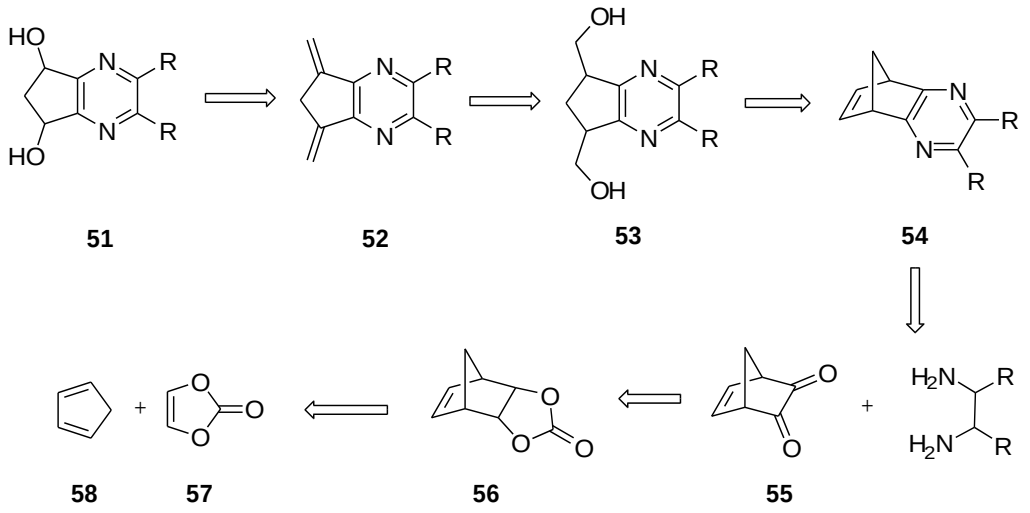
As shown in *Scheme 26*, the pyrazine should be formed by a condensation reaction between a non-cyclic diamine and cyclic 1,2-diketone **45** which can be obtained from commercially available

cyclopentanone (**46**).




***Scheme 27***: Attempted synthesis of pyrazine **50** starting from cyclopentanone (**46**).

In the first step, cyclopentanone is brominated to give α-bromoketone **47** which is then transformed into enol **48** with 21% yield over two steps.[54] Next, reaction of the enol with ethylenediamine should lead to imine **49** which we wanted to oxidize immediately to pyrazine **50** due to its instability.[55] However, the pyrazine could not be isolated and only an unidentifiable mixture was obtained. Formation of the imine worked according to GCMS but the heteroarene could not be detected. The same problem occurred already in the synthesis of methyl substituted pyrazines with a six-membered carbocycle (*Scheme 12* and *13*). Therefore, we changed our synthetic plan again and came up with a new route (*Scheme 28*).

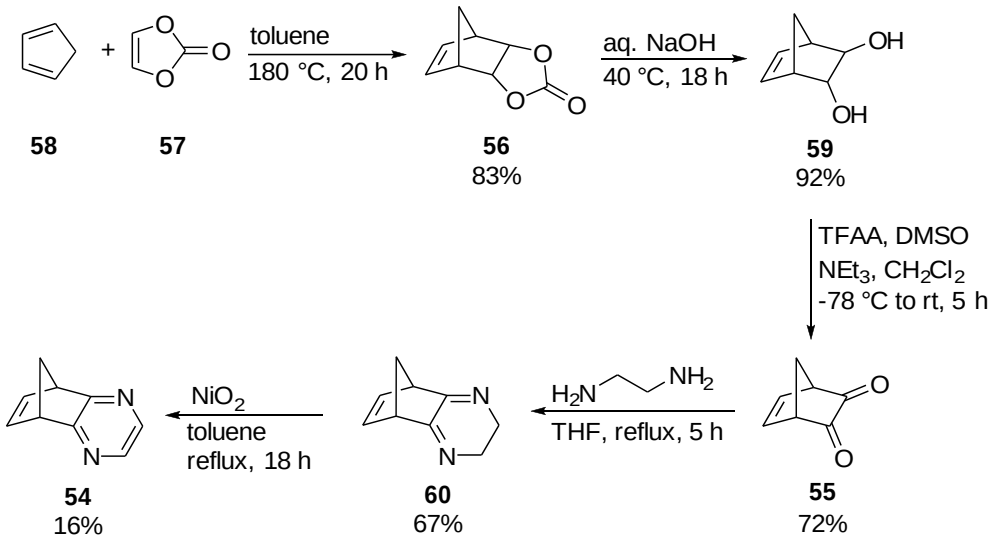



**51** **52** **53** **54**

**58** **57** **56** **55**

***Scheme 28***: Changed retrosynthetic plan starting from cyclopentadiene (**58**).

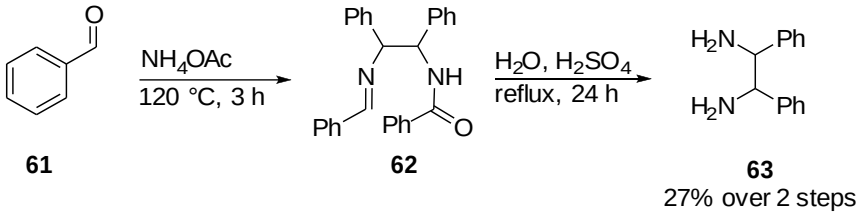
Diol **51** should be accessible from diolefin **52** by ozonolysis followed by reductive workup. The terminal alkene can be obtained from diol **53** by transformation of the hydroxy group into a leaving group and subsequent base induced elimination. The diol should be available from tricyclic olefin **54** by another ozonolysis with reductive workup. This route had already been previously applied for the synthesis of a similar molecule where one of the primary alcohols of **53** was protected as a silyl ether.[56] Pyrazine **54** can be formed by condensation of diketone **55** with a 1,2-diamine followed by oxidation. The synthesis of diketone **55** is literature known and includes a Diels-Alder reaction and a Swern oxidation.[57] This strategy includes many steps which is a drawback but the first steps are literature known and the last reactions were reported for a similar molecule, so we tried to obtain diol **51** by this route (*Scheme 29*).




***Scheme 29***: Synthesis of tricyclic pyrazine **54**.

The synthesis started by a Diels-Alder reaction between cyclopentadiene (**58**) and vinylene carbonate (**57**) to give cyclohexene **56** in 83% yield. Hydrolysis of the cyclic carbonate with sodium hydroxide led to almost quantitative formation of diol **59** which was subsequently oxidized under Swern conditions to give diketone **55**. Treatment with ethylenediamine gave access to diimine **60** which was finally oxidized to pyrazine **54** using nickel oxide with an overall yield of 6% over five steps. The drawback of this synthesis is the last step with a yield of only 16%. Moreover, the use of nickel oxide is problematic due to its environmental and health risks and its high costs. We also tried to perform the oxidation with DDQ but this did not lead to product formation. Instead, a unidentifiable mixture was obtained.

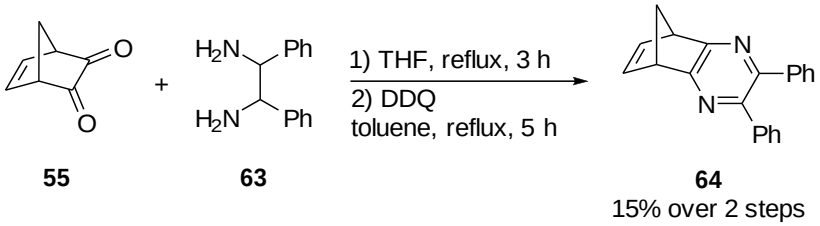
We also studied the synthesis of pyrazine **64** with two phenyl groups at the aromatic ring, to see if it is accessible by oxidation of the corresponding diimine with DDQ as it was the case for the phenyl substituted tetrahydroquinoxaline **22** (*Scheme 11*). The required diphenylethylenediamine (**63**) was prepared according to *Scheme 30*.




***Scheme 30***: Synthesis of diphenylethylenediamine.

The formation of the diamine involved two steps following a procedure described by Hu.[58] In the

first step, four equivalents of benzaldehyde (**61**) reacted with ammonium acetate to give amide **62**. Hydrolysis of the amide under acidic conditions led to formation of the desired diamine **63** in 27% yield over both steps. With the diamine in hand we investigated the synthesis of the pyrazine (*Scheme 31*).




**55** **63** **64**
15% over 2 steps

***Scheme 31***: Synthesis of phenyl substituted pyrazine **64**.

We performed the transformation under the same conditions as before for the first step and used DDQ for the oxidation of the diimine. We were pleased to see that we could obtain pyrazine **64** by this procedure. As already observed in previous reactions, it seems that the phenyl substituents stabilize the diimine which allows the use of DDQ as oxidant instead of nickel oxide. However, the yield was unsatisfying with only 15% over two steps and only insignificantly higher than for unsubstituted pyrazine **54** (11% over the two steps). Because of the low yields obtained for the preparation of pyrazines which make the synthesis rather unattractive and the problems we encountered in the complexation of the ligands with a six-membered carbocycle, we discontinued this project at this stage.

## 2.4 Summary

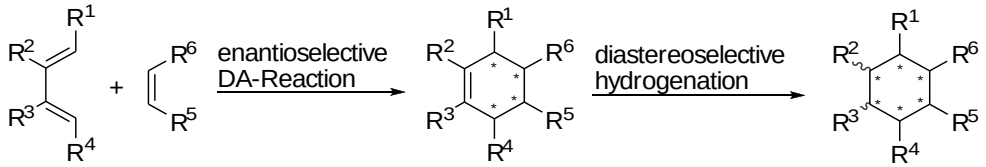
We synthesized two precursors of a new *C2*-symmetric ligand class, which can form dinuclear metal complexes, in three and/or five steps from commercially available starting materials. The procedure developed for related pyridine phosphinite ligands could no be applied so that a new strategy had to be found. One ligand was isolated and identified by $^{1}$H-NMR. However, iridium complexes of these ligands could not be isolated even though $^{31}$P-NMR indicated formation of them. Various methods were tested to obtain the complexes but it seemed that they were not stable and decomposed. In one case it could be shown that the crude product obtained by complexation can be used to reduce an alkene. However, the nature of the catalytically active species could not be determined.

For ligands with a five-membered carbocycle we developed a synthesis of potential precursors. However, these studies were discontinued because of the low yield for the pyrazine formation and the problems which occurred in the complexation of the ligands with a six-membered carbocycle. The remaining transformations to the desired ligands are literature known for similar substrates and should work but the synthesis would not be very efficient due to a high number of steps and low yield.

# 3 Chiral Diels-Alder products as substrates for iridium-catalyzed asymmetric hydrogenation

## 3.1 Introduction

Cyclohexane rings are ubiquitous structural elements occurring I many important natural and synthetic compounds. Among the many possible routes to cyclohexanes,[59-61] ring formation via Diels-Alder reaction stands out because it gives access to a wide range of polysubstituted cyclohexenes from simple precursors in a regio-, diastereo- and also enantioselective manner. Moreover, by reaction at the C=C bond Diels-Alder products can be modified in a variety of ways. For instance, if the C=C bond bears one or two substituents, one or two additional stereogenic centers can be introduced by hydrogenation (*Scheme 32*). This strategy is most useful if C=C bond reduction can be carried out diastereoselectively.




***Scheme 32***: Synthesis of cyclohexanes by chiral Diels-Alder reaction followed by iridium-catalyzed hydrogenation.

Diastereoselectivity can be achieved by substrate or by catalyst control. The scope of substrate control is limited and strongly dependent on the specific substituents present in the cyclohexene ring. Furthermore, only one of two diastereomeric products is accessible by a susbtrate controlled transformation.

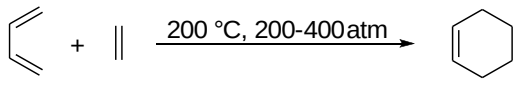
A more widely applicable approach is an enantioselective Diels-Alder reaction followed by hydrogenation under catalyst control. By this way, both diastereomeric hydrogenation products are available depending on the absolute configuration of the catalyst.

## *3.2* Objectives of this work

Our goal was to synthesize different chiral cyclohexenes with a substituent at the double bond by enantioselective Diels-Alder reactions. In the second step, the products should be reduced diastereoselectively under catalyst control employing the chiral iridium catalysts developed in our group (*Scheme 32*). This Diels-Alder-hydrogenation sequence has been applied in the synthesis of several natural products.[62] Mulzer's synthesis of valerenic acid involved a hydroxy-directed asymmetric Diels-Alder reaction. A subsequent hydroxy-directed diastereoselective hydrogenation of the double bond using Crabtree's catalyst led to the product in 91% yield.[62a] To date, no examples have been reported, in which a chiral catalyst is used for the hydrogenation.
Depending on the choice of the starting materials for the Diels-Alder reaction, the tandem Diels-Alder-hydrogenation strategy allows the introduction of different substituents in various positions of the cyclohexane ring diastereoselectively.

## 3.3 Enantioselective Diels-Alder reaction

The Diels-Alder reaction is a powerful tool for the synthesis of cyclohexene derivatives and was first reported by the German chemists Otto Paul Hermann Diels and Kurt Alder in 1928.[63] The reaction became a very efficient method for the formation of six-membered rings. In 1950, the two chemists obtained the Nobel Prize for “their discovery and development of the diene synthesis”. Due to its high regio- and stereoselectivity the method was applied in many transformations and is often used as a key step in natural product synthesis. For example, Woodward adopted it in the synthesis of cortisone and cholesterol.[64,65]
The simplest example for a Diels-Alder reaction is the reaction of butadiene (**65**) with ethylene (**66**) (*Scheme 33*).



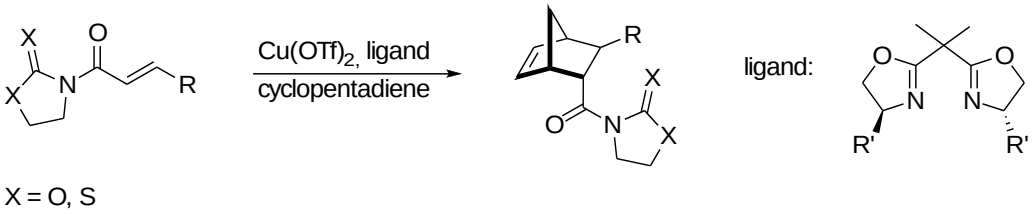

**65** **66** **67**
18%

***Scheme 33***: Diels-Alder reaction of 1,3-butadiene **65** with ethylene **66**.[66]

This reaction only proceeds at high temperature and pressure and in poor yield. However, by

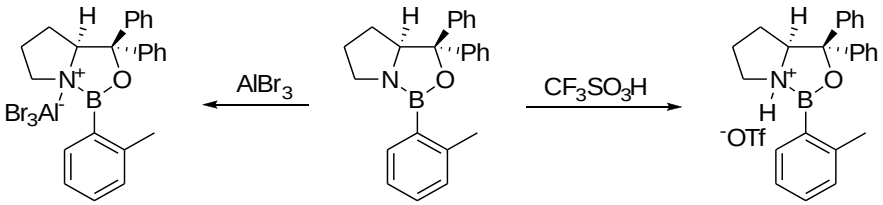
introducing electron-withdrawing substituents at the dienophile the reaction is accelerated and can occur at room temperature due to lowering the LUMO energy of the dienophile.[67] The reactivity can be further increased by using a catalyst, either a Lewis acid[68] or an organocatalyst,[69] which interacts and/or reacts with a carbonyl group at the dienophile. By employing a chiral catalyst, the synthesis can be done in an enantioselective fashion.

The first example for a catalytic system which allowed the synthesis of various cyclohexenes by an asymmetric Diels-Alder reaction was published by Evans in 1993.[68a] He used $C_2$-symmetric bis(oxazoline)copper complexes to react cyclopentadiene with several imides and thiazolidine-2-thione analogs and obtained the corresponding cyclohexenes with enantioselectivities higher than 90% (*Scheme 34*).




***Scheme 34***: Enantioselective Diels-Alder reaction by Evans.[68a]

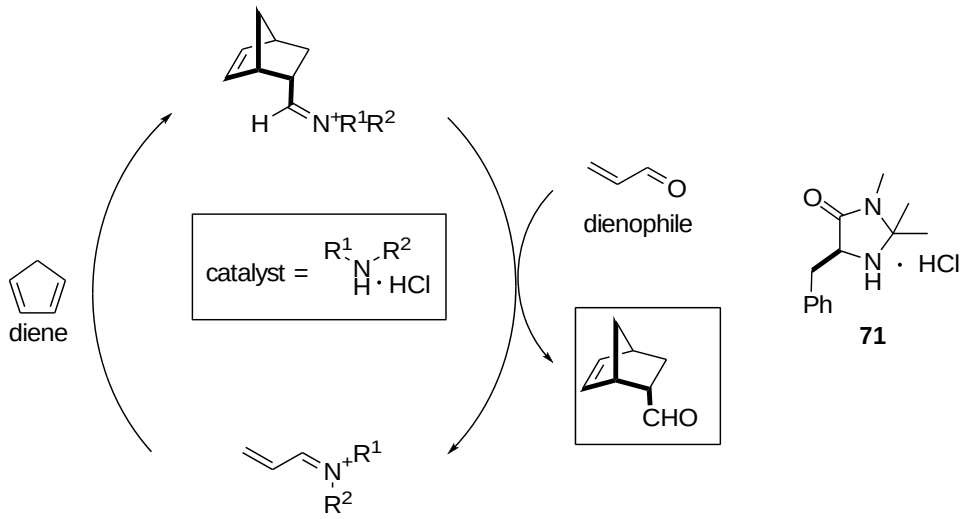
Corey used chiral oxazaborolidines as catalysts for the enantioselective Diels-Alder reaction of various dienes and furans with different dienophiles (*Scheme 35*).[68c] By treating oxazaborolidine **68** with a strong Brønsted acid or aluminum tribromide very strong Lewis acids **69** and **70** are formed which give excellent results for the investigated reactions. High *endo*/*exo*-selectivities and enantioselectivities over 90% were reached in most cases at low temperatures.




***Scheme 35***: Chiral oxazaborolidines as catalysts for asymmetric Diels-Alder reaction by Corey[68c].

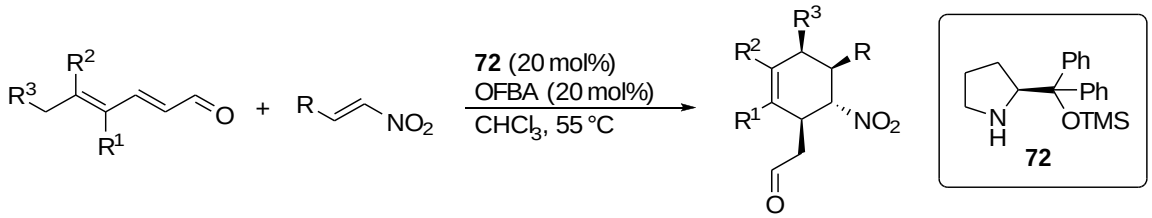
MacMillan published a protocol for enantioselective Diels-Alder reactions using amine **71** as orgonacatalyst.[69a] The amine reacts with the carbonyl group of the dienophile and forms a chiral

iminium ion which then reacts with the diene. After hydrolysis the product is obtained and the catalyst released (*Scheme 36*).




***Scheme 36***: Mechanism of the organocatalyzed Diels-Alder reaction by MacMillan.[69a]

Another example for a method employing organocatalysts was developed by the group of Chen.[69f] They used the Jørgensen-Hayashi catalyst (**72**) in combination with o-fluorobenzoic (OFBA) acid as an additive to react several nitroalkenes with various 2,4-dienals to obtain multiply-substituted cyclohexenes with high diastereo- and enantioselectivities (*Scheme 37*). During the reaction, a trienamine is formed in the first step which attacks the nitroalkene to initiate the formation of the cyclohexene. Furthermore, they observed an unexpected exo-selectivity which they explain by an electrostatic repulsion between the nitro group and the π-electrons of the enamine.

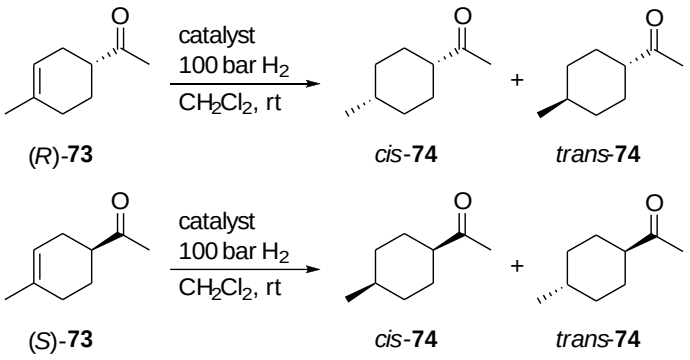



***Scheme 37***: Enantioselective Diels-Alder reaction by Chen.[69f]

## 3.4 Previous results

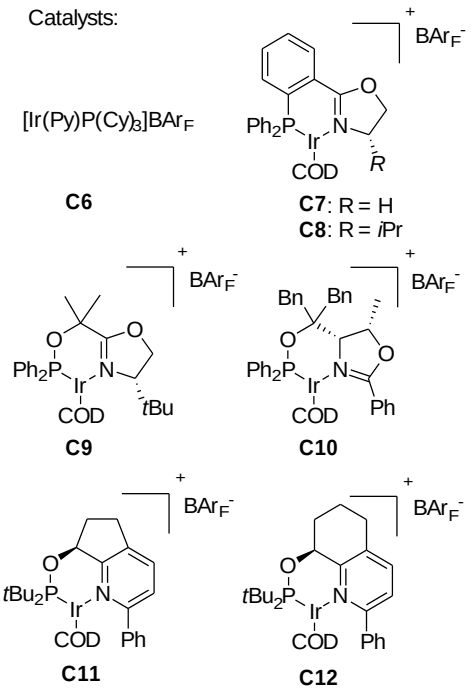
The project was started by Jaroslav Padevet who presented first results in his dissertation.[70] He began his investigations with an optimization of the hydrogenation of the (*R*)- and (*S*)-enantiomer of limonene derived ketone **73** *(Table 4*). The substrate was obtained in a three-step synthesis with 30% yield starting from commercially available limonene. It was chosen because of the directing effect of coordinating groups, as described by Crabtree which induces reduction at the side of the keto group.[71] The goal was to find a catalytic system which enables reversal of the diastereoselectivity obtained by substrate control.

***Table 4***: Catalyst screening for the diastereoselective hydrogenation of model substrate **73**.[70]




| Catalyst | Conv. of (*R*)-**73** (%) | **74** (*cis*/*trans*) | Conv. of (*S*)-**73** (%) | **74** (*cis*/*trans*) |
|---|---|---|---|---|
| **C6** | >99 | 0.5:99.5 | 97 | 0.6:99.4 |
| **C7** | 95 | 1:9.7 | 94 | 1:4.6 |
| **C8**[a)] | 76 | 1:23.4 | 14 | 1:3.8 |
| **C9** | 5 | 1:4.7 | 68 | 4.9:1 |
| **C10** | 51 | 1:16.2 | >99 | 2.8:1 |
| **C11** | >99 | 7.5:1 | >99 | 1:9.1 |
| **C12**[a)] | >99 | 2.6:1 | >99 | 1:4.5 |

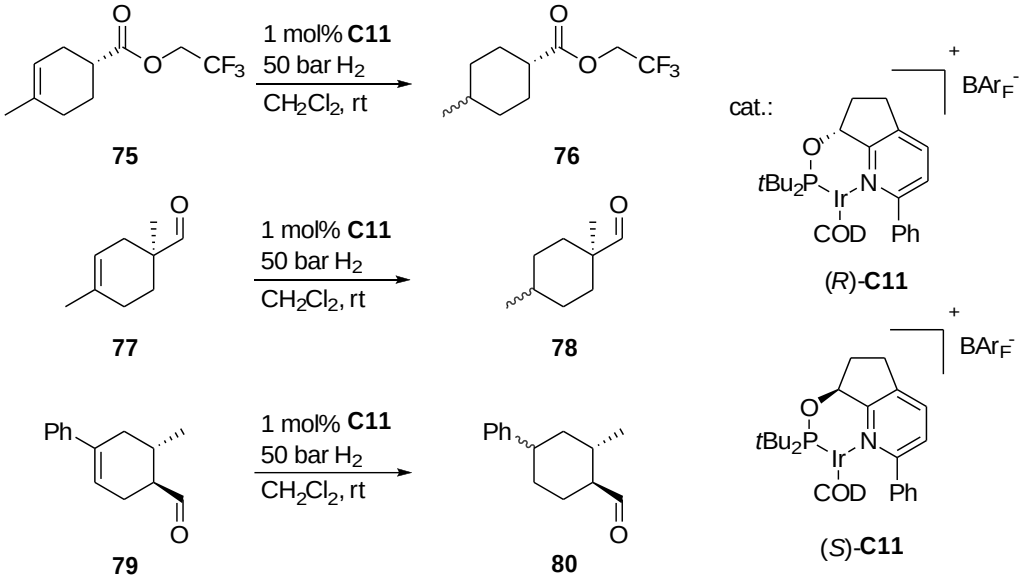
Standard conditions: 1 mol% catalyst, 0.4 M substrate conc., overnight reaction time.
a) Reactions run with 3 mol% catalyst, 0.14 M substrate conc.




The hydrogenation of both enantiomers of cyclohexene **73** was investigated to determine the degree of substrate versus catalyst control. Using Crabtree's catalyst with $BAr_F$ as counterion (**C6**), perfect selectivity for the *trans*-product was observed in both cases (**C6**). The same major product was obtained with catalysts **C7** and **C8** but with lower selectivity. However, the diastereomeric ratios for the two enantiomers of the substrate differed between the reactions of the (*R*)- and (*S*)-substrate.

When using chiral iridium-PHOX catalysts **C9** and **C10**, the *cis*/*trans*-selectivity was reversed though conversion and/or *cis*/*trans*-ratio were only moderate. The best results were obtained for iridium catalysts with pyridine-phosphinite ligands **C11** and **C12**. For both catalysts full conversion was observed. Furthermore, the selectivity could be inverted from *cis* to *trans* depending on which enantiomer of the substrate was used which means that the outcome of the reaction is mainly catalyst-controlled. Catalyst **C11** with a five-membered carbocycle and two *tert*-butyl groups at the phosphorus atom gave the best results and was therefore used as catalyst of choice for further studies.Next, Jaroslav Padevet tested the scope investigating the asymmetric reduction of different substrates with similar structure (*Table 5*). Trifluoroethylester **75** and aldehyde **77** were synthesized following Corey's procedure,[68c] as well as phenyl substituted cyclohexene **79** using MacMillan's protocol.[68a] To see whether the stereoselectivity can be controlled by the catalyst both enantiomers of **C11** were tested in the asymmetric hydrogenation.

***Table 5***: Hydrogenation results for Diels-Alder products.[70]




| Entry | Hydrogenated product | Cat. (*R*)-**C11** | | Cat. (*S*)-**C11** | |
|---|---|---|---|---|---|
| | | Conversion (%) | *dr* | Conversion (%) | *dr* |
| 1 | **76** | full | 49:1 | full | 1:49 |
| 2 | **78** | full | 19:1 | 0 | n. d. |
| 3 | **80** | 10 | 8:1 | 10 | 1:24 |

Reaction conditions: 1 mol% catalyst, 50 bar $H_2$, 0.2 M substrate conc. in $CH_2Cl_2$, 16 h reaction time.

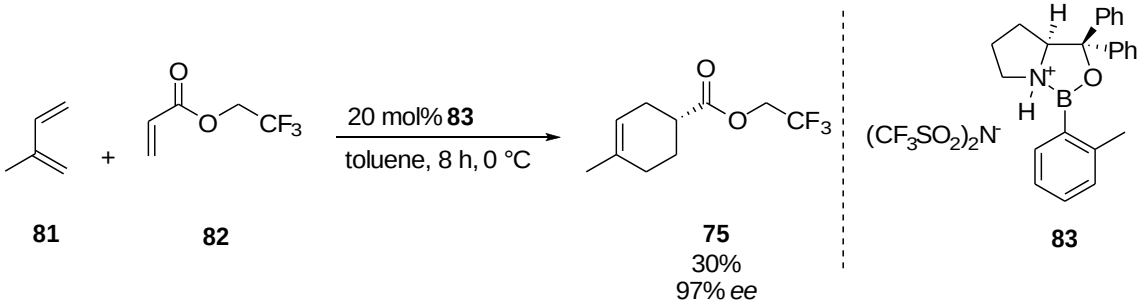
For ester **75** the reduced product **76** could be obtained with full conversion and excellent diastereoselectivity of 49:1 (entry 1). Furthermore, the selectivity was completely catalyst-

controlled and could be reversed by using the other enantiomer of the catalyst. When aldehyde **77** was tested, product formation was only observed for the (*R*)-enantiomer of the catalyst while the other enantiomer gave no reactivity at all (entry 2). Even at higher hydrogen pressure (90 bar) no reduction took place. The (*R*)-enantiomer led to complete conversion and a high diastereomeric ratio (19:1). Substrate **79** with a phenyl group at the double bond proved to be unreactive and only 10% of the reduced cyclohexane **80** could be detected for both catalysts (entry 3). The diastereomeric ratio was good for both enantiomers (8:1 and 1:24) and the relative conformation of the major product was reversed again.

One explanation for the bad results obtained for substrates **77** and **79** could be that the aldehyde group might interact with the iridium catalyst causing catalyst deactivation, e. g. by forming an iridium-acyl or -carbonyl complex. The goal of my studies was to confirm the results which were obtained by J. Padevet during his investigations and to further examine the influence of the aldehyde group on the asymmetric hydrogenation by transforming the aldehyde into other functional groups.

## 3.5 Confirmation of previous results

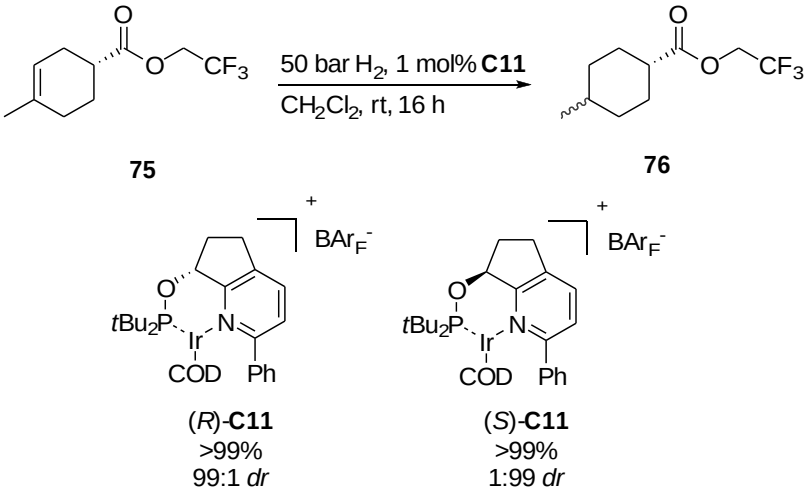
The reproducibility of the reduction of substrate **75** was examined first. Cyclohexene **75** was synthesized usng a procedure described by Corey (*Scheme 38*).[68c]




***Scheme 38***: Synthesis of substrate **75** using Corey's protocol.

Using 20 mol% of oxazaborolidine **83** the ester could be obtained with moderate yield and excellent enantiomeric ratio by reacting isoprene (**81**) with the α,β-unsaturated ester **82** at 0 °C.

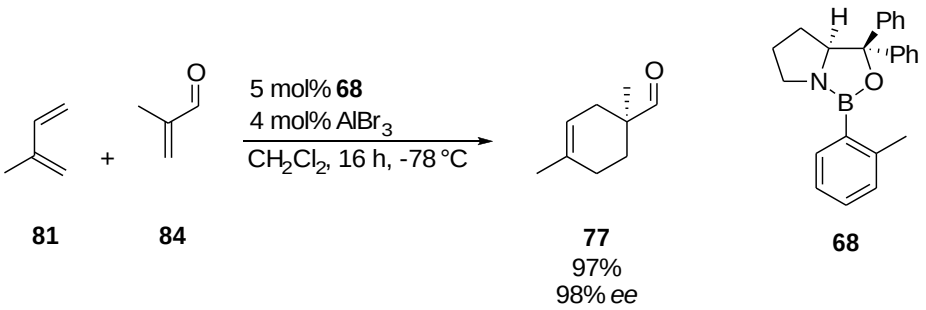
Next, the asymmetric hydrogenation was studied to see if the results of Jaroslav Padevet could be confirmed (*Scheme 39*).




***Scheme 39***: Asymmetric hydrogenation of substrate **75**.

To compare the results the same conditions as before were used. The hydrogenation was performed at 50 bar hydrogen pressure in methylene chloride at room temperature and a catalyst loading of 1 mol% was chosen. These conditions were used in all further hydrogenation studies if not otherwise mentioned. Full conversion and an excellent diastereomeric ratio could be obtained with both enantiomers of catalyst **C11**. The selectivity completely changed from one enantiomer to the other. The reactions were done by Romina Aliakbarkamrani during her Maturaarbeit in the group. The fact that Romina has no experience in synthetic chemistry shows that this method is very reliable and can be easily reproduced.

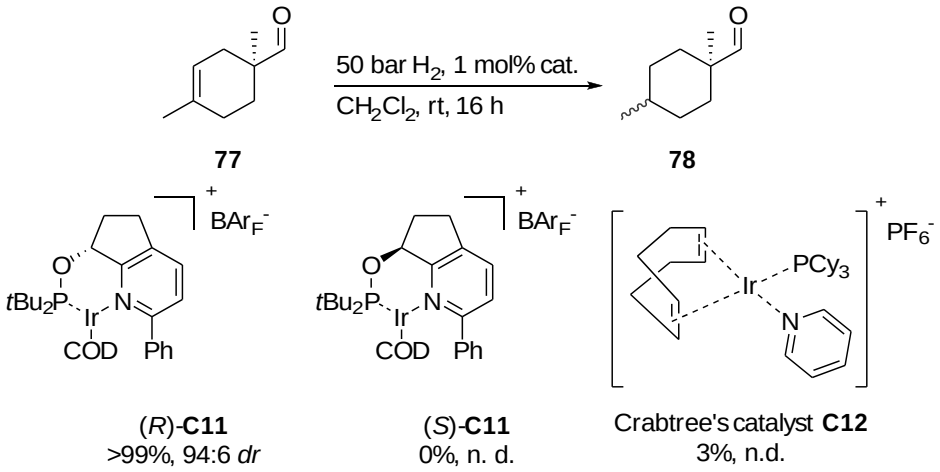
Next, the hydrogenation of aldehyde **77** was investigated. Again, Corey's procedure[68c] was applied to synthesize the substrate (*Scheme 40*).




***Scheme 40***: Synthesis of aldehyde **77** following Corey's procedure.

By mixing aluminum tribromide with the oxazaborolidine **68** the corresponding complex **70** was

obtained which catalyzed the Diels-Alder reaction between isoprene (**81**) and methacrolein (**84**) effectively to get the desired product in excellent yield with high enantiomeric excess. To reach high yields for this reaction it is very important to be careful when removing solvents since the product is very volatile. With the substrate in hand we tested the reproducibility of the previously obtained result that only the (*R*)-enantiomer of the catalyst is active in the asymmetric reduction. Furthermore, Crabtree's catalyst (**C12**) was also tested to see which influence the chirality of the substrate has on the outcome of the reaction (*Scheme 41*).



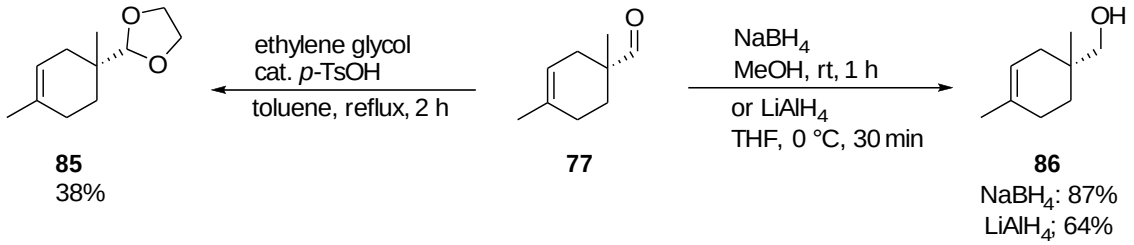

***Scheme 41***: Iridium-catalyzed hydrogenation of substarte **77**.

As observed before, the (*S*)-enantiomer of the catalyst showed no activity at all while the other enantiomer gave full conversion. The selectivity is 94:6 and almost identical with the previous report (95:5). Furthermore, achiral catalyst **C12** showed also almost no activity and only led to 3% product formation. It was surprising that the activity of the catalyst varies so much by changing from one catalyst enantiomer to the other and since substrate **79** also gave only 10% conversion for both enantiomers (*Table 5*) we wondered if these problems were due to the aldehyde group. Hence, we decided to synthesize some derivatives of aldehyde **77** to see if these substrates are more easily reduced by our iridium catalysts. Furthermore, we also wanted to investigate the hydrogenation of other cyclohexenes with different substitution pattern.

### 3.6 Substrate synthesis

### 3.6.1 *Derivatisation of the aldehyde group*

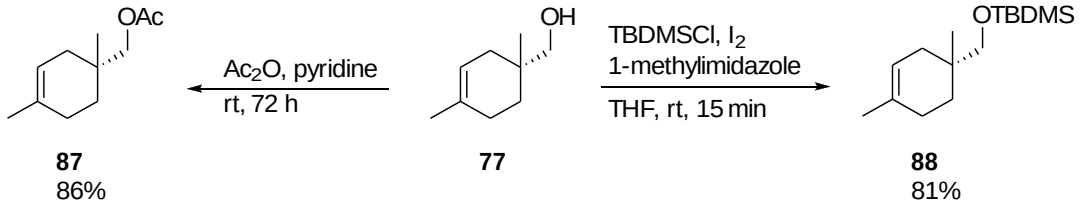
Acetal (**85**) and alcohol **86** were considered as a potential substrates. Both derivatives can be obtained in one step from the aldehyde (*Scheme 42*).




***Scheme 42***: Synthesis of acetal **85** and alchohol **86**.

The acetal was synthesized by reacting the aldehyde with an excess of ethylene glycol (2 eq.) under acidic conditions. The yield was only moderate (38%) but enough product was obtained so that no further investigations in the optimization of the reaction were done. Reduction of the aldehyde was first performed with sodium borohydride and full conversion was observed. However, after column chromatography the maximum yield obtained was around 50%. Since Williard reported the reduction of the same compound with lithium aluminum hydride with 94% yield[72] we also tested his protocol. Unfortunately, the yield was still only 64%. However, in further experiments the yield in the reduction with sodium borohydride could be improved to 87%.

As a hydroxy group is also a strong coordinating group it was considered to protect the alcohol in different ways and to test these compounds in the asymmetric hydrogenation. Therefore, the corresponding acetate (**87**) and a silyl ether (**88**) were synthesized (*Scheme 43*).



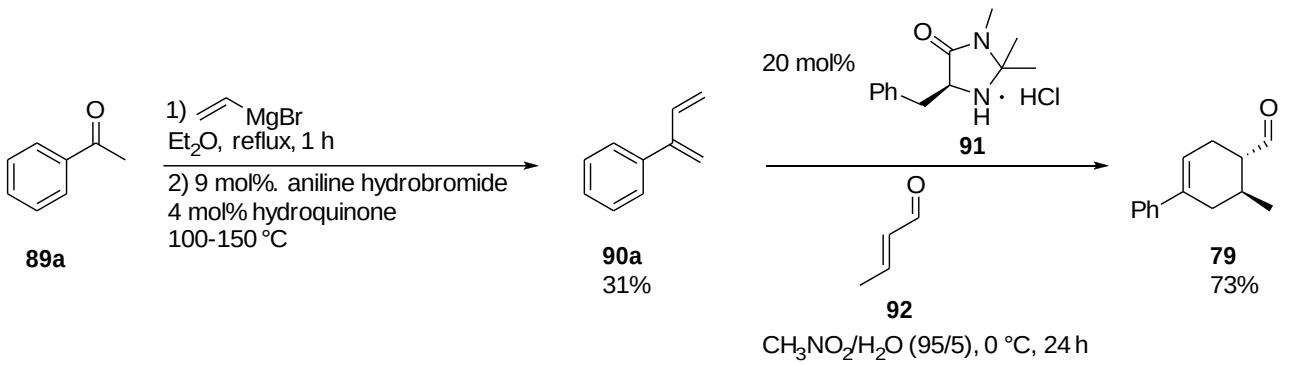

***Scheme 43***: Synthesis of acetate **87** and silyl ether **88**.

The acetate was formed using a protocol from Vollhardt[73] by treating the alcohol with acetic anhydride in pyridine to get the product in 86% yield. The TBDMS-ether **88** was synthesized

following a procedure described by Bartoszewicz.[74] The alcohol was treated with TBDMS-chloride, iodine and 1-methylimidazole to give the silyl ether in 81% yield. The iodine accelerates the reaction and is believed to act as a scavenger for the chloride ion which is formed after reaction of TBDMS-chloride with imidazole. By removing the chloride ion from the equilibrium through formation of $I_2Cl^-$ it speeds up product formation.

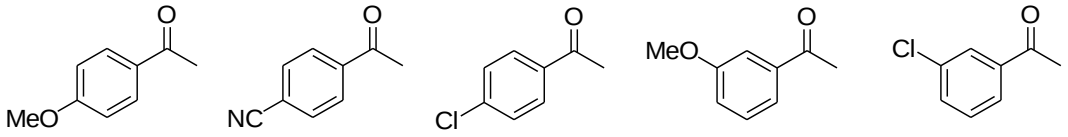
### 3.6.2 *Introduction of substituents on the phenyl ring*

Since the hydrogenation of aldehyde **79** did not give satisfying results (10% conv., see *Table 2*), π-donor and -acceptor groups were introduced to study their influence on the reactivity. The substrates were synthesized in the same way as the parent compound (*Scheme 44*).[70]




***Scheme 44***: Synthesis of substrate **79**.[70]

J. Padevet obtained 2-phenyl-1,4-butadiene (**90a**) following a synthesis of Marvel and Woolford.[75] Acetophenone (**89a**) was treated with vinylmagnesium bromide in a Grignard-reaction to form a tertiary alcohol which was dehydrated in a second step by slowly distilling it under acidic conditions affording the diene in moderate yield (31%). The Diels-Alder reaction was performed using MacMillan's imidazolidinone catalyst **91**. After reacting the diene with an excess of *trans*-crotonaldehyde (**92**), cyclohexene **79** was obtained in 73% yield as a 4:1 mixture of regioisomers.

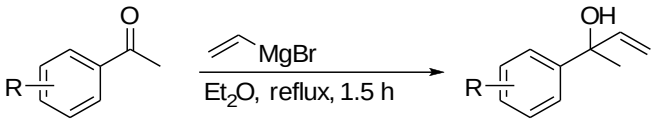



**89b** **89c** **89d** **89e** **89f**

***Figure 12***: Structure of acetophenones used for the synthesis of the corresponding dienes.

From differently substituted acetophenones **89b-f** the corresponding butadienes should be synthesized following the same procedure (*Figure 12*).

***Table 6***: Synthesis of tertiary alcohols.

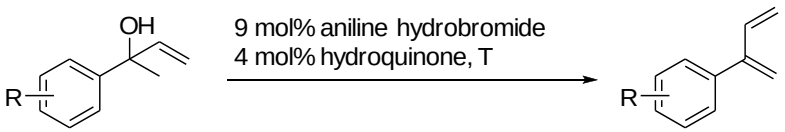



**89x** **93x**

| Entry | Product | R | Yield (%) |
|---|---|---|---|
| 1 | **93b** | *p*-OMe | 92 |
| 2 | **93c** | *p*-CN | 63 |
| 3 | **93d** | *p*-Cl | 97 |
| 4 | **93e** | *m*-OMe | 82 |
| 5 | **93f** | *m*-Cl | 54 |

All the desired alcohols could be isolated with moderate to excellent yields. With a π-acceptor group in *para* position the products were obtained in almost quantitative yield (entries 1 and 3). For the *para*-cyano derivative the yield was only 63% (entry 2). For the *meta* substituted acetophenones the yield was lower compared to the corresponding *para* substituted compounds (entries 4 and 5).

***Table 7***: Synthesis of dienes by dehydration.

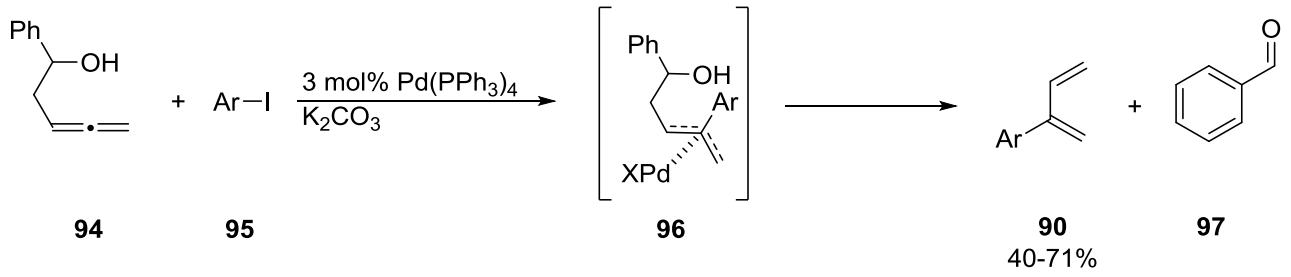



**93x** **90x**

| Entry | Product | R | Temperature (°C) | Yield (%) |
|---|---|---|---|---|
| 1 | **90b** | *p*-OMe | 80 | 38 |
| 2 | **90c** | *p*-CN | 150 | 0 |
| 3 | **90d** | *p*-Cl | 120 | 13 |
| 4 | **90e** | *m*-OMe | 130 | 14 |
| 5 | **90f** | *m*-Cl | 140 | 0 |

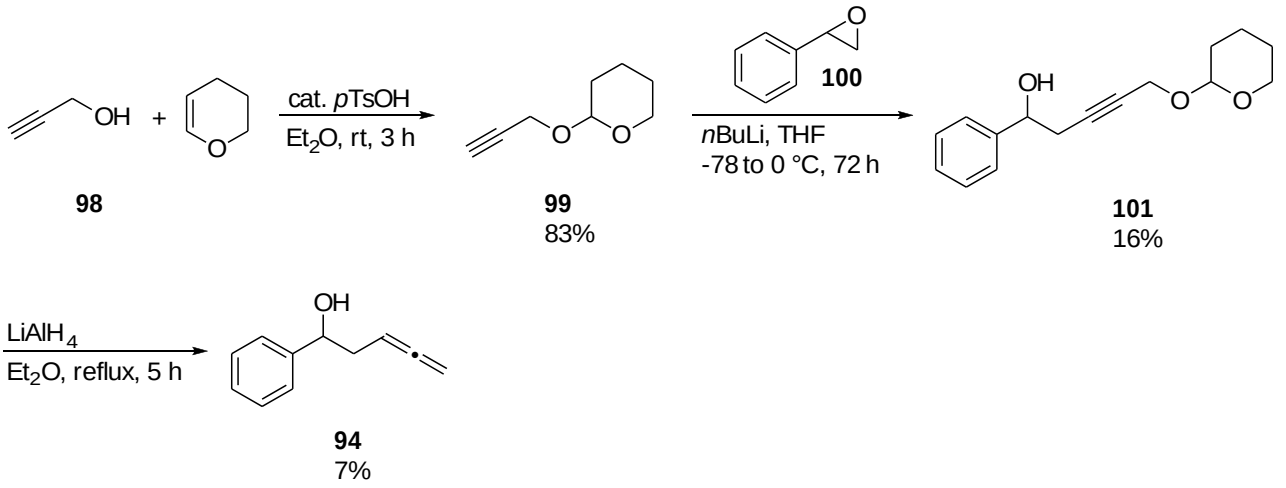
Next, the dehydration of alcohols **93b-f** was investigated (*Table 7*). Elimination was induced by heating the alcohol with a catalytic amount of aniline hydrobromide and hydroquinone while continuously distilling the product. For the *para*-methoxy substituted alcohol **93b** the yield was almost the same as for the unsubstituted substrate (entry 1). However, the reaction could be performed at 80 °C while 150 °C were necessary in the other case. In contrast, nitrile **93c** did not react even at elevated temperatures (entry 2). Chloride **93d** was converted to the diene in an unsatisfying yield of only 13% after heating to 120 °C (entry 3). A similar result was obtained for *meta*-substituted anisole derivative **93e** (entry 4). *Meta*-substituted chloride **93f** proved to be unreactive like the nitrile. Even at high temperature no product formation was observed (entry 5). In general, the same trend as for the Grignard reaction was observed. Electron-rich aryl groups gave better results than electron-poor aryl groups and *para*-substituted derivatives were more reactive than *meta*-substituted derivatives. The lack of reactivity of the *para*-cyano derivative is consistent with an E1-elimination via a carbocation, which is destabilized by an electron-withdrawing group at in the phenyl ring.

Because only one diene could be obtained in satisfying yield, other methods to synthesize 2-phenylbutadienes were sought. Among several protocols, a procedure by Oh[76] was chosen because the starting allene **94** can be coupled with various commercially available iodoarenes **95** giving access to several butadienes (*Scheme 45*).




***Scheme 45***: Formation of butadienes by Pd-catalyzed coupling of allene **94** with iodoarenes by Oh.

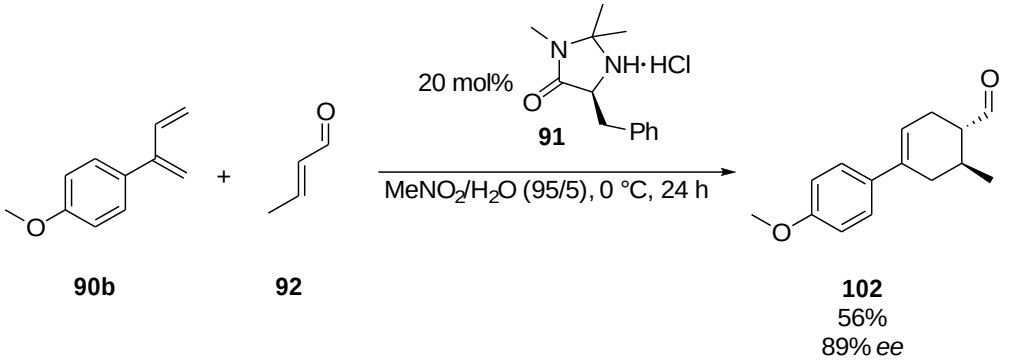
In the first step, the palladium catalyst reacts with allene **94** to generate allylpalladium intermediate **96**. After reductive C-C bond cleavage, butadiene **90** and benzaldehyde (**97**) are formed. The synthesis of allene **94** is literature known[77] and can be performed in three steps starting from commercially available propargylic alcohol (**98**) (*Scheme 46*).




***Scheme 46***: Three step synthesis of allene **94**.

In the first step, propargylic alcohol was protected as its corresponding THP-ether **99** under acidic conditions. The reaction worked nicely and the alkyne was isolated in 83% yield. Next, the alkyne was deprotonated to react with styrene oxide (**100**) at the sterically less hindered position to give alcohol **101** in only 16% yield. In the literature, 85% yield was reported, but even after several trials this could not be reached. In the last step, the alkyne was treated with lithium aluminum hydride to eliminate tetrahydropyranol in a $S_N2'$-reaction and to form allene **94** in low yield (7%). Again, literature yield of about 50% could not be achieved. Because of synthetic difficulties it was decided to not further investigate the synthesis of 2-phenylbutadienes.

Next, butadiene **90b**, which was the only derivative that was isolated in a reasonable amount, was used for the Diels-Alder reaction (*Scheme 47*).




***Scheme 47***: Synthesis of cyclohexene **102** by imidazolidinone-catalyzed Diels-Alder reaction.

Cyclohexene **102** was synthesized using MacMillan's imidazolidinone **26** as chiral catalyst for the reaction between butadiene **90b** and *trans*-crotonaldehyde (**92**). The product was obtained in moderate yield (56%) and good enantiomeric excess (89%).

### 3.6.3 *Synthesis of other substrates*

After a literature search three additiona potentially interesting substrates were considered for hydrogenation studies (*Figure 13*).

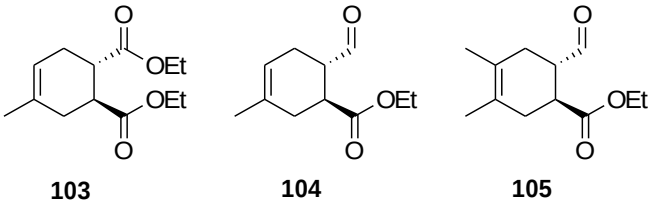
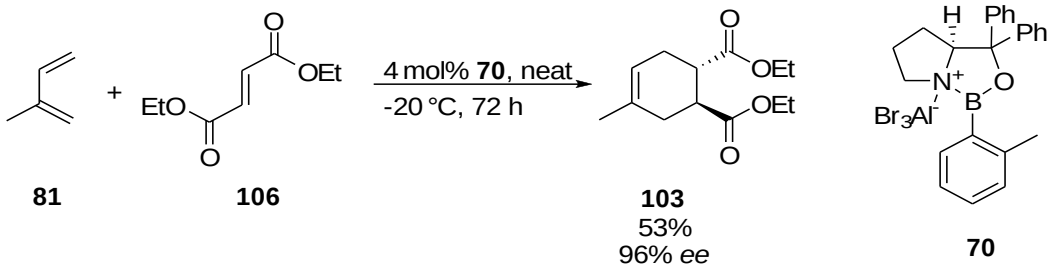



***Figure 13***: Structure of other substrates for the diastereoselective hydrogenation.

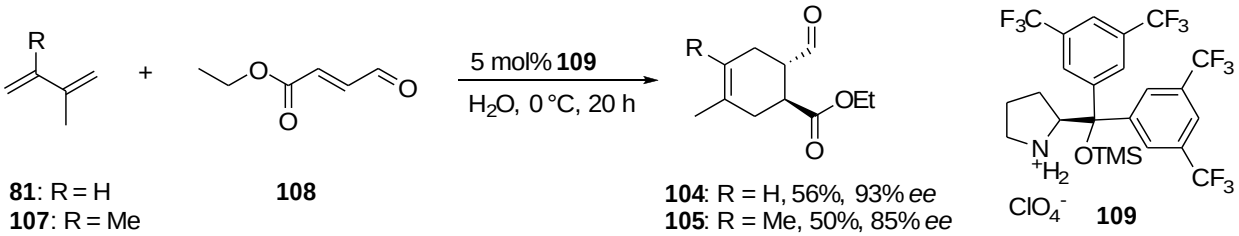
Substrates **103** and **104** contain a trisubstituted C=C bond, while compound **105** has two methyl groups at the double bond which should make it a challenging substrate for the hydrogenation, as a tetrasubstituted double bonds are not very reactive and hard to reduce.
Diethylester **103** was synthesized following Corey's protocol (*Scheme 48*).[68c]




***Scheme 48***: Synthesis of substrate **103**.

An excess of isoprene (**81**) was used and reacted with dienophile **106** without any solvent over three days to form the desired product in moderate yield and excellent enantioselectivity. Activated oxazaborolidine **70** was used to catalyze the reaction in an enantioselective fashion.

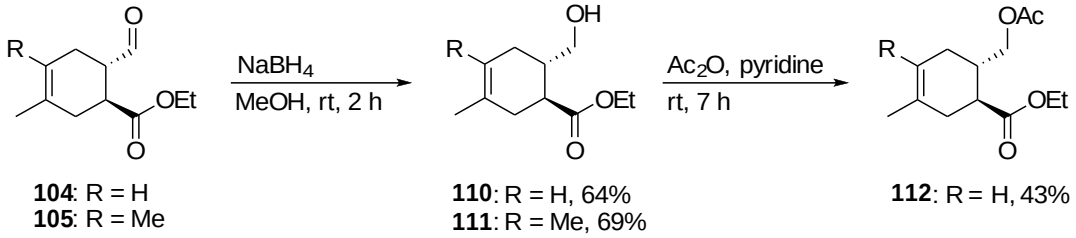
The synthesis of cyclohexenes **104** and **105** was performed following Hayashi's procedure[69c] using an organocatalyst (*Scheme 49*).




***Scheme 49***: Synthesis of Diels-Alder products **104** and **105**.

The products were obtained after the reaction of enal **108** with three equivalents of either isoprene (**81**) or 2,3-dimethylbutadiene (**107**) in water at 0 °C. The catalyst for this reaction was the ammonium perchlorate salt of Jørgensen catalyst **109**. Trisubstituted alkene **104** could be isolated with moderate yield (56%) and high enantiomeric excess of 93%. For the tetrasubstituted alkene **105**, both the yield (50%) and enantioselectivity (85%) were a bit lower. While the yields for cyclohexenes **104** and **105** were lower than the literature values (93% and 89%, respectively) the selectivities matched the reported data.

Since the aldehyde group was considered to be responsible that reduction was observed only for one of the catalyst enantiomers in the asymmetric hydrogenation of compound **77** (see *Scheme 41*), we decided to synthesize and test the alcohol and acetate derivatives of substrates **104** and **105** to see if the same trend can be observed (*Scheme 50*).



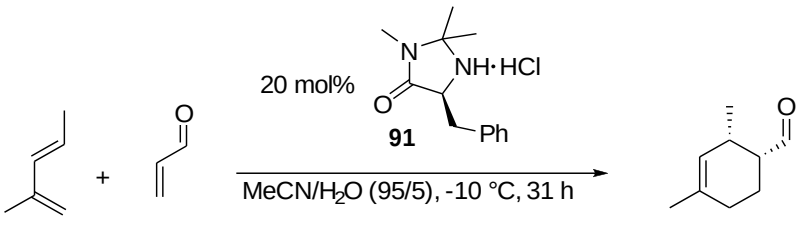

**104**: R = H
**105**: R = Me

**110**: R = H, 64%
**111**: R = Me, 69%

**112**: R = H, 43%

***Scheme 50***: Derivatisation of cyclohexenes.

The reduction of the aldehyde was achieved using sodium borohydride. For both substrates, full reduction could be observed but the alcohols could only be isolated in 64% yield in case of the trisubstituted alkene **110** and in 69% yield in case of the tetrasubstituted alkene **111**. The same problem was encountered previously in the reduction of aldehyde **77**. The acetate was prepared by treating the alcohol with acetic anhydride in pyridine. Cyclohexene **112** with only one methyl group was thereby obtained in 43% yield. The acetate of the tetrasubstituted alkene was not synthesized.
Another interesting class of substrates are cyclohexenes with a substituent next to the double bond, such as compound **115** synthesized by MacMillan using his enantioselective Diels-Alder approach (*Scheme 51*).[69a]

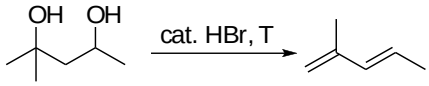



**113** **114**

**115**
75%
90% *ee*

***Scheme 51***: Synthesis of substrate **115** by MacMillan.[69a]

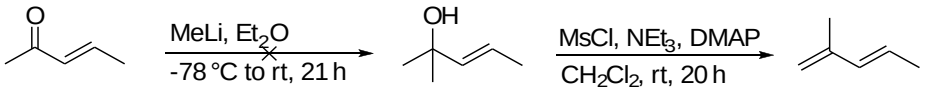
The Diels-Alder reaction between 2-methyl-1,3-pentadiene (**113**) and acrolein (**114**) led to the formation of cyclohexene **115** with a methyl group next to the double bond. MacMillan reported the product **115** in 75% yield and 90% *ee* and an *endo*/*exo* ratio of 5:1 in favor of the *endo*-product. The diene **113** is not commercially available and reported syntheses were not promising.[78-82] Either they use relatively complicated starting materials or they produce mixtures of isomers or polymerize. We decided to try a method described by Bacon and Farmer[79] which consists of the dehydration of hexylene glycol (**116**) under acidic conditions (*Scheme 52*).




**116** **113**

***Scheme 52***: Synthesis of the diene by double dehydration of hexylene glycol.

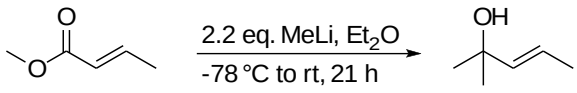
The glycol was mixed with 1% vol. of hydrobromic acid and the mixture was continuously distilled under heating. Heating to 80 °C was necessary until a reaction took place which could be seen by the fact that the product started to boil. To distill off the formed product the temperature had to be increased to 120 °C. Unfortunately, the desired product could not be isolated but only a mixture of unidentified products was obtained. It probably contained polymers of the diene and therefore, the same reaction was tried again under vacuum to perform the distillation at lower temperature which should reduce the formation of polymers. But even when the temperature was kept below 85 °C pentadiene **113** could not be isolated as a pure compound but only as a minor isomer together with other olefins. Since the purification by distillation did not work and a separation by column chromatography was not possible, an alternative synthesis of diene **113** was sought. We thought that it might be easier to start with an alcohol where one double bond is already formed and only one hydroxy group has to be eliminated. This alcohol should be accessible from commercially available ketone **117** reacting with methyl lithium. The elimination of this hydroxy group could further be simplified by transforming it to a better leaving group like a mesylate for example (*Scheme 53*).




**117** **118** **113**

***Scheme 53***: Proposed alternative synthesis of pentadiene **113**.

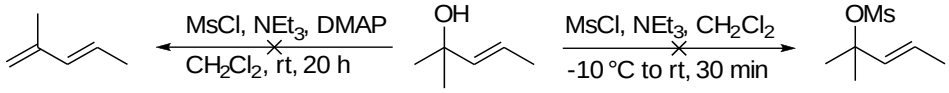
In the first step, allylic alcohol **118** should be formed by treating 3-penten-2-one (**117**) with methyl lithium. However, the reaction did not work and the alcohol could not be isolated. Therefore, we followed a procedure from the literature[83] where they reacted methyl ester **119** with two equivalents of methyl lithium (*Scheme 54*).




**119** **118** 60%

***Scheme 54***: Synthesis of allylic alcohol **118**.

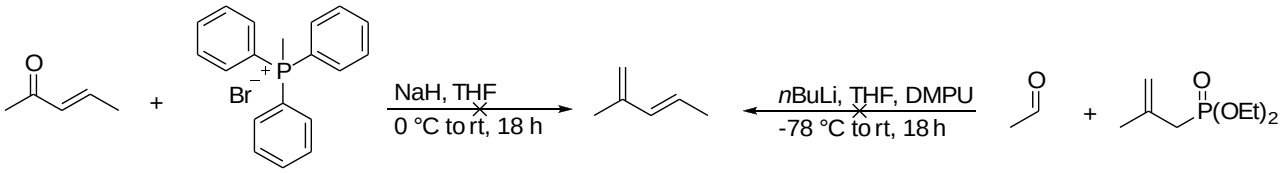
We were pleased to see that we were able to obtain the alcohol in 60% yield. Next, we wanted to transform the alcohol into its corresponding mesylate **120** to ease the elimination to give pentadiene **113** (*Scheme 55*).




**113** **118** **120**

***Scheme 55***: Transformation of the alcohol to the mesylate.

A one pot procedure consisting of mesylation followed by immediate elimination of the mesylate to form the diene was tried but only an unidentifiable mixture was obtained. Hence, it was attempted to isolate mesylate **120** first by treating the alcohol with methanesulfonyl chloride under basic conditions but no product formation was observed. Since the synthesis of the diene was not successful by this method another strategy based on a Wittig reaction or a Horner-Wadsworth-Emmons (HWE) reaction was explored (*Scheme 56*).



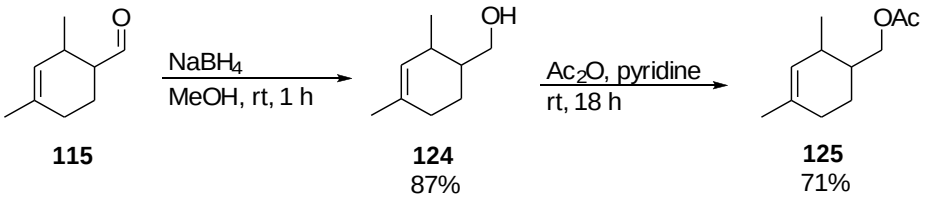

**117** **121** **113** **122** **123**

***Scheme 56***: Attempted synthesis of the diene by a Wittig or a HWE-reaction.

Since there are two double bonds in the pentadiene there are also two possibilities where the new double bond may be formed. First, we tried to form the terminal C=C bond by a Wittig reaction because *E*/*Z*-selectivity is not an issue there. Unfortunately, the reaction between ketone **117** and phosphonium bromide **121** did not lead to any product formation. Next, a method used for the synthesis of several terminal 1,3-dienes (but not **113**) by a reaction between phosphonate **123** and

different aldehydes reported by Wang and West was tried.[84] In the publication they reported slightly better yields with HMPA as additive instead of DMPU but for reasons of health the less toxic DMPU was used. When we performed the reaction between acetaldehyde (**122**) and phosphonate **123** applying West's conditions we were disappointed to see that again no product formation could be observed.

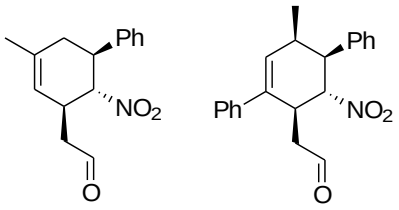
Because the racemic Diels-Alder product **115** is commercially available as mixture of the diastereomers we tried to separate the components by semi preparative HPLC on a chiral stationary phase. Unfortunately, a chromatographic separation was not possible with any of our chiral columns. Because it is often difficult to separate aldehydes by HPLC and we were also interested in the corresponding alcohol and acetate as substrates, we decided to synthesize these derivatives to see if we could achieve separation (*Scheme 57*).




***Scheme 57***: Derivatisation of cyclohexene **115**.

Aldehyde **115** was reduced with sodium borohydride to form alcohol **124** in good yield of 87% followed by acetylation with acetic anhydride and pyridine to afford acetate **125** with 71% yield. Next, it was tried to separate the isomers by semi preparative HPLC. Unfortunately, for both derivatives only a partial separation could be achieved which was not sufficient for our hydrogenation experiments.

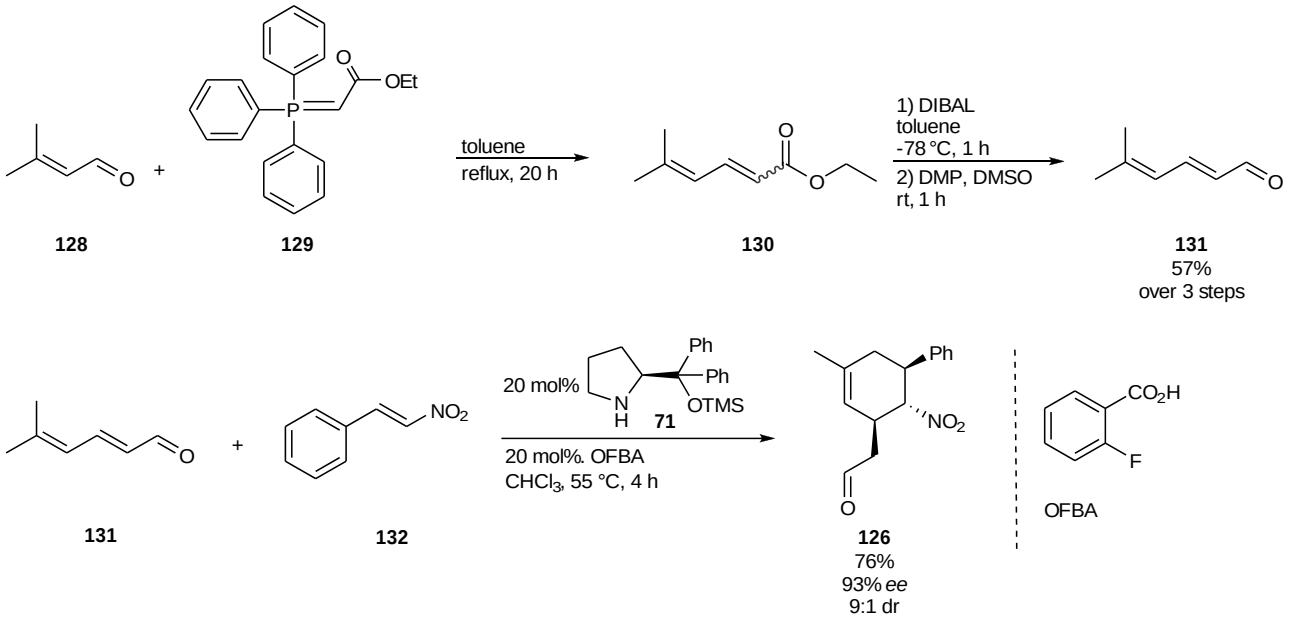
Because we were not able to obtain one of the isomers of cyclohexenes **124** or **125** in enantiomerically pure form we decided to prepare other Diels-Alder products for our studies. As previously mentioned, Chen described the synthesis of various nitrocyclohexenes using Jørgensen-Hayashi catalyst with an acetaldehyde moiety next to the double bond (*Scheme 36*). Because of this substitution pattern and the nitro group which is also a synthetically valuable functional group we chose olefin **126** and **127** as substrates for the diastereoselective hydrogenation (*Figure 14*).




**126** **127**

***Figure 14***: Structure of nitrocyclohexenes synthesized by Chen's procedure.

Cyclic olefin **126** with a methyl group at the double bond was synthesized in a four step procedure starting from 3-methylcrotonaldehyde **128** (*Scheme 58*) following Chen's protocol.[69f]

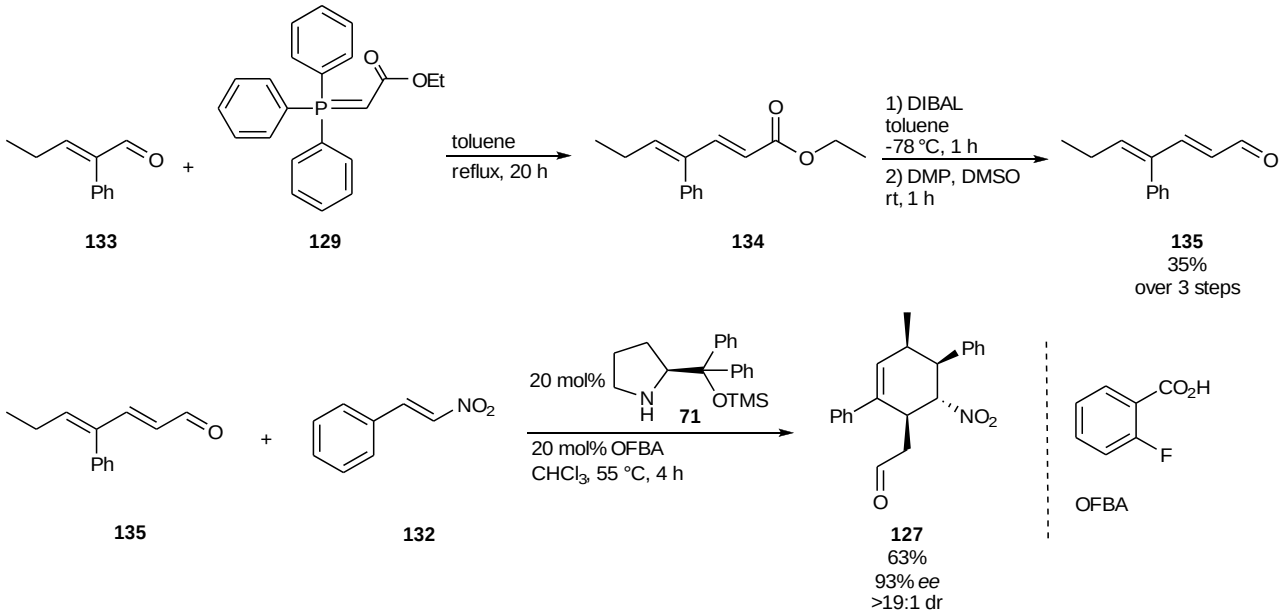



***Scheme 58***: Synthesis of nitrocyclohexene **126**.

In the first step, the aldehyde reacted with phosphonium ylide **129** to give α,β,γ,δ-unsaturated ester **130** as a 6:1 mixture of the *E*,*E*- and *E*,*Z*-product with the *E*,*E*-isomer as the main product. The isomers were not separated and used together in the next step. The ester was reduced to its corresponding alcohol using DIBAL and then oxidized with Dess-Martin periodinane to give dienal **131** in 57% yield over three steps. Interestingly, after the oxidation the *E*,*Z*-isomer was not observed anymore and only the all *trans*-product was formed which means that the double bond isomerized during the reaction. The dienal is quite unstable and decomposes if not stored in the freezer. In the freezer it is stable for several weeks. In the next step cyclohexene **126** is formed in a Diels-Alder reaction between an excess of the dienal (2 eq.) and *trans*-β-nitrostyrene. Organocatalyst **71** and *o*-

flurobenzoic acid (OFBA) as an additive deliver the desired product in 76% yield with excellent enantio- and diastereoselectivity.

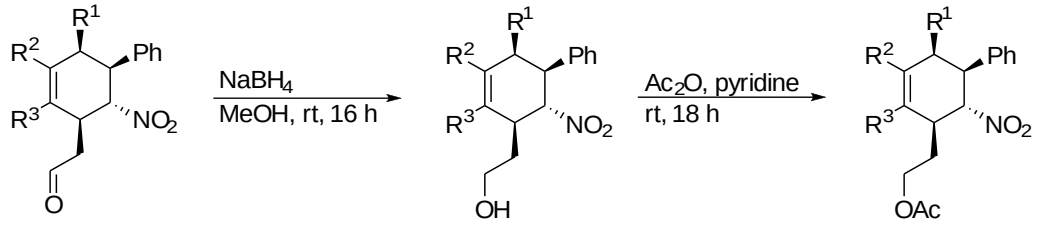
The second nitrocyclohexene **127** was obtained following the same strategy starting from (*E*)-2-phenylpent-2-enal (**133**) (*Scheme 59*).




***Scheme 59***: Synthesis of nitrocyclohexene **127**.

Unsaturated ester **134** is formed in a Wittig reaction between the phosphonium ylide **129** and enal **133**. This time no formation of the *Z*-isomer was observed and only the all *trans*-product was obtained. Next, ester **134** was reduced to the alcohol and oxidized to the aldehyde under the same conditions as before to give dienal **135** in 35% yield over three steps. In the last step, the diene reacted with nitroolefin **132** applying the same conditions as before to give the desired product in a good yield of 63% and excellent selectivity of 93% *ee* and over 19:1 diastereomeric ratio.

To see if the observations made in the hydrogenation of aldehyde **77** and its derivatives also apply to this substrate class, we synthesized the corresponding alcohol and acetate derivatives of nitrocyclohexenes **126** and **127** as well (*Scheme 60*).




**126**: $R^1 = R^3 = H$, $R^2 = Me$
**127**: $R^1 = Me$, $R^2 = H$, $R^3 = Ph$
**136**: $R^1 = R^3 = H$, $R^2 = Me$, 88%
**137**: $R^1 = Me$, $R^2 = H$, $R^3 = Ph$, 89%
**138**: $R^1 = R^3 = H$, $R^2 = Me$, 43%
**139**: $R^1 = Me$, $R^2 = H$, $R^3 = Ph$, 79%

***Scheme 60***: Synthesis of derivatives of nitrocyclohexene.

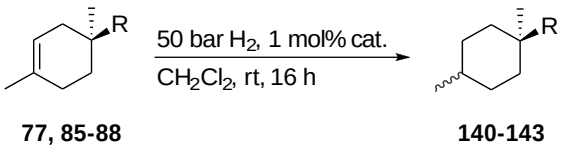
Both aldehydes **126** and **127** could be reduced with excellent yield using sodium borohydride to the corresponding alcohols **136** and **137,** respectively. After treating these alcohols with acetic anhydride in pyridine overnight the acetates were formed. While cyclohexene **138** with a methyl group at the double bond could only be isolated with a moderate yield of 43%, cyclohexene **139** with a phenyl group was obtained in good yield (79%).

## 3.7 Diastereoselective hydrogenation of chiral cyclohexenes

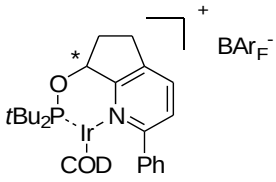
### 3.7.1 *Hydrogenation of derivatives of previous substrates*

With the chiral Diels-Alder products in hand we started to investigate the diastereoselective reduction of these cyclohexenes. All hydrogenations were performed under the same conditions as for the substrates mentioned above. For each substrate, both enantiomers of catalyst **C11** were tested as well as an achiral catalyst. First, the asymmetric reduction of derivatives **65-68** of aldehyde **77** was investigated (*Table 8*).

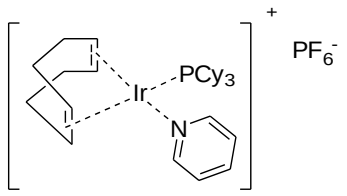
***Table 8***: Diastereoselective reductions of derivatives of aldehyde **77**.




**77, 85-88** **140-143**




**C11**




**C12**

| Entry | R | Product | (*R*)-**C11** | | (*S*)-**C11** | | **C12** | |
|---|---|---|---|---|---|---|---|---|
| | | | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] |
| 1 |  | **140** | >99 | 60:40 | >99 | 27:73 | 38 | 15:85 |
| 2 | $CH_2OH$ | **141** | >99 | 64:36 | >99 | 3:97 | 75 | 3:97 |
| 3 | $CH_2OAc$ | **142** | >99 | 92:8 | >99 | 11:89 | 9 | 36:64 |
| 4 | $CH_2OTBDMS$ | **143** | 58 | 75:25 | 60 | 7:93 | 6 | 12:88 |

a) Determined by GCMS.

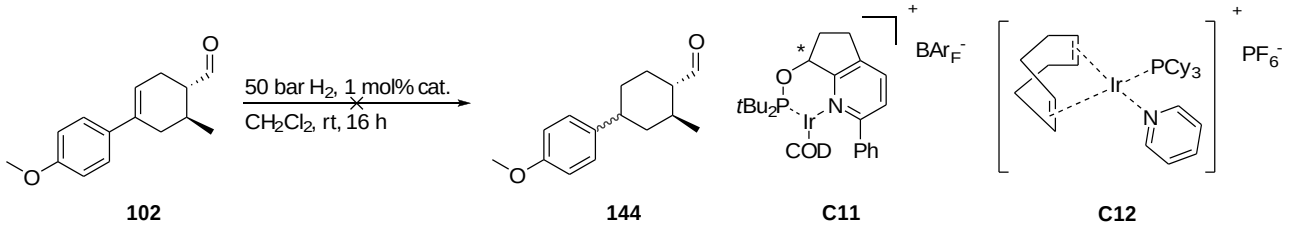
In contrast to aldehyde **77**, all its derivatives could be reduced with both the (*R*)- and (*S*)-enantiomer of catalyst **C11** with the same conversion. While the acetal, the alcohol and the acetate gave full conversions (entries 1-3), the silyl ether only gave 60% conversion. Achiral catalyst **C12** showed generally lower activity. Furthermore, the diastereomeric ratio was reversed by changing from one catalyst enantiomer to the other. For acetal **140** the best diastereomeric ratio was obtained with Crabtree's catalyst but conversion was only 38%. (*S*)-**C11** showed a selectivity of 1:3 while (*R*)-**C11** gave a 3:2 mixture (entry 1). These results imply that the diastereoselective outcome of the reaction is mainly substrate-controlled and that for (*R*)-**C11** there is a mismatched case. For alcohol **141**, only low selectivity could be obtained with the (*R*)-**C11** (2:1). On the other hand, with (*S*)-**C11** and catalyst **C12** an excellent diastereomeric ratio of 3:97 was observed. However, Crabtree's catalyst led only to 75% product formation. From these experimental results, it can be concluded that the reduction is mainly substrate-controlled, this time even stronger than in case of the acetal.

We were pleased to see that in the hydrogenation of acetate **142** the results for both enantiomers of **C11** were almost identical. With both catalysts we obtained full conversion and a selectivity of about 9:1. With the achiral catalyst we observed only 9% product formation and a diastereomeric ratio of 36:64. This implies that this time the diastereoselectivity is mainly catalyst-controlled and,

consequently, almost no selectivity is obtained with the achiral catalyst **C12**. Silyl ether **88** was harder to reduce and the corresponding cyclohexane **143** could only be hydrogenated with about 60% conversion using the (*R*)- or (*S*)-enantiomer of **C11** and 6% conversion with catalyst **C12**. The lowest selectivity was observed with the (*R*)-catalyst (3:1). The other two catalysts gave excellent diastereomeric ratios with the best result for the (*S*)-catalyst (7:93). Notably, all products have a mirror plane and therefore are achiral.

The best results were obtained for the alcohol and for the acetate (entry 2 and 3). The selectivities in the hydrogenation of the acetal and the silyl ether derivatives were not very promising and, therefore, only the alcohol and acetate derivatives were tested in further investigations of other substrates.

Next, the hydrogenation of aryl-substituted compound **102** was investigated. Unfortunately, no reduction to cyclohexane **144** could be observed for all catalysts under these conditions (*Scheme 61*).



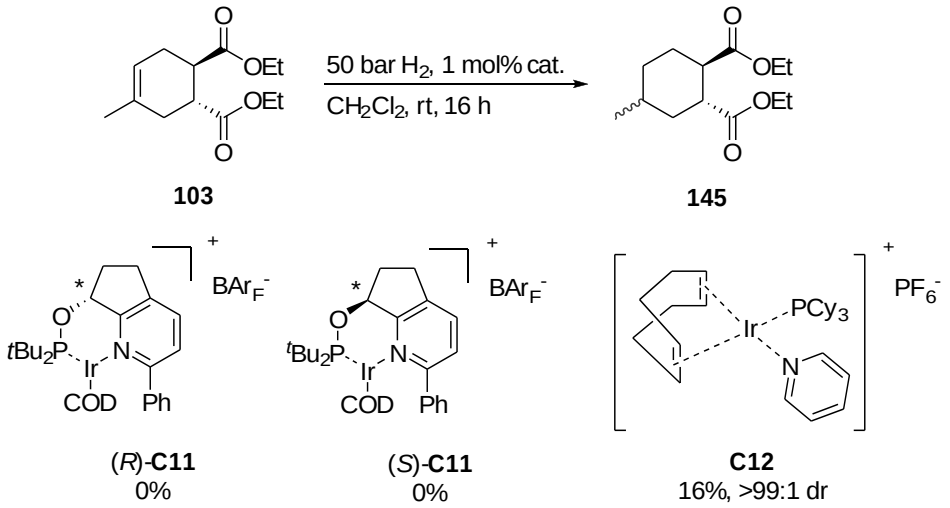

**102** **144** **C11** **C12**

***Scheme 61***: Unsuccessful reduction of olefin **102** to cyclohexane **144**.

The reduction of cyclohexene **79** with no substituent on the phenyl ring was already very sluggish (only 10% conversion, see *Table 5*) and it seems that an electron-donating group makes the double bond even less reactive.

### 3.7.2 *Hydrogenation of ethyl esters*

Another substrate class we synthesized for the asymmetric reduction were cyclohexenes with carboxylic ester substituents.




***Scheme 62***: Iridium-catalyzed hydrogenation of diester **103**.

We were disappointed to see that both enantiomers of chiral iridium catalyst **C11** did not lead to any product formation. Only Crabtree's catalyst gave cyclohexane **145** in 16% conversion but with perfect diastereomeric ratio of over 99:1. An explanation for this low reactivity might be steric reasons since an ester group is tolerated as will be shown below.

Next, we investigated the reduction of mono ethyl ester **104** and its derivatives (*Table 9*). This time we used palladium on charcoal as achiral catalyst.

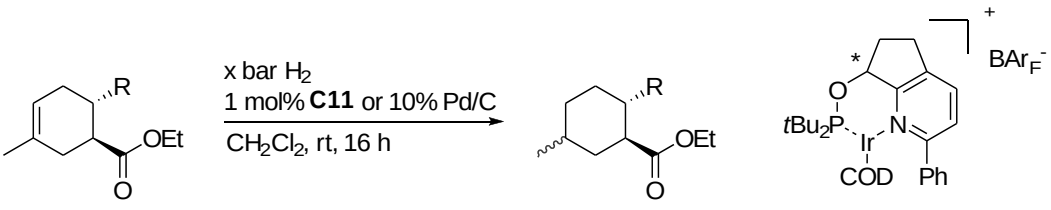



***Table 9***: Asymmetric reduction of mono ethyl ester **104**.

| Entry | R | Product | bar $H_2$ | (*R*)-**C11** | | (*S*)-**C11** | | Pd/C | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] |
| 1 | CHO | **146** | 50 | 0 | n.d. | 0 | n.d. | >99 | 75:25 |
| 2 | CHO | **146** | 100 | 0 | n.d. | 0 | n.d. | not tested | |
| 3 | $CH_2OH$ | **147** | 50 | 92 | 85:15 | 75 | 33:67 | >99 | 90:10 |
| 4 | $CH_2OAc$ | **148** | 50 | 94 | 79:21 | 94 | 15:85 | 92 | 66:34 |

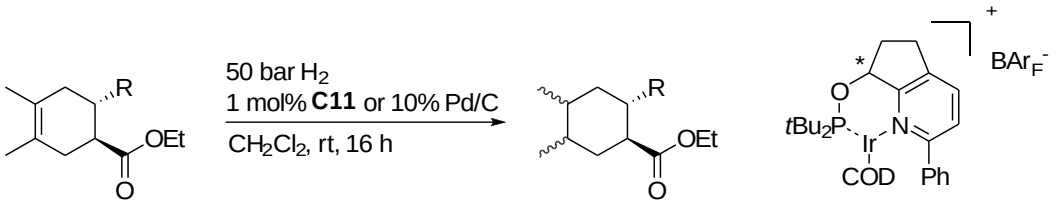
a) Determined by GCMS.

No formation of cyclohexane **146** was observed when trisubstituted olefin **104** was hydrogenated using chiral catalyst **C11** (entry 1). None of the two enantiomers showed any activity while we got full conversion with palladium on charcoal. However, the diastereoselectivity was low with 3:1. At 100 bar hydrogen pressure as well no reaction was observed (entry 2). Since we had already obtained bad results in the hydrogenation of aldehyde **77** and assumed that the lack of reactivity is due to the aldehyde group, we decided to test the reduction of alcohol **110** and acetate **112**. When we examined the asymmetric hydrogenation of the alcohol we were pleased to see that product **147** was formed with 92% conversion using catalyst (*R*)-**C11** and 75% using (*S*)-**C11** (entry 3). The diastereomeric ratio was relatively high with (*R*)-**C11** (85:15) but (*S*)-**C11** only showed a selectivity of 1:2. The best result was again obtained with palladium on charcoal. This catalyst led to full conversion and a selectivity of 9:1. The best results of all substrates were determined for acetate **148** (entry 4). For all three catalysts conversion to cyclohexane **148** was over 90% with slightly better values for the chiral catalysts. This time the achiral catalyst showed the lowest selectivity (2:1). The diastereomeric ratio for the two enantiomers of catalyst **C11** was similar with 79:21 for (*R*)-**C11** and 15:85 for (*S*)-**C11**. This indicates that the outcome is mainly catalyst-controlled for the acetate-susbtituted cyclohexene.

In general, the values for this substrate class are comparable to those obtained for aldehyde **77** and its derivatives. Moderate to good results were obtained for the alcohol and the acetate. Aldehyde **104** could not be reduced neither with the (*R*)- nor the (*S*)-catalyst while for aldehyde **77** the (*S*)-catalyst showed activity at least.

After this, tetrasubstituted olefin **109** and the corresponding alcohol **111** were investigated (*Table 10*).

***Table 10***: Hydrogenation of tetrasubstituted olefins.




**109:** R = CHO
**111:** R = $CH_2OH$

**149:** R = CHO
**150:** R = $CH_2OH$

**C11**

| Entry | R | Product | (*R*)-**C11** | | (*S*)-**C11** | | Pd/C | |
|---|---|---|---|---|---|---|---|---|
| | | | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] |
| 1 | CHO | **149** | 0 | n.d. | 0 | n.d. | >99 | 75:25 |
| 2 | $CH_2OH$ | **150** | 0 | n.d. | 0 | n.d. | 0 | n.d. |

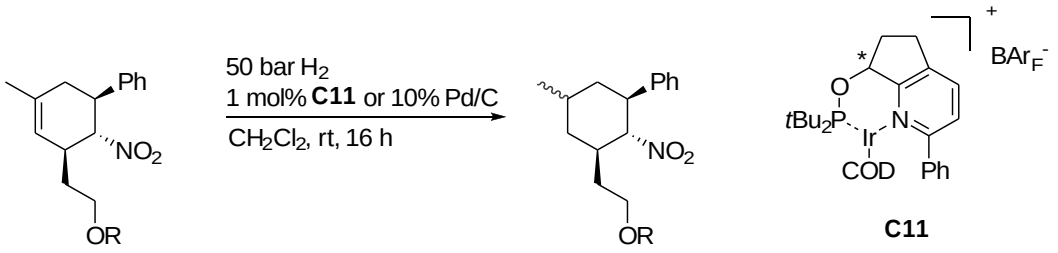
a) Determined by GCMS.

Aldehyde **149** could only be obtained using palladium on charcoal as catalyst with full conversion and a selectivity of 3:1 (entry 1). For the two enantiomers of catalyst **C11** no product formation could be detected. This was expected since no reaction had been observed for the trisubstituted substrate **108** and the tetrasubstituted C=C bond should be even harder to hydrogenate. We hoped to see improved reactivity with the corresponding alcohol **111** as before, but when we investigated the hydrogenation of alcohol **111** we observed no formation of the saturated alcohol **150** with all three catalysts (entry 2). Even palladium on charcoal proved to be inactive which was surprising because this catalyst was able to reduce aldehyde **109**. Since all three catalysts did not lead to any product formation we decided not to test the corresponding acetate.

### 3.7.3 *Hydrogenation of nitrocyclohexenes*

Next, we examined the hydrogenation of nitro-substituted cyclohexenes. First, we tested the reduction the substrates **136** and **138** with a methyl group at the double bond (*Table 11*). Aldehyde **127** was not tested due to the poor reactivity generally obtained for substrates with an aldehyde group.

***Table 11***: Hydrogenation of nitrocyclohexenes with a methyl group at the double bond.




**136:** R = H
**138:** R = Ac

**151:** R = H
**152:** R = Ac

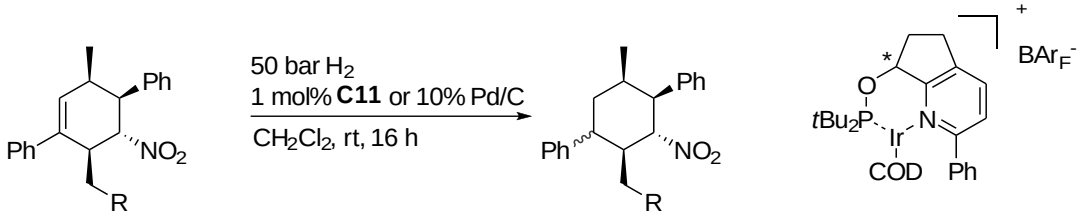
| Entry | R | Product | (*R*)-**C11** | | (*S*)-**C11** | | Pd/C | |
|---|---|---|---|---|---|---|---|---|
| | | | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] |
| 1 | H | **151** | 0 | n.d. | 80 | >99:1 | >99 | 83:17 |
| 2 | Ac | **152** | 0 | n.d. | 0 | n.d. | 23 | 58:42 |

a) Determined by $^{1}$H-NMR.

When applying the (*R*)-enantiomer of catalyst **C11** no product formation could be observed while the use of the other enantiomer led to 80% conversion to cyclohexane **151** and perfect diastereoselectivity (>99:1). Palladium on charcoal gave full conversion but a lower diastereomeric ratio of 83:17. We were surprised to see that only one catalyst enantiomer gave good results while the other was not active at all. On the other hand the substrate has three stereogenic centerswith one close to the C=C bond which means that the outcome is strongly influenced by the substrate itself. This might explain the pronounced difference in reactivity. For acetate **138** the saturated compound **152** could not be obtained for any of the enantiomers of the catalyst (entry 2). Only the achiral catalyst led to low conversion, with almost no selectivity (58:42). This time the alcohol gave better results than the acetate. This is different from the previously investigated cases in which the acetate gave the best results.

Finally, we investigated the hydrogenation of phenyl substituted nitrocyclohexenes (*Table 12*). We expected this substrate class to be difficult to reduce since we had encountered already problems with aryl substituted double bonds earlier. Furthermore, the fact that there are four stereogenic centers makes these cyclohexenes demanding substrates.

***Table 12***: Asymmetric hydrogenation of phenyl substituted nitrocyclohexenes.




**127:** R = CHO
**138:** R = $CH_2OH$
**140**: R = $CH_2OAc$

**153:** R = CHO
**154:** R = $CH_2OH$
**155**: R = $CH_2OAc$

| Entry | R | Product | (*R*)-**C11** | | (*S*)-**C11** | | Pd/C | |
|---|---|---|---|---|---|---|---|---|
| | | | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] | Conv. (%)[a)] | dr[a)] |
| 1 | CHO | **153** | 0 | n.d. | 0 | n.d. | 0 | n.d. |
| 2 | $CH_2OH$ | **154** | 0 | n.d. | 0 | n.d. | 0 | n.d. |
| 3 | $CH_2OAc$ | **155** | 0 | n.d. | 0 | n.d. | 57 | 90:10 |

a) Determined by $^1$H-NMR.

Unfortunately, neither the saturated aldehyde **153** nor the alcohol **154** could be obtained by using any of the three catalysts (entry 1 and 2). Only acetate **139** could be reduced to the corresponding cyclohexane **155** but only when employing palladium on charcoal (entry 3). The chiral iridium catalysts proved to be inactive. With the achiral catalyst the product was formed with moderate conversion (57%) and good selectivity (9:1).

## 3.8 Summary

Several chiral cyclohexenes were synthesized by asymmetric Diels-Alder reactions following different literature known procedures. Furthermore, products bearing an aldehyde group were modified to give access to further substrates for the diastereoselective iridium-catalyzed hydrogenation. All cyclohexene derivatives were tested in the asymmetric reduction using an achiral catalyst and the two enantiomers of a chiral iridium catalyst with a pyridine phosphinite ligand.

Previously obtained results could be confirmed and it seems that the chiral catalyst is rather inactive for cyclohexene substrates with an aldehyde substituent. When investigating the corresponding alcohols and acetates conversion was usually high and good to excellent diastereomeric ratios could

be obtained (*Figure 15*). In general the acetates gave better results than the alcohols.

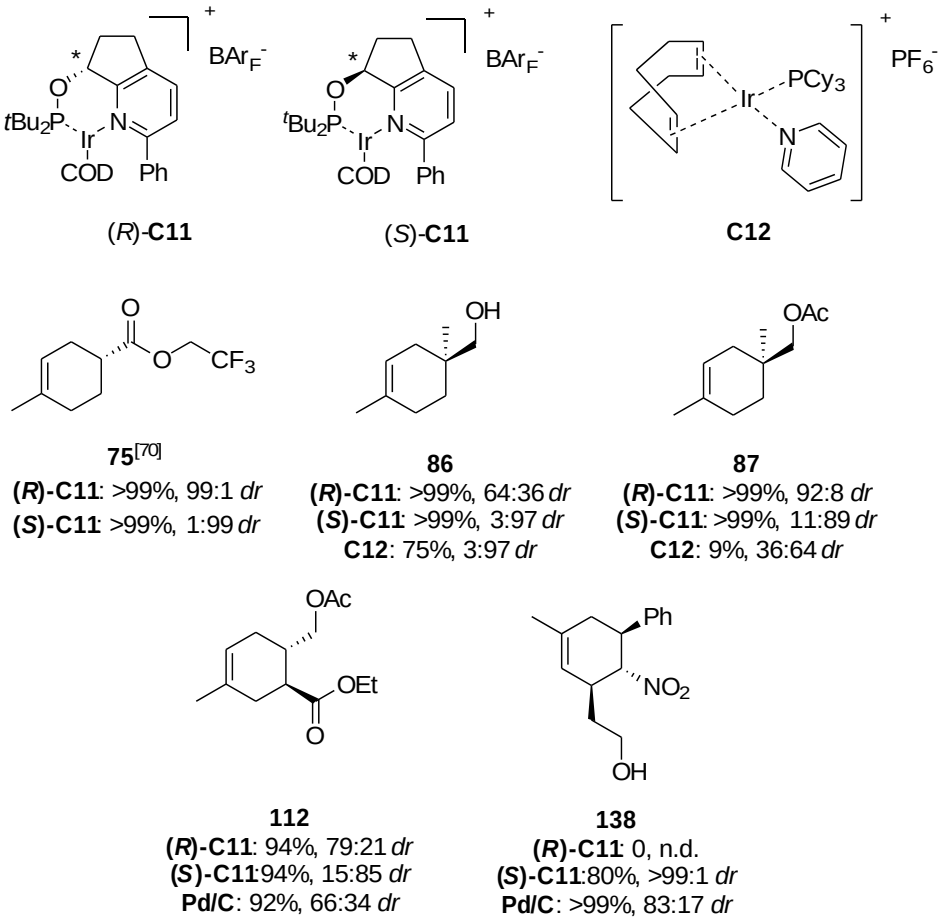



***Figure 15***: Best results obtained in the diastereoselective hydrogenation of chiral cyclohexenes.

For more challenging substrates like cyclohexenes with a tetrasubstituted C=C bond and highly substituted cyclohexenes the chiral catalyst proved to be inactive and only with palladium on charcoal reduction of the olefins was observed in some cases. We showed one example where a cyclohexene with already four stereogenic centers could be hydrogenated. This means that we were able to synthesize a cyclohexane with five stereogenic centers in two steps.

# 4 Investigations of NeoPHOX ligands in asymmetric hydrogenation and allylic substitution reactions

## 4.1 Introduction

Since their first application in enantioselective palladiun catalyzed allylic substitution in 1993,[85] PHOX ligands have become a widely used ligand class, especially in iridium catalyzed asymmetric hydrogenation (see *Chapter 1.2.2*). However, the substrate scope was limited at first and, therefore, many different ligand classes have been developed to find catalytic systems which can reduce different substrate classes efficiently. Initially developed ThrePHOX and SimplePHOX ligands showed high selectivity and could be prepared in only a few steps[25-28]. However, the ligands proved to be very sensitive towards air and moisture which resulted in low yields in the formation of the corresponding iridium complexes. By replacing the P-O bond by a P-C bond the stability of the ligands could be increased which facilitated the synthesis of the iridium complexes. Due to their neopentyl backbone these ligands are called NeoPHOX ligands.

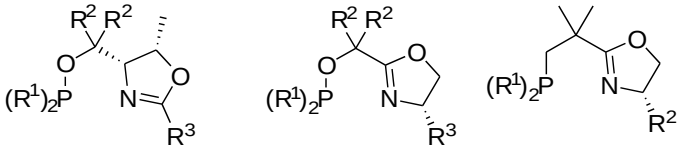
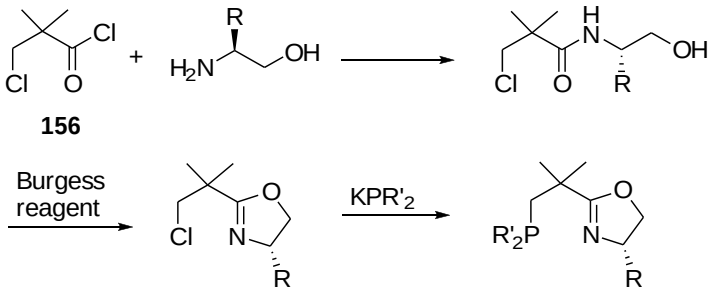



***Figure 16***: Structure of selected PHOX ligands.

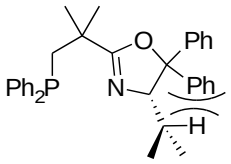
The first generation of NeoPHOX ligands was synthesized in three steps starting from 3-chloropivaloyl chloride (**156**) and an aminoalcohol (*Scheme 63*).[85] Due to the higher stability of the ligands, the efficiency of the synthesis could be much improved compared to ThrePHOX and SimplePHOX ligands. The most efficient ligand in asymmetric hydrogenation bears a *tert*-butyl group at the oxazoline ring. The drawback of its synthesis is the high cost of *tert*-leucinol as starting material which makes it unattractive for large scale application.




**156**

***Scheme 63***: Synthesis of 1st generation NeoPHOX ligands.

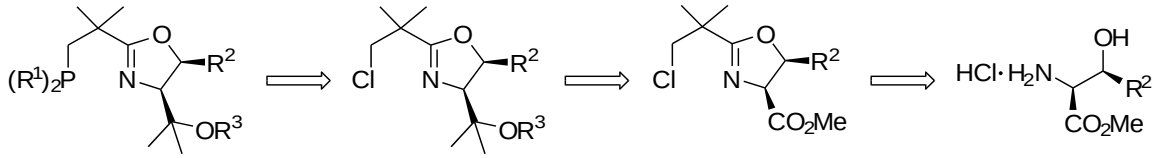
One possibility to avoid this problem is to use *L*-valine as starting material which is much less expensive. The lower steric hindrance of the isopropyl group may be compensated by the introduction of two substituents at C5 (*Figure 16*). However, ligands of this type gave distinctly lower selectivities than the *tert*-butyl substituted ligand.[86]




**L11**

***Figure 17***: Structure of *L*-valine derived NeoPHOX ligand with two phenyl groups at C5.

Another approach which had been previously applied in the synthesis of PHOX ligands uses threonine or serine as starting material.[87] A synthesis which gives access to this 2nd generation of NeoPHOX ligands was developed in our group by Jaroslav Padevet (*Scheme 64*).[70]



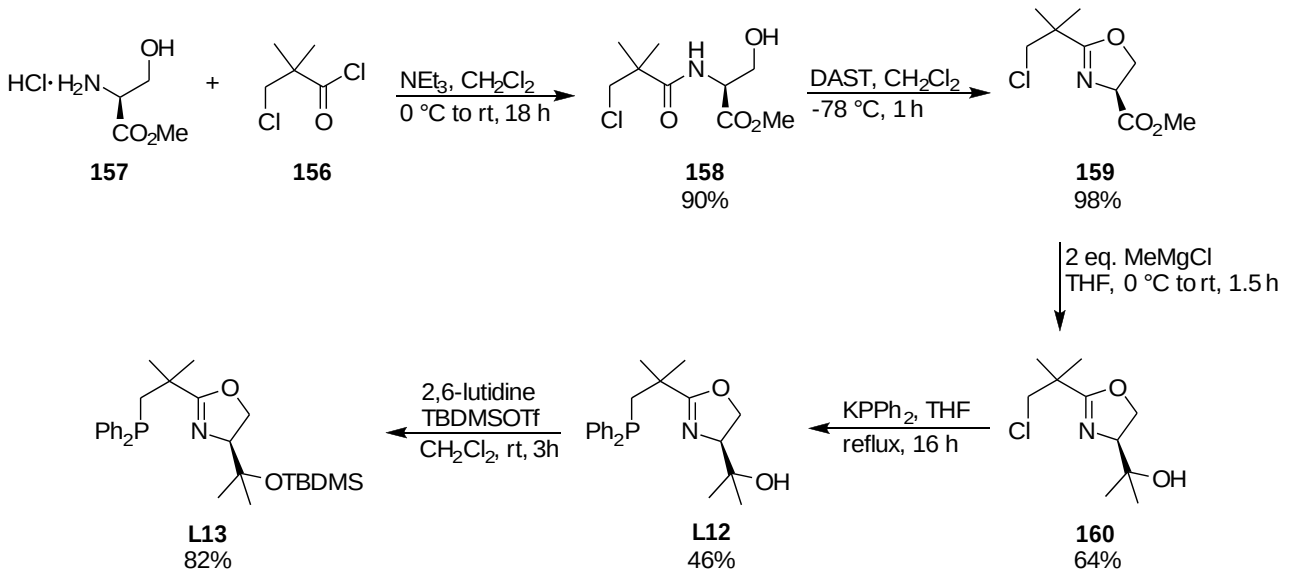

***Scheme 64***: Retrosynthetic analysis for 2nd generation of NeoPHOX ligands.

The synthesis resembles that of the 1st generation. The tertiary alcohol which mimics the *tert*-butyl group of *tert*-leucine was formed by double addition of a Grignard reagent to the methyl ester. Protection of the alcohol as a silyl ether or acetate allowed further optimization of the steric properties. Additionally, a second stereogenic center at C5 could be introduced by starting from threonine.

Jaroslav Padevet synthesized several iridium complexes of these ligands and successfully applied them in the asymmetric hydrogenation of some test substrates. Within the frame of this thesis, additional hydrogenation studies were carried out in order to obtain a more complete picture of the scope of this ligands. Furthermore, we applied these ligands in enantioselective palladium catalyzed allylic substitution reactions since PHOX ligands were initially developed for this type of transformation.[35,88]

## 4.2 Synthesis of iridium complexes

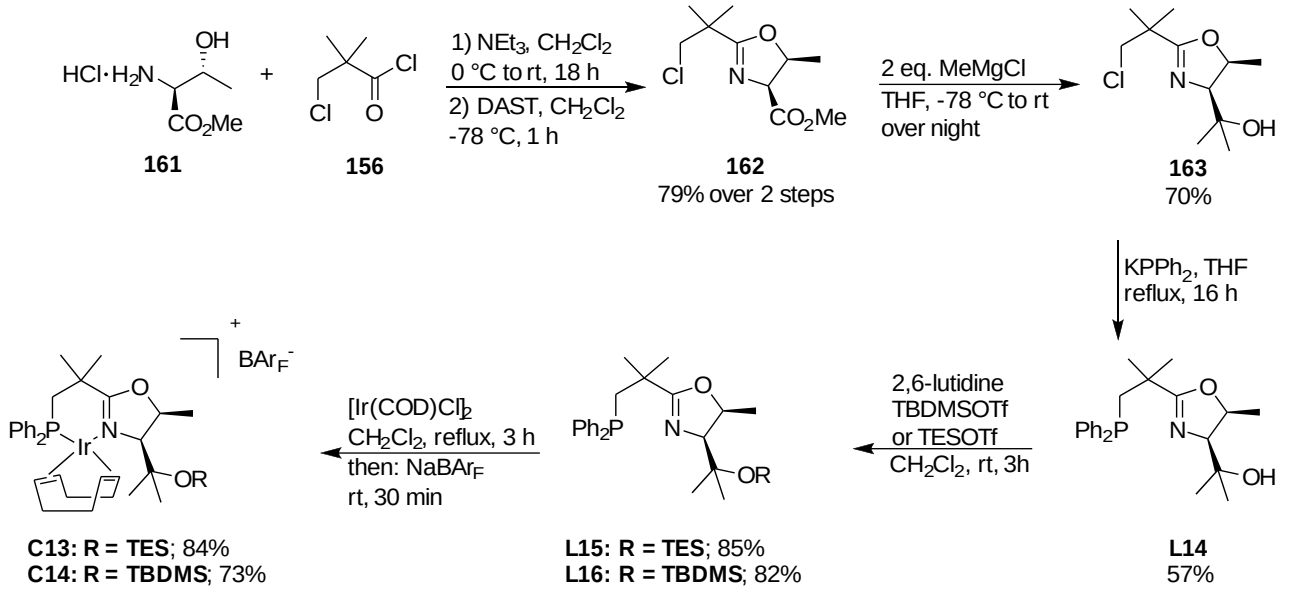
Several NeoPHOX derivatives and two of the corresponding iridium complexes were synthesized following the procedure reported by J. Padevet (*Scheme 65*).[70]




***Scheme 65***: Synthesis of serine derived NeoPHOX ligands.

In the first step, amide **158** was formed by $S_N2$ reaction between serine methylester hydrochloride (**157**) and acid chloride **156** under basic conditions. Next, oxazoline **159** was prepared using diethylaminosulfur trifluoride (DAST) in quantitative yield. Addition of two equivalents of methylmagnesium chloride led two the formation tertiary alcohol **160** which was converted to ligand **L12** by treatment with potassium diphenylphosphide with moderate yield for both steps. Finally, the hydroxy group was protected as silyl ether to obtain sterically more demanding ligand **L13** in good yield.

Starting from threonine methylester hydrochloride (**161**) we synthesized three more ligands and two of their corresponding iridium complexes (*Scheme 66*).



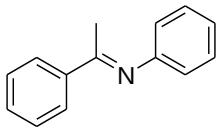

***Scheme 66***: Synthesis of threonine derived NeoPHOX ligands and their iridium complexes.

Amide formation and ring closure to build oxazoline **162** worked nicely with 79% yield over two steps. Next, addition of the Grignard reagent had to be performed this time at –78 °C to give alcohol **163** in satisfying yield. Transformation of the chloride to the phosphine resulted in isolation of ligand **L14** in moderate yield. The hydroxy group was again protected as TBDMS ether to give ligand **L16**. Additionally, TES protected silyl ether **L15** was also synthesized. Finally, the iridium complexes of the protected alcohols were prepared to give catalyst **C13** and **C14** in 84% and 73% respectively. With the two iridium catalysts in hand we tested them in the asymmetric hydrogenation of an imine and an allylic alcohol.

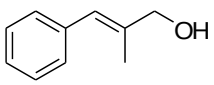
### 4.3 Hydrogenation of test substrates

J. Padevet investigated the enantioselective reduction of several alkenes and imine **164** using various iridium catalysts with NeoPHOX ligands of the 2nd generation. In this work we tested catalysts **C13** and **C14** for these two substrates to determine the influence of the silyl group. The results are presented in *Table 13*.

***Table 13*:** Hydrogenation of imine 164 and allylic alcohol 165 using various 2nd generation NeoPHOX catalysts.

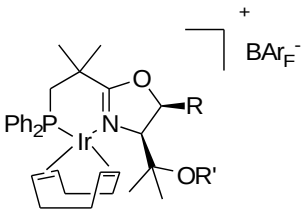



**164**




**165**

| Catalyst | **164** conversion (%)[a] *ee* (%)[b] | **165** conversion (%)[a] *ee* (%)[b] |
|---|---|---|
| **C13** | 8/32[c] 68/62[c] (*S*) | 60/>99[c] 89/88[c] (+) |
| **C14** | 79 49 (*S*) | >99 91 (+) |
| **C15**[70] | 4 7 (*S*) | 10 41 (+) |
| **C16**[70] | 73 16 (*S*) | 92 90 (+) |
| **C17**[70] | 5 67 (*S*) | 82 88 (+) |
| **C18**[70] | 79 77 (*S*) | >99 84 (+) |




**C13**: R = Me, R' = TES
**C14**: R = Me, R' = TBDMS
**C15**: R = Me, R' = H
**C16**: R = Me, R' = OAc
**C17**: R = Me, R' = TMS
**C18**: R = H, R' = TBDMS

Reaction conditions: 50 bar $H_2$, rt, 2 h, 1 mol% catalyst, 0.1 mmol substrate, 0.5 mL $CH_2Cl_2$.
a) Determined by $^1$H-NMR; b) Determined by chiral HPLC; c) reaction time 16 h.

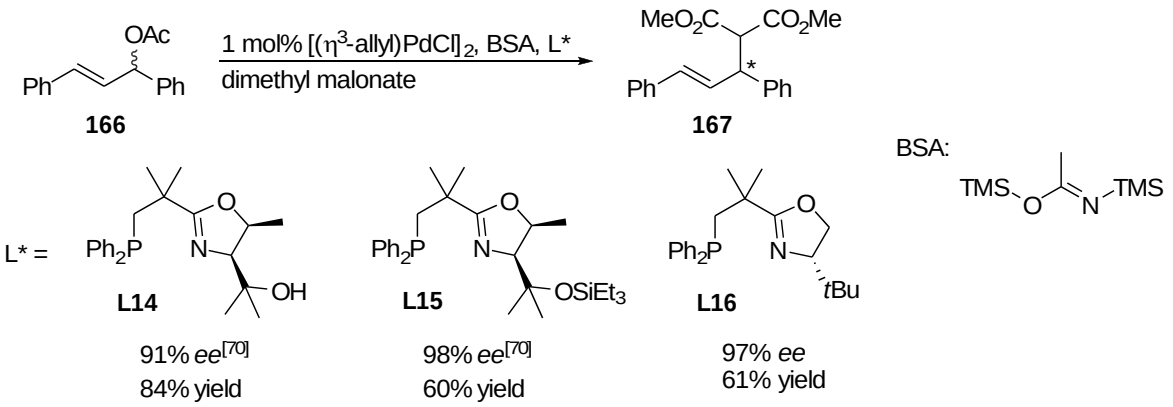
None of the tested catalysts induced high enantioselectivities in the hydrogenation of imine **164** and also the conversion was low in most cases. Catalyst **C13** with a TES group showed only 8% conversion and a moderate enantiomeric excess. Even prolonged reaction time increased conversion only slightly. Iridium complex **C14** gave the highest conversion (79%) but only 49% *ee*. The best results for this substrate were obtained with serine derived catalyst **C18** with 79% conversion and 77% enantiomeric excess. With iridium complexes **C15-C17** either low conversion or low *ee* was observed.

The asymmetric reduction of olefin **165** with NeoPHOX catalysts was more efficient. Catalyst **C13** showed good enantioselectivity but only 60% conversion under standard conditions. However, longer reaction time led to full conversion. The best results were obtained for the TBMDS protected catalyst **C14** with full conversion and an *ee* of 91%. Iridium complex **C18** gave full conversion as

well but the enantiomeric excess was lower. Good performance was also observed for catalysts **C16** and **C17** while **C15** turned out to be inefficient for this substrate.

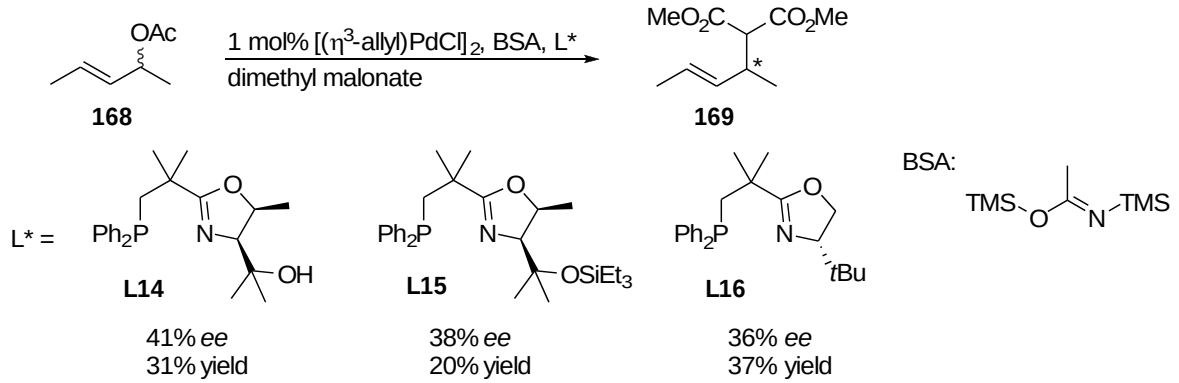
### 4.4 Application in allylic substitution reactions

Next, we tested NeoPHOX ligands in asymmetric palladium-catalyzed allylic substitution. Due to their good performance in asymmetric hydrogenation we chose 2nd generation ligands **L14** and **L15** as well as 1st generation ligand **L16** which also had given excellent results.[70] For a test reaction we chose the standard substrate **166** which had already been used by J. Padevet in a preliminary study (*Scheme 67*).



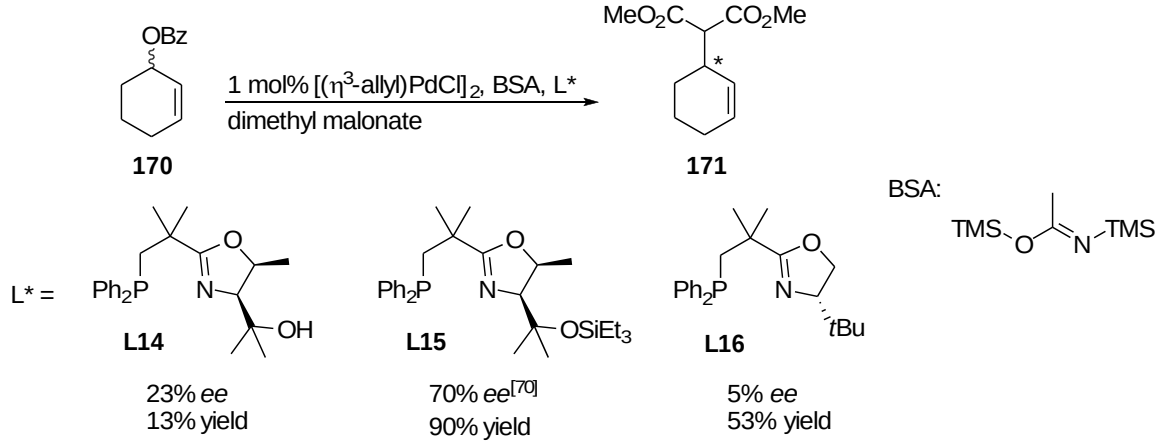

***Scheme 67***: Palladium-catalyzed allylic substitution with *rac*-(*E*)-1,3-diphenylallyl acetate (**166**).

Both catalysts derived from 2nd generation NeoPHOX ligands with a free hydroxy group and the corresponding TES-protected derivative performed well, yielding enantioselectivities of 90% and 98% *ee*, respectively. Ligand **L1**5 gave the best result and was even more selective than *tert*-leucine derived NeoPHOX ligand **L16** (97% *ee*). However, the best yield was obtained for least selective ligand **L14** (84%). Next, we investigated the palladium-catalyzed allylic substitution of (*E*)-1,3-dimethylallyl acetate (*Scheme 68*).




***Scheme 68***: Palladium-catalyzed allylic substitution with *rac*-(*E*)-1,3-dimethylallyl acetate (**168**).

All three tested ligands gave disappointing results. The yield was low in all cases and the enantiomeric excess reached only 41% for the best ligand **L14**. Interestingly, the sterically more demanding ligand **L15** did not lead to higher selectivity as for 1,3-diphenylallyl acetate. Last, we also tested the ligands on more demanding cyclic substrate **170** (*Scheme 69*).




***Scheme 69***: Asymmetric palladium-catalyzed allylic substitution with cyclic substrate **170**.

In allylic substitution with substrate **170** a notable enantiomeric excess of 70% together with 90% yield was achieved using TES-protected ligand **L15**. In contrast, standard PHOX ligands have been found to give extremely low enantioselectivities with cyclic substrates of this type. With ligand **L14** with a free hydroxy group the result was less satisfying. Not only the yield dropped to 53% but also an *ee* of only 23% was observed. For 1st generation NeoPHOX ligand **L16** the enantiomeric excess was even lower. These results demonstrate the potential that 2nd generation NeoPHOX ligands possess for palladium-catalyzed allylic substitution reactions.

## 4.5 Summary

We prepared five 2nd generation NeoPHOX ligands and two of their corresponding iridium complexes following a previously developed synthesis. The iridium complexes were tested in the asymmetric hydrogenation of an imine and an allylic alcohol giving similar results as other NeoPHOX catalysts. For the allylic alcohol catalyst **C14** showed the best performance of all iridium complexes. Furthermore, we investigated the palladium-catalyzed allylic substitution of three substrates with two NeoPHOX ligands of the 2nd generation and one ligand of the 1st generation. While excellent results were obtained for all three ligands with (*E*)-1,3-diphenylallyl acetate, none of them performed well with (*E*)-1,3-dimethylallyl acetate. In the reaction with cyclohex-2-en-1-yl benzoate ligand **L15** gave promising results showing the potential of this ligand class.

# 5 Experimental Part

## 5.1 Analytical Methods

### NMR-Spectroscopy

$^{1}$H- and $^{13}$C-spectra were recorded on a *Bruker* Advance 400 MHz instrument. All measurements were performed at 25 °C. Chemical shifts (δ) were referred to the signal of the solvent ($^{1}$H-NMR: $CHCl_3$, s, δ = 7.26 ppm, $^{13}$C-NMR: $CHCl_3$, t, δ = 77.16 ppm). $^{13}$C-, $^{19}$F- and $^{31}$P-spectra were recorded in a broadband decoupled mode. For splitted signals, the chemical shift is characterised by the arithmetic mean of the signal lines. Coupling constants (*J*) are given in hertz (Hz). The signals were assigned as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad).

### Infrared Spectroscopy (IR)

Infrared spectra were measured on a *Shimadzu* FTIR-8400S. Compounds were measured as pure substances via ATR-technique. Absorption bonds are given in wave numbers ($\tilde{\nu}$ = $cm^{-1}$, s: strong, m: medium, w: weak).

### Gas Chromatography-Mass Spectrometry (GC-MS)

Measurements were carried out on a *Shimadzu* GCMS-QP2010SE, AOC-20i (auto injector). As column a Rtx-5MS was used, 30 m (length), 0.25 µm (thickness), 0.25 mm (diameter). Either method A (EI, 70 eV, $Me_2Si$, 60 kPa, 60/3/3-140/0/40-250/5), method B (EI, 70 eV, $Me_2Si$, 60 kPa, 100/2/7-250/10) method C (EI, 70 eV, $Me_2Si$, 100 kPa, 50/2/30-250/5) or method D (EI, 70 eV, $Me_2Si$, 100 kPa, 120/3/20-250/25) was the method of choice.

### Gas Chromatography(GC)

Gas chromatograms were recorded on a Carlo Erba HRGC Mega2 Series 800 instrument. Separations on chiral phases were performed on a γ-cyclodextrin column (30 m × 0.25 mm × 0.25 µm).

**High-Performance Liquid Chromatography (HPLC)**

HPLC measurements were carried out on a *Shimadzu* Class-VP version 5.0, SCL-10A (system), CTO-10AC (column oven), LC-10AD (pump system), DGU-14A (degaser), SPD-M10A (diode array detector) or on a *Shimadzu* SIL-20A (auto sampler), CTO-10AS (column oven), LC-20AD (pump system), DGU-20$A_3$ (degaser), SPD-M20A (diode array detector). Separations were done on an OD-H or AD-H column (25 cm × 0.46 cm) from Daicel Chemical Industries.

**Thin Layer Chromatography (TLC)**

All thin layer chromatograms were carried out on *Macherey-Nagel* plates (Polygram®-SIL G/$UV_{254}$ with fluorescence indicator, 40×80 mm, 0.2 mm silica). For visualization UV-light (254 nm) or basic permanganate solution was used.

**Optical Rotation (α)**

Angles of rotation were measured on a *Perkin-Elmer* polarimeter 341 in a cuvette ($l$ = 1 dm) at 20 °C and 589 nm in $CHCl_3$.

**Melting Point (m.p.)**

The melting points were measured on a *Büchi* 535 instrument. The values are not corrected.

## 5.2 Reagents and Techniques

**Chemicals and Solvents**

Commercially available chemicals and absolute solvents were purchased from *Acros Organics*, *Aldrich*, *Alfa Aesar* or *Fluka* and were used without further purification.

**Syntheses**

Air- and moisture-sensitive syntheses were carried out under argon atmosphere in pre-dried glassware using standard Schlenk techniques.

**Column Chromatography**

All chromatographic separations were carried out under increased nitrogen pressure using *Merck* silica gel 60 (0.040-0.063 mm). Column dimension (diameter × height) and mixture of the eluent

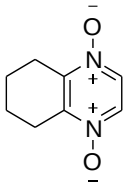
(v/v) are given in parentheses. Solvents were technical grade and were purified by distillation prior to use.

**Autoclaves**

For hydrogenations autoclaves from *PREMEX Reactor AG* of the type HPM-005 with a capacity of 50 mL were used .

## 5.3 Synthesis of pyrazine phosphinite ligands and precursors

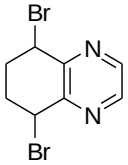
### 5,6,7,8-Tetrahydroquinoxaline 1,4-dioxide (28)



In a round bottom flask 5,6,7,8-tetrahydroquinoxaline **27** (2.00 g, 14.9 mmol, 1.0 eq.) and sodium hydrogen carbonate (6.26 g, 74.5 mmol, 5.0 eq.) were dissolved in methanol (100 mL). Oxone (27.5 g, 44.7 mmol, 3.0 eq.) was added followed by water (40 mL) and the reaction mixture was stirred at 50 °C for 20 hours. The suspension was filtrated, methanol was removed by rotatory evaporator and the remaining reaction mixture was extracted with methylene chloride (3 x 40 mL), washed with water (40 mL), dried over sodium sulfate and concentrated. The product was obtained as a colorless solid (2.05 g, 83%).

$C_8H_{10}N_2O_2$ (166.18 g/mol)
**m.p.**: 195-198 °C
**TLC**: $R_f$ = 0.50 (methylene chloride:methanol = 9:1, UV).
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.98 (s, 2H), 2.90-2.87 (m, 4H), 1.88-1.85 (m, 4H).
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 147.0, 133.3, 24.2, 20.5
**GC-MS** (Method D, $t_R$ = 9.1 min): *m/z* (%) 167 ([$M^+$+1], 36), 150 (11), 149 (100), 113 (11), 71 (21), 70 (17), 57 (23), 43 (14), 41 (10).
**IR**: ṽ = 3079 (w), 2934 (w), 2868 (w), 1397 (s), 1338 (m), 1252 (m), 1170 (m), 1070 (m), 971 (m), 815 (m), 780 (s), 698 (m).

### 5,8-Dibromo-5,6,7,8-tetrahydroquinoxaline



A solution of 5,6,7,8-tetrahydroquinoxaline **27** (1.91 g, 13.5 mmol, 1.0 eq.), *N*-bromosuccinimide (6.07 g, 33.8 mmol, 2.5 eq.) and AIBN (0.11 g, 0.68 mmol, 0.05 eq.) in carbon tetrachloride

(60 mL) was heated to reflux for two hours in a round bottom flask. After cooling to room temperature the reaction mixture was filtrated and the filtrate was concentrated to obtain the crude product as a brown oil which was purified by column chromatography (silica gel, 3 cm × 17 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a yellow liquid (3.70 g, 94%).

$C_8H_8Br_2N_2$ (291.97 g/mol)

**TLC**: $R_f$ = 0.25 (cyclohexane:EtOAc = 9:1, UV).

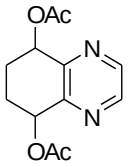
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.45 (s, 2H), 5.52-5.50 (m, 2H), 2.78-2.75 (m, 2H), 2.38-2.34 (m, 2H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 150.2, 144.9, 48.9, 28.3.

**GC-MS** (Method B, $t_R$ = 16.5 min): *m/z* (%) 292 ($M^+$, 2), 211 (10), 132 (21), 131 (100), 104 (12), 77 (13), 52 (10).

**IR**: ṽ = 3050 (w), 2968 (w), 2912 (w), 2842 (w), 1407 (m), 1194 (s), 1048 (m), 929 (s), 699 (s), 579 (s), 530 (m), 426 (s).

**5,6,7,8-Tetrahydroquinoxaline-5,8-diyl diacetate (38)**




In a round bottom flask 5,8-dibromo-5,6,7,8-tetrahydroquinoxaline (3.70 g, 12.7 mmol, 1.0 eq.) was dissolved in absolute DMF (15 mL) and acetic acid (45 mL). At 0 °C silver acetate (5.30 g, 31.8 mmol, 2.5eq) was added and the mixture was stirred for 22 hours at room temperature. The reaction mixture was filtrated and the filtrate was concentrated under high vacuum. Water (20 mL) and saturated $NaHCO_3$-solution (20 mL) were added and the aqueous phase was extracted with MTBE (3 x 60 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and concentrated to get a brown liquid (2.26 g, 71%) which was used without further purification in the next step. The product was a 2:1 mixture of the *cis*- and *trans*-isomer with the *trans*-product as the main product.

$C_{12}H_{14}N_2O_4$ (250.25 g/mol)

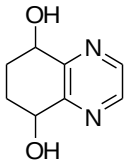
**TLC**: $R_f$ = 0.26 (cyclohexane:EtOAc = 1:1, UV).**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.57 (s, 2H), 6.10-6.08 (m, 2H), 2.38-2.33 (m, 2H), 2.26-2.16 (m, 2H), 2.10 (s, 6H) all *trans*, 8.56 (s, 2H), 6.04-6.02 (m. 2H), 2.13 (s, 6H), 2.12-2.05 (m, 4H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 170.2, 150.2, 144.8, 69.6, 24.7, 21.3 all *trans*, 170.4, 150.5, 144.6, 69.6, 24.7, 21.3 all *cis*.

**GC-MS** (Method B, $t_R$ = 17.6 min (*trans*), 17.8 min (*cis*)): *m/z* (%) 208 ([$M^+$–42], 24), 149 (10), 148 (100), 147 (79), 131 (31), 120 (18), 119 (28), 43 (48) all *trans*.

**IR**: $\tilde{\nu}$ = 3050 (w), 2968 (w), 2912 (w), 2842 (w), 1407 (m), 1194 (s), 1048 (m), 929 (s), 699 (s), 579 (s), 530 (m), 426 (s).

**5,6,7,8-Tetrahydroquinoxaline-5,8-diol (29)**




In a round bottom flask, 1 M NaOH-solution (40 mL) was given to a solution of 5,6,7,8-tetrahydroquinoxaline-5,8-diyl diacetate **38** (1.97 g, 7.87 mmol, 1.0 eq.) in methanol (80 mL) and the mixture was stirred at room temperature for 72 hours. The reaction mixture was acidified with 1 M HCl-solution (pH 5) and concentrated. The residue was dissolved in a 1:1 mixture of ethanol and chloroform (50 mL), filtrated and concentrated. The crude product was separated by column chromatography (silica gel, 3 cm × 15 cm, 3% methanol in methylene chloride) to obtain the *trans*-product (0.66 g, 52%) and the *cis*-product (0.34 g, 25%) as a brown solid.

$C_8H_{10}N_2O_2$ (166.18 g/mol)

Analytical data for the *trans*-isomer:

**m.p.**: 96-97 °C

**TLC**: $R_f$ = 0.27 (methylene chloride:methanol = 19:1, UV).

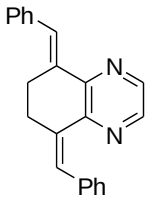
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.51 (s, 2H), 4.87-4.81 (m, 2H), 3.45 (brs, 2H), 2.51-2.45 (m, 2H), 1.90-1.81 (m, 2H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 153.4, 143.3, 68.8, 28.1.

**GC-MS** (Method B, $t_R$ = 11.7 min): *m/z* (%) 166 ($M^+$, 7), 149 (10), 148 (100), 147 (44), 138 (18), 120 (20), 119 (41), 110 (52), 109 (15), 107 (27), 81 (23), 80 (15), 54 (11), 53 (11), 52 (15).
**IR**: $\tilde{\nu}$ = 3195 (w), 2956 (w), 2927 (w), 2864 (w), 2832 (w), 1329 (m), 1156 (w), 1062 (s), 1025 (m), 914 (w), 858 (w), 494 (w).

Analytical data for the *cis*-isomer:
**m.p.**: 97-98 °C
**TLC**: $R_f$ = 0.24 (methylene chloride:methanol = 19:1, UV).
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.46 (s, 2H), 4.78 (s, 2H), 4.58 (brs, 2H), 2.20-2.05 (m, 4H).
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 153.1, 143.5, 68.1, 26.2.
**GC-MS** (Method B, $t_R$ = 12.1 min): *m/z* (%) 166 ($M^+$, 36), 148 (49), 147 (56), 138 (36), 137 (10), 120 (26), 119 (46), 110 (100), 109 (25), 107 (98), 94 (13), 92 (11), 81 (33), 80 (23), 79 (11), 78 (12), 65 (11), 55 (11), 54 (17), 53 (18), 52 (22), 41 (15).
**IR**: $\tilde{\nu}$ = 3233 (m), 2951 (w), 2938 (w), 2869 (w), 2829 (w), 1403 (m), 1337 (m), 1069 (s), 968 (s), 880 (m), 567 (m), 528 (m).

**5,8-Di((*E*)-benzylidene)-5,6,7,8-tetrahydroquinoxaline (33)**




Under inert atmosphere 5,6,7,8-tetrahydroquinoxaline **27** (200 mg, 1.49 mmol, 1.0 eq.) and benzaldehyde (791 mg, 7.45 mmol, 5.0 eq.) were dissolved in acetic acid anhydride (4 mL) in a Schlenk flask and heated to 180 °C for five days. The reaction mixture was concentrated under high vacuum, 2 M NaOH-solution (30 mL) was added and the aqueous phase was extracted with methylene chloride (3 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 18 cm, cyclohexane:EtOAc = 19:1, then 9:1) to obtain the product **33** (292 mg, 63%) as a brown solid and 125 mg of the mono olefin **35**.

$C_{22}H_{18}N_2$ (310.40 g/mol)

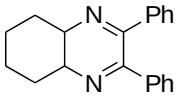
**TLC**: $R_f$ = 0.22 (cyclohexane:EtOAc = 9:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.46 (s, 2H), 7.95 (s, 2H), 7.43-7.37 (m, 8H), 7.31-7.27 (m, 2H), 2.93 (s, 4H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 147.9, 142.9, 137.3, 134.3, 129.7, 129.1, 128.4, 127.5, 26.4.

**GC-MS** (Method D, $t_R$ = 32.7 min): *m/z* (%) 310 ($M^+$, 34), 309 (100), 308 (14), 154 (29), 153 (12), 147 (15).

**2,3-Diphenyl-4a,5,6,7,8,8a-hexahydroquinoxaline**




In a round bottom flask, benzil **21** (4.99 g, 43.3 mmol, 1.0 eq.) and 1,2-diaminocyclohexane **20** (9.10 g, 43.3 mmol, 1.0 eq.) were dissolved in THF (100 mL). Then, a catalytic amount of acetic acid and the reaction mixture was heated to reflux for three hours. The solvent was removed and the crude product was recrystallized from hot ethanol to give the product (10.0 g, 80%) as a brown solid.

$C_{20}H_{20}N_2$ (288.39 g/mol)

**m.p.**: 155-157 °C.

**TLC**: $R_f$ = 0.35 (cyclohexane:EtOAc = 9:1, UV).

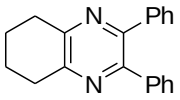
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.41-7.38 (m, 4H), 7.30-7.27 (m, 2H), 7.25-7.21 (m, 4H), 2.86-2.82 (m, 2H), 2.52-2.49 (m, 2H), 1.92-1.87 (m, 2H), 1.66-1.59 (m, 2H), 1.46-1.40 (m, 2H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 159.8, 137.9, 129.6, 128.2, 128.1, 59.7, 33.6, 25.6.

**GC-MS** (Method C, $t_R$ = 13.1 min): *m/z* (%) 288 ($M^+$, 44), 287 (10), 104 (100), 82 (19), 67 (29), 54 (10).

**IR**: $\tilde{\nu}$ = 2935 (w), 2855 (w), 1552 (w), 1443 (w), 1261 (w), 1022 (w), 765 (m), 694 (s), 547 (w).

**2,3-Diphenyl-5,6,7,8-tetrahydroquinoxaline (22)**




In a round bottom flask, a solution of DDQ (10.0 g, 43.3 mmol, 1.0 eq.) in absolute toluene (80 mL) was added to a solution of 2,3-diphenyl-4a,5,6,7,8,8a-hexahydroquinoxaline (12.5 g, 43.3 mmol, 1.0 eq.) in absolute toluene (80 mL) and the reaction mixture was heated under reflux for 60 hours. The reaction mixture was cooled down to room temperature, filtrated, the solvent removed and the residue was recrystallized from hot ethanol to obtain the product as a yellow solid (10.4 g, 84% over two steps).

$C_{20}H_{18}N_2$ (286.38 g/mol)

**m.p.**: 77-80 °C.

**TLC**: $R_f$ = 0.42 (cyclohexane:EtOAc = 9:1, UV).

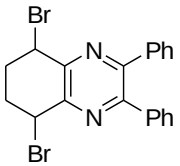
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.40-7.38 (m, 4H), 7.28-7.24 (m, 6H), 3.08-3.04 (m, 4H), 2.01-1.97 (m, 4H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 150.7, 149.7, 139.2, 129.8, 128.3, 128.3, 32.0, 23.0.

**GC-MS** (Method B, $t_R$ = 28.3 min): *m/z* (%) 287 (14), 286 ($M^+$, 77), 285 (100), 52 (11).

**IR**: ṽ = 2942 (w), 2862 (w), 2231 (w), 1937 (m), 1220 (m), 1142 (m), 1083 (m), 990 (w), 901 (w), 767 8m), 697 (s).

**5,8-Dibromo-2,3-diphenyl-5,6,7,8-tetrahydroquinoxaline**




A solution of 2,3-diphenyl-5,6,7,8-tetrahydroquinoxaline **22** (1.69 g, 5.90 mmol, 1.0 eq.), *N*-bromosuccinimide (3.18 g, 17.7 mmol, 3.0 eq.) and AIBN (0.05 g, 0.30 mmol, 0.05 eq.) in carbon tetrachloride (25 mL) was heated to reflux for 2.5 hours in a round bottom flask. After cooling to room temperature the reaction mixture was filtrated and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, 3 cm × 12 cm, cyclohexane:EtOAc = 49:1) to obtain the product as a yellow solid (1.12 g, 43%).

$C_{20}H_{16}Br_2N_2$ (444.17 g/mol)

**m.p.**: 154-155 °C.

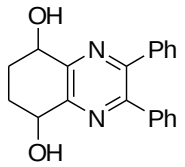
**TLC**: $R_f$ = 0.23 (cyclohexane:EtOAc = 49:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.49-7.46 (m, 4H), 7.37-7.28 (m, 6H), 5.70-5.68 (m, 2H), 2.98-2.92 (m, 2H), 2.53-2.46 (m, 2H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 152.6, 146.7, 137.8, 129.9, 129.3, 128.5, 49.4, 28.7.

**IR**: $\tilde{\nu}$ = 2942 (w), 1388 (m), 1216 (m), 948 (m), 775 (m), 731 (m), 699 (s), 673 (m), 588 (m), 555 (m), 433 (w).

**2,3-Diphenyl-5,6,7,8-tetrahydroquinoxaline-5,8-diol (40)**




In a round bottom flask 5,8-dibromo-2,3-diphenyl-5,6,7,8-tetrahydroquinoxaline (200 mg, 0.45 mmol, 1.0 eq.) was dissolved in absolute DMF (1 mL) and acetic acid (3 mL). At room temperature silver acetate (188 mg, 1.13 mmol, 2.5 eq) was added and the mixture was stirred for 4.5 hours at room temperature. The reaction mixture was filtrated and the filtrate was concentrated. Saturated $NaHCO_3$-solution (30 mL) was added and the aqueous phase was extracted with MTBE (3 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate and concentrated to obtain a brown liquid.

The residue was dissolved in methanol (4 mL) and 1 M NaOH-solution (2 mL) was added. The mixure was stirred at room temperature for 60 hours. The reaction mixture was acidified with 1 M HCl-solution (pH 4) and concentrated. The residue was dissolved in a 1:1 mixture of ethanol and chloroform, filtrated and concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 15 cm, methylene chloride, then methylene chloride:methanol = 49:1) to obtain the *trans*-diol (37.2 mg, 26%) and the *cis*-diol (17.2 mg, 12%) as brown solids.

$C_{20}H_{18}N_2O_2$ (318.38 g/mol)

Analytical data for the *trans*-isomer:

**m.p.**: 185-190 °C.

**TLC**: $R_f$ = 0.35 (methylene chloride:methanol = 49:1, UV).

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.43-7.28 (m, 10H), 4.93-4.85 (m, 2H), 3.71 (brs, 2H), 2.55-2.48 (m, 2H), 1.95-1.84 (m, 2H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 151.3, 150.2, 138.0, 129.8, 129.0, 128.4, 68.7, 28.2.

**GC-MS** (Method D, $t_R$ = 9.2 min): *m/z* (%) 279 ([$M^+$–39], 13), 167 (37), 150 (11), 149 (100), 113 (11), 71 (22), 70 (18), 57 (25), 55 (10), 43 (20), 41 (16).

**IR**: $\tilde{\nu}$ = 3254 (w), 3060 (w), 3032 (w), 2945 (w), 2870 (w), 1388 (m), 1025 (m), 977 (w), 767 (m), 695 (s).

Analytical data for the *cis*-isomer:

**m.p.**: 188-192 °C

**TLC**: $R_f$ = 0.27 (methylene chloride:methanol = 49:1, UV).

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.42-7.28 (m, 10H), 4.87 (s, 2H), 3.52 (brs, 2H), 2.26-2.13 (m, 4H).

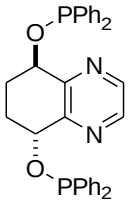
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 151.7, 150.1, 138.0, 129.8, 129.0, 128.4, 68.1, 26.4.

**GC-MS** (Method D, $t_R$ = 9.2 min): *m/z* (%) 279 ([$M^+$–39], 18), 167 (46), 150 (10), 149 (100), 113 (13), 71 (14), 70 (18), 57 (30), 55 (12), 43 (17), 41 (16).

**General working procedure for the formation of pyrazine-bisphosphinite ligands**

A 25 mL Schlenk tube was charged with the diol (0.09 mmol, 1.0 eq) and DMAP (22.2 mg, 0.18 mmol, 2.0 eq), evacuated and filled with argon. The mixture was dissolved in absolute methylene chloride (3 mL), the chlorophosphine (0.22 mmol, 2.4 eq) was added and the solution was stirred at room temperature for 2.5 hours. The reaction mixture was filtrated through a pipette with silica gel (0.5 cm × 2 cm) under inert atmosphere and washed with absolute THF(2 x 2 mL). The solvent was removed under high vacuum to give the ligand which was directly used for the formation of the iridium complex.

*trans*-5,8-Bis((diphenylphosphanyl)oxy)-5,6,7,8-tetrahydroquinoxaline (**L10**)

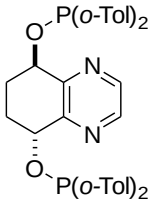



$C_{32}H_{28}N_2O_2P_2$ (534.16 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.34 (s, 2H), 7.44-7.39 (m, 4), 7.29-7.22 (m, 10H), 7.19-7.14 (m, 6), 5.12-5.09 (m, 2H), 2.36-2.34 (m, 2H), 2.08-2.05 (m, 2H).

**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = 114.4.

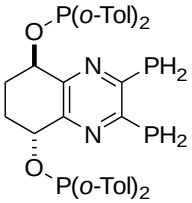
***trans*-5,8-Bis((di-o-tolylphosphanyl)oxy)-5,6,7,8-tetrahydroquinoxaline**




$C_{36}H_{36}N_2O_2P_2$ (590.64 g/mol)

**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = 95.5.

***trans*-5,8-Bis((di-o-tolylphosphanyl)oxy)-2,3-diphenyl-5,6,7,8-tetrahydroquinoxaline**




$C_{48}H_{44}N_2O_2P_2$ (742.84 g/mol)

**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = 102.7.

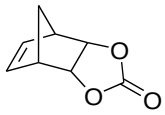
**General working procedure for the formation of the iridium complexes**

The ligand (0.09 mmol, 1.0 eq) was dissolved in absolute methylene chloride (2 mL) and $[Ir(COD)Cl]_2$ (40.3 mg, 0.09 mmol 1.0 eq) was added and the reaction mixture stirred for 1.5 hours at room temperature. $NaBAr_F$ (159 mg, 0.18 mmol, 2.0 eq) was added and stirring continued under reflux for 1 hour. The solvent was removed and the crude product was separated by column chromatography (silica gel, 3 cm × 15 cm, methylene chloride, then methylene chloride:methanol = 90:10) to obtain a red or foam. In all cases, the $^1$H-NMR-spectra revealed that an unidentifiable mixture was obtained and the desired iridium complexes could not be isolated (see *Figure 9* as a typical example).

**Working procedure for the formation of iridium complexes with $Ir(COD)_2BAr_F$**

The ligand (0.09 mmol, 1.0 eq) and $[Ir(COD)_2BAr_F$ (230 mg, 0.18 mmol, 2.0 eq) were dissolved in absolute methylene chloride (3 mL) and the mixture was stirred overnight at room temperature. The solvent was removed and the crude product was dissolved in DCM (5 mL), layered with heptane (5 mL) and stored in the freezer overnight. The precipitate was filtered off and dried under high vacuum to get a red solid. The $^1$H-NMR spectra revealed that an unidentifiable mixture was obtained.

**3a,4,7,7a-Tetrahydro-4,7-methanobenzo[d][1,3]dioxol-2-one (56)[57]**




In a round bottom flask under inert atmosphere, freshly prepared cyclopentadiene **58** (4.93 g, 74.6 mmol, 1.0 eq.) and vinylene carbonate **57** (19.3 g, 224 mmol, 3.0 eq) were dissolved in absolute toluene (3 mL) and stirred at 180 °C for 20 hours. The reaction mixture was concentrated and the crude product was distilled under high vacuum (120 °C oil bath temperature) to obtain the product as a colorless wax (9.43 g, 83%).

$C_8H_8O_3$ (152.15 g/mol)
**m.p.**: 98-99 °C.

**TLC**: $R_f$ = 0.67 (cyclohexane:EtOAc = 1:1, $KMnO_4$).

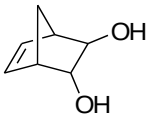
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 6.23 (t, $^3J_{HH}$ = 1.8 Hz, 2H), 4.99 (dd, $^3J_{HH}$ = 2.3 Hz, $^3J_{HH}$ = 1.8 Hz, 2H), 3.29 (t, $^3J_{HH}$ = 1.8 Hz, 2H), 1.77 (dt, $^2J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 1.9 Hz, 1H), 1.28 (d, $^2J_{HH}$ = 10.4 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 155.6, 134.4, 79.0, 45.7, 42.6.

**GC-MS** (Method B, $t_R$ = 10.5 min): *m/z* (%) 107 ([$M^+$–45], 2), 79 (40), 77 (23), 66 (100).

**IR**: $\tilde{\nu}$ = 2995 (w), 1778 (s), 1368 (s), 1159 (s), 1079 (s), 1048 (s), 947 (m), 822 (m), 757 (s), 705 (s).

**Bicyclo[2.2.1]hept-5-ene-2,3-diol (59)** [57]




3a,4,7,7a-tetrahydro-4,7-methanobenzo[d][1,3]dioxol-2-one **56** (3.03 g, 19.9 mmol, 1.0 eq.) was dissolved in 1 M NaOH-solution (25 mL) and stirred at 40 °C for 18 hours. The reaction mixture was neutralized with 1 M HCl-solution and extracted with MTBE (3 x 30 mL), dried over sodium sulfate and concentrated to obtain the product (2.32 g, 92%) as a colorless solid.

$C_7H_{10}O_2$ (126.16 g/mol)

**m.p.**: 166-168 °C.

**TLC**: $R_f$ = 0.36 (cyclohexane:EtOAc = 1:1, $KMnO_4$).

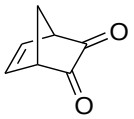
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 6.23 (t, $^3J_{HH}$ = 1.8 Hz, 2H), 4.17 (dd, $^3J_{HH}$ = 2.4 Hz, $^3J_{HH}$ = 1.5 Hz, 2H), 3.03-3.00 (m, 2H), 1.50 (dt, $^2J_{HH}$ = 9.6 Hz, $^3J_{HH}$ = 1.8 Hz, 1H), 1.20 (d, $^2J_{HH}$ = 9.7 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 135.3, 71.2, 47.8, 42.0

**GC-MS** (Method B, $t_R$ = 15.3 min): *m/z* (%) 79 ([$M^+$–47], 13), 77 (10), 67 (100), 66 (85), 65 (13), 60 (55), 41 (12).

**IR**: $\tilde{\nu}$ = 3444 (w), 3392 (m), 3206 (w), 2982 (w), 2920 (w), 1385 (w), 1252 (w), 1112 (s), 1098 (s), 1041 (s), 923 (w), 778 (w), 733 (s), 709 (s), 589 (m), 454 (w).

**Bicyclo[2.2.1]hept-5-ene-2,3-dione (55)** [57]



In a round bottom flask with dropping funnel, trifluoroacetic anhydride (21.0 mL, 151 mmol, 2.8 eq.) was added within 30 minutes to a solution of DMSO (11.9 mL, 167 mmol, 3.1 eq.) in methylene chloride (90 mL) at −78 °C, followed by a solution of bicyclo[2.2.1]hept-5-ene-2,3-diol **59** (6.80 g, 53.9 mmol, 1.0 eq.) in methylene chloride (30 mL) within 10 minutes. The solution was stirred for two hours at −78 °C. Then, triethylamine (37.9 mL, 270 mmol, 5.0 eq.) was added and the reaction mixture was stirred for another three hours while slowly warming to room temperature. 1 M HCl-solution (20 mL) was added and the reaction mixture was extracted with methylene chloride (5 x 50 mL). The combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by vacuum distillation (0.1 mbar, 70 °C oil bath temperature) to obtain the product as a yellow solid (4.75 g, 72%).

$C_7H_6O_2$ (122.12 g/mol)

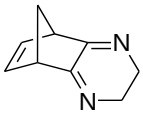
**b.p.**: 29 °C, 0.1 mbar.

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 6.50 (s, 2H), 3.32-3.31 (m, 2H), 2.95 (dt, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 2.1 Hz, 1H), 2.49 (d, $^2J_{HH}$ = 10.9 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 195.8, 137.9 51.7, 43.8.

**GC-MS** (Method C, $t_R$ = 5.9 min): *m/z* (%) 122 ($M^+$, 17), 66 (100), 65 (17), 40 (19).

**2,3,5,8-Tetrahydro-5,8-methanoquinoxaline (60)**



In a round bottom flask with Dean-Stark apparatus bicyclo[2.2.1]hept-5-ene-2,3-dione **55** (117 mg, 0.96 mmol, 1.0 eq.), ethylene diamine (69.1 mg, 1.15 mmol, 1.2 eq.) and *p*-toluene sulfonic acid (15.6 mg, 0.33 mmol, 0.1 eq.) were dissolved in absolute toluene (5 mL) and heated to reflux for four hours. The reaction mixture was washed with $NaHCO_3$-solution (5 mL) and brine (5 mL), dried over sodium sulfate and concentrated to obtain the product as a yellow liquid (80 mg, 67%) which was used without further purification.

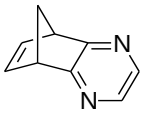
$C_9H_{10}N_2$ (146.19 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 6.35 (t, $^3J_{HH}$ = 1.6 Hz, 2H), 3.58-3.48 (m, 2H), 3.45-3.56 (m, 2H), 3.34-3.32 (m, 2H), 2.30 (dt, $^2J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 1.7 Hz, 1H), 1.20 (d, $^2J_{HH}$ = 9.3 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 163.7, 137.0, 49.8, 48.3, 45.7.

**GC-MS** (Method B, $t_R$ = 7.9 min): *m/z* (%) 146 ($M^+$, 64), 145 (29), 119 (27), 118 (11), 92 (34), 91 (15), 80 (12), 66 (100), 65 (17).

**5,8-Dihydro-5,8-methanoquinoxaline (54)**

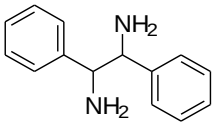



In a round bottom flusk, a solution of nickel dioxide (645 mg, 7.11 mmol, 13.0 eq) and 2,3,5,8-tetrahydro-5,8-methanoquinoxaline **60** (80.0 mg, 0.55 mmol, 1.0 eq) in absolute toluene (2 mL) was heated under reflux over night. The mixture was filtrated and the solvent removed. The crude product was purified by column chromatography (silica gel, 2 cm × 15 cm, cyclohexane:EtOAc = 19:1) to obtain the product as a yellow liquid (0.35 g, 15%).

$C_9H_8N_2$ (144.18 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.86 (s, 2H), 6.90 (t, $^3J_{HH}$ = 1.7 Hz, 2H), 3.89-3.87 (m, 2H), 2.66 (dt, $^2J_{HH}$ = 8.2 Hz, $^3J_{HH}$ = 1.7 Hz, 1H), 2.54 (d, $^2J_{HH}$ = 8.2 Hz, 1H).

**1,2-Diphenylethane-1,2-diamine (63)**




In a round bottom flask benzaldehyde **61** (10.0 g, 94.2 mmol, 1.0 eq.) and ammonium acetate (22.2 g, 282 mmol, 3.0 eq.) were stirred at 120 °C for 3.5 hours. The reaction mixture was cooled to room temperature and washed with water. The remaining yellow sticky solid was recrystallized from hot ethanol (20 mL) to obtain a white solid (3.7 g). The solid was dissolved in water (40 mL) and concentrated sulfuric acid (13 mL) and was refluxed over the weekend. After cooling to room temperature the mixture was filtrated and 6 M NaOH-solution (20 mL) was given to the filtrate.

Solid NaOH was added until pH 14 was reached. The precipitate was filtrated off and recrystallized from hot cyclohexane (10 mL) to obtain the product as pale brown crystals (1.96 g, 39%).

$C_{14}H_{16}N_2$ (212.30 g/mol)

**m.p.**: 113-114 °C.

**TLC**: $R_f$ = 0.37 (methylene chloride:methanol = 19:1, UV).

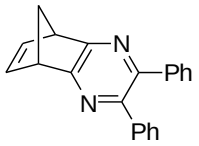
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.40-7.34 (m, 8H), 7.31-7.28 (m, 2H), 4.03 (s, 2H), 1.47 (brs, 4H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 143.1, 128.6, 127.8, 127.7, 63.0.

**GC-MS** (Method B, $t_R$ = 18.3 min): *m/z* (%) 106 ([$M^+$–106], 100), 79 (20), 77 (11).

**IR**: ṽ = 3342 (w), 3272 (w), 3027 (w), 1773 (m), 1452 (m), 1160 (s), 1081 (s), 756 (s), 696 (s), 614 (s).

**2,3-Diphenyl-5,8-dihydro-5,8-methanoquinoxaline (64)**




In a round bottom flask, 1,2-diphenylethane-1,2-diamine **63** (1.68 g, 7.91 mmol, 1.0 eq.) and bicyclo[2.2.1]hept-5-ene-2,3-dione (0.97 g, 7.91 mmol, 1.0 eq.) **55** were dissolved in THF (50 mL), followed by a catalytic amount of *p*-toluene sulfonic acid and the reaction mixture was heated to reflux for three hours. The solvent was removed and the residue was dissolved in absolute toluene (30 mL). A solution of DDQ (1.83 g, 7.91 mmol, 1.0 eq.) in absolute toluene (30 mL) was added and the reaction mixture was heated under reflux for five hours. The mixture was filtrated and the solvent removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 3 cm × 15 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a brown solid (0.35 g, 15%).

$C_{21}H_{16}N_2$ (296.37 g/mol)

**TLC**: $R_f$ = 0.37 (methylene chloride:methanol = 9:1, UV).

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.40-7.35 (m, 4H), 7.27-7.24 (m, 6H), 6.96 (t, $^{3}J_{HH}$ = 1.9 Hz, 2H), 4.02-4.00 (m, 2H), 2.74 (dt, $^{2}J_{HH}$ = 8.2 Hz, $^{3}J_{HH}$ = 1.7 Hz, 1H), 2.64 (d, $^{2}J_{HH}$ = 8.2 Hz, 1H).

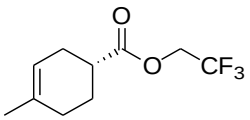
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 166.2, 145.6, 143.0, 139.6, 130.0, 128.3, 128.0, 67.1, 50.0.

**GC-MS** (Method B, $t_R$ = 28.7 min): *m/z* (%) 296 ($M^+$, 100), 295 (95), 193 (12), 165 (10), 90 (18), 89 (22).

**IR**: $\tilde{\nu}$ = 3061 (w), 3006 (w), 2976 (w), 2937 (w), 1660 (m), 1364 (m), 1210 (m), 828 (m), 763 (m), 693 (s), 523 (m).

## 5.4 Synthesis of Diels-Alder products and derivatives

### 2,2,2-Trifluoroethyl (*R*)-4-methylcyclohex-3-ene-1-carboxylate (75) [68c]




Under inert atmosphere, bis(trifluoromethanesulfonyl)imide (0.65 g, 2.70 mmol, 0.2 eq.) was dissolved in absolute toluene (12 mL) and cooled to –25 °C. A solution of oxazaborolidine **68** (0.5 M in toluene, 6.40 mL, 3.20 mmol, 0.05 eq.) was added and the mixture was stirred for 10 minutes. A solution of 2,2,2-trifluoroethyl acrylate **82** (2.03 g, 13.2 mmol, 1.0 eq.) in absolute toluene (12 mL) and isoprene **81** (0.99 g, 14.5 mmol, 1.10 eq) were added and the reaction mixture was stirred at 0 °C for eight hours. The reaction was quenched with triethylamine (0.4 mL), warmed to room temperature and the solvent was removed. The crude product was purified by column chromatography (silica gel, 3 cm × 15 cm, pentane:ether = 49:1) to obtain the product as a colorless liquid (0.89 g, 30%).

$C_{10}H_{13}F_3O_2$ (222,21 g/mol)

**TLC**: $R_f$ = 0.61 (pentane:ether = 49:1, $KMnO_4$).

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.39-5.36 (m, 1H), 4.55-4.41 (m, 2H), 2.65-2.57 (m, 1H), 2.27-2.23 (m, 2H), 2.08-1.96 (m, 3H), 1.80-1.69 (m, 1H), 1.65 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 174.5, 134.0, 123.2 (q, $^{1}J_{CF}$ = 277 Hz), 118.9, 60.3 (q, $^{2}J_{CF}$ = 36 Hz), 39.0, 29.2, 27.6, 25.4, 23.6.

**$^{19}$F-NMR** (376 MHz, $CDCl_3$): δ (ppm) = –73.9.

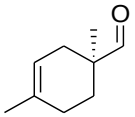
**GC-MS** (Method A, $t_R$ = 12.7 min): *m/z* (%) 222 ($M^+$, 14), 123 (13), 122 (31), 95 (59), 94 (100), 93 (16), 79 (68), 77 (17), 68 (19), 67 (29), 55 (19), 53 (10), 41 (13).

**GC** (γ-TA, 65 °C): $t_{r(major)}$ = 31.8 min, $t_{r(minor)}$ = 31.1 min, 97% *ee*.

**IR**: $\tilde{\nu}$ ($cm^{-1}$) = 2968 (w), 2932 (w), 1753 (s), 1443 (w), 1410 (w), 1277 (s), 1224 (w), 1140 (s), 1075 (w), 1053 (w), 978 (m), 650 (w).

**$[\alpha]^{20}_D$** = +62.1 (c = 0.98, $CHCl_3$).

**(*S*)-1,4-Dimethylcyclohex-3-enecarbaldehyde (77)** [68c]




In the glove box, a solution of oxazaborolidine **68** (0.5 M in toluene, 1.50 mL, 0.75 mmol, 0.05 eq.) was diluted with absolute DCM (10 mL). Outside the box, the solution was cooled to –40 °C and $AlBr_3$ (0.16 g, 0.60 mmol, 0.04 eq.) was added (weighed in the glove box). After stirring for 30 min the temperature was further decreased to –78 °C, isoprene **81** (7.56 mL, 75.0 mmol, 5.0 eq.) and methacroleine **84** (1.38 mL, 15.0 mmol, 1.0 eq.) were added and the reaction mixture was stirred at this temperature over night. The reaction was quenched with triethylamine (2.4 mL), warmed to room temperature and the solvent was removed. The crude product was purified by column chromatography (silica gel, 4 cm × 15 cm, pentane:ether = 49:1) to obtain the product as a colorless liquid (2.01 g, 97%).

$C_9H_{14}O$ (138.21 g/mol)

**TLC**: $R_f$ = 0.38 (pentane:ether = 49:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.46 (s, 1H), 5.38-5.35 (m, 1H), 2.34-2.28 (m, 1H), 1.95-1.94 (m, 2H), 1.88-1.78 (m, 2H), 1.63 (s, 3H), 1.95-1.63 (m, 1H), 1.03 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 206.3, 133.9, 118.5, 44.5, 31.9, 29.1, 27.0, 23.5, 20.8.

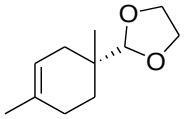
**GC-MS** (Method A, $t_R$ = 9.8 min): *m/z* (%) 138 ($M^+$, 61), 123 (45), 120 (13), 110 (18), 109 (31), 107 (13), 105 (26), 95 (82), 94 (17), 93 (19), 91 (26), 81 (40), 80 (14), 79 (35), 77 (25), 69 (11), 68 (51), 67 (100), 65 (12), 55 (30), 53 (19), 43 (38), 41 (41).

**HPLC** (ODH, *n*heptane:*i*PrOH 99:1, 1.0 mL/min, 25 °C): $t_{r(major)}$ = 3.5 min, $t_{r(minor)}$ = 4.3 min, 98% *ee*.

**IR**: $\tilde{\nu}$ ($cm^{-1}$) = 2963 (w), 2913 (m), 2838 (w), 2691 (w), 1724 (s), 1438 (w), 1376 (w), 1156 (w), 1061 (w), 910 (w), 803 (w), 765 (w).

$\mathbf{[\alpha]^{20}_D}$ = +32.6 (c = 0.98, $CHCl_3$).

**(*S*)-2-(1,4-Dimethylcyclohex-3-en-1-yl)-1,3-dioxolane (85)**



To a solution of (*S*)-1,4-dimethylcyclohex-3-enecarbaldehyde **77** (200 mg, 1.45 mmol, 1.0 eq.) in absolute toluene (5 mL) in a round bottom flask with Dean-Stark apparatus was added *p*-toluene sulfonic acid (27.6 mg, 0.15 mmol, 0.1 eq.) followed by ethylene glycol (180 mg, 2.90 mmol 2.0 eq.) and the reaction mixture was heated to reflux for 2 hours. Saturated $NaHCO_3$-solution (15 mL) was added and the phases were separated. The aqueous phase was extracted with ether (2 x 20 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 14 cm, pentane:ether = 49:1, $KMnO_4$) to obtain the pure product as a colorless liquid (100 mg, 38%).

$C_{11}H_{18}O_2$ (182.26 g/mol)

**TLC**: $R_f$ = 0.17 (pentane:ether = 49:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.31-5.29 (m, 1H), 4.58 (s, 1H) 3.93-3.85 (m, 4H), 2.10-2.03 (m, 1H), 2.02-1.88 (m, 2H), 1.74-1.67 (m, 1H), 1.64 (s, 3H), 1.58-1.51 (m, 1H), 1.48-1.41 (m, 1H), 0.88 (s, 3H).

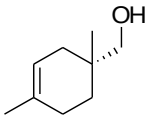
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 132.9, 119.1, 109.8, 65.4, 65.4, 35.6, 32.6, 29.2, 26.8, 23.5, 18.0.

**GC-MS** (Method B, $t_R$ = 8.8 min): *m/z* (%) 182 ($M^+$, 4), 120 (15), 113 (15), 73 (100), 45 (18).

**IR**: $\tilde{\nu}$ ($cm^{-1}$) = 2962 (w), 2910 (m), 2876 (m), 2837 (m), 1438 (w), 1392 (w), 1145 (m), 1116 (s), 1061 (m), 1038 (m), 994 (m), 806 (w).

$\mathbf{[\alpha]^{20}_D}$ = −13.8 (c = 1.19, $CHCl_3$).

**(*S*)-(1,4-Dimethylcyclohex-3-en-1-yl)methanol (86)**




Sodium borohydride (0.41 g, 10.9 mmol, 1.5 eq.) was added slowly to a solution of (*S*)-1,4-dimethylcyclohex-3-enecarbaldehyde **77** (1.00 g, 7.24 mmol, 1.0 eq.) in methanol (50 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 60 minutes. Then, 2 M HCl-solution (20 mL) was added and stirred for a few minutes. The aqueous phase was extracted with ether (4 x 40 mL). The combined organic phases were washed with saturated $NaHCO_3$-solution (40 mL) and water (40 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 13 cm, pentane:ether = 4:1, $KMnO_4$) to obtain the alcohol as a yellow liquid (0.88 g, 87%).

$C_9H_{16}O$ (140.23 g/mol)

**TLC**: $R_f$ = 0.34 (cyclohexane:EtOAc = 4:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.31-5.29 (m, 1H), 3.38 (d, $^2J_{HH}$ = 20.0 Hz, 1H), 3.36 (d, $^2J_{HH}$ = 20.0 Hz, 1H), 1.94-1.87 (m, 3H), 1.72-1.66 (m, 1H), 1.65 (s, 3H), 1.54-1.47 (m, 1H), 1.42-1.37 (m, 1H), 1.31 (brs, 1H), 0.91 (s, 3H).

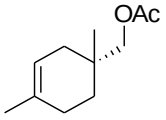
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 133.1, 119.4, 71.6, 34.3, 33.5, 30.7, 27.3, 23.5, 22.4.

**GC-MS** (Method B, $t_R$ = 5.4 min): *m/z* (%) 140 ($M^+$, 30), 122 (27), 109 (86), 107 (55), 94 (34), 93 (100), 91 (31), 81 (22), 79 (41), 77 (22), 68 (38), 67 (84), 55 (19), 53 (15), 43 (21), 41 (31).

**IR**: $\tilde{\nu}$ ($cm^{-1}$) = 3319 (w), 2960 (m), 2909 (s), 2871 (m), 2835 (w), 1437 (m), 1376 (m), 1155 (w), 1031 (s), 803 (w).

**$[\alpha]^{20}_D$** = –7.5 (c = 0.92, $CHCl_3$).

**(*S*)-(1,4-Dimethylcyclohex-3-en-1-yl)methyl acetate (87)**




Acetic anhydride (68.8 mg, 0.67 mmol, 1.05 eq.) was added to a solution of (*S*)-(1,4-dimethylcyclohex-3-en-1-yl)methanol **86** (90 mg, 0.64 mmol 1.0 eq.) in pyridine (0.5 mL) in a round bottom flask at 0 °C. After addition the mixture was stirred for 72 hours at room temperature. The reaction mixture was concentrated and the crude product was purified by column

chromatography (silica gel, 2 cm × 15 cm, *n*-hexane:EtOAc = 9:1) to obtain the product as a colorless liquid (95.0 mg, 81%).

$C_{11}H_{18}O_2$ (182.26 g/mol)

**TLC**: $R_f$ = 0.61 (cyclohexane:EtOAc = 9:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.29-5.27 (m, 1H), 3.85 (d, $^2J_{HH}$ = 19.4 Hz, 1H), 3.82 (d, $^2J_{HH}$ = 19.4 Hz, 1H), 2.06 (s, 3H), 1.94-1.89 (m, 3H), 1.75-1.70 (m, 1H), 1.64 (s, 3H), 1.56-1.49 (m, 1H), 1.43-1.36 (m, 1H), 0.92 (s, 3H).

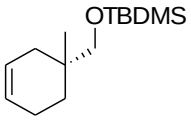
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 171.6, 133.0, 119.0, 72.1, 34.5, 32.0, 31.0, 27.1, 23.5, 22.8, 21.1.

**GC-MS** (Method B, $t_R$ = 7.6 min): *m/z* (%) 123 ([$M^+$–59], 6), 122 (53), 109 (16), 107 (71), 94 (66), 93 (100), 91 (24), 81 (14), 79 (36), 77 (14), 68 (17), 67 (33), 55 (10), 43 (58), 41 (17).

**IR**: $\tilde{\nu}$ = 2961 (w), 2912 (w), 2882 (w), 2838 (w), 1739 (s), 1438 (w), 1373 (m), 1240 (s), 1036 (m).

**$[\alpha]^{20}_D$** = –8.3 (c = 0.61, $CHCl_3$).

**(*S*)-*tert*-Butyl((1,4-dimethylcyclohex-3-en-1-yl)methoxy)dimethylsilane (88)**




In a round bottom flask (*S*)-(1,4-dimethylcyclohex-3-en-1-yl)methanol **86** (120 mg, 0.86 mmol, 1.0 eq.), *N*-methylimidazole (211 mg, 2.57 mmol, 3.0 eq.) and iodine (217 mg, 0.86 mmol, 1.0 eq.) were dissolved in absolute THF (3 mL). *tert*-Butyldimethylsilyl chloride (141 mg, 0.94 mmol, 1.1 eq.) was added and the reaction mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated and the residue redissolved in EtOAc (10 mL) and washed with concentrated sodium thiosulfate-solution (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 2 cm × 16 cm, cyclohexane:EtOAc = 4:1, $KMnO_4$) to obtain the product as a colorless liquid (187 mg, 86%).

$C_{15}H_{30}OSi$ (254.49 g/mol)

**TLC**: $R_f$ = 0.82 (cyclohexane, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.30-5.29 (m, 1H), 3.28 (d, $^2J_{HH}$ = 26.8 Hz, 1H), 3.26 (d, $^2J_{HH}$ = 26.8 Hz, 1H), 1.91-1.87 (m, 3H), 1.64 (s, 3H), 1.65-1.59 (m, 1H), 1.53-1.47 (m, 1H), 1.34-1.26 (m, 1H), 0.89 (s, 9H), 0.85 (s, 3H), 0.02 (s, 6H).

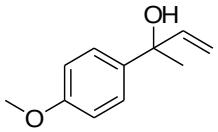
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 132.9, 119.8, 71.3, 34.4, 33.7, 30.7, 27.4, 26.1, 23.6, 22.5, 18.5, 5.3.

**GC-MS** (Method B, $t_R$ = 10.6 min): *m/z* (%) 239 ([$M^+$–15], 2), 198 (10), 197 (59), 122 (65), 121 (94), 107 (27), 94 (42), 93 (62), 91 (10), 89 (30), 81 (12), 79 (12), 77 (10), 75 (100), 73 (28),

**IR**: $\tilde{\nu}$ = 2953 (m), 2927 (m), 2883 (m), 2855 (m), 1471 (w), 1448 (w), 1252 (m), 1093 (s), 1006 (w), 837 (s), 775 (m), 666 (w).

**$[\alpha]^{20}_D$** = –9.0 (c = 1.02, $CHCl_3$).

**2-(4-Methoxyphenyl)but-3-en-2-ol (93b)**




Under inert atmosphere a solution of 4-methoxyacetophenone **89b** (1.00 g, 6.68 mmol, 1.0 eq.) in absolute THF (2 mL) was added to a solution of vinylmagnesium bromide in THF (1 M, 8.0 mL, 8.00 mmol, 1.2 eq.) via a dropping funnel and the mixture was stirred for one hour under reflux. Saturated ammonium chloride-solution (5 mL) was added and the aqueous phase was extracted with THF (2 x 15 mL). The combined organic layers were dried over sodium sulfate and concentrated. The crude product was obtained as a yellow liquid (1.09 g, 92%) and was used without further purification.

$C_{11}H_{14}O_2$ (178.23 g/mol)

**TLC**: $R_f$ = 0.24 (cyclohexane:EtOAc = 9:1, $KMnO_4$).

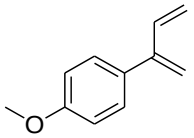
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.41-7.37 (m, 2H), 6.89-6.86 (m, 2H), 6.16 (dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 10.6 Hz, 1H), 5.29 (dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HH}$ = 1.1 Hz, 1H), 5.13 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 1.1 Hz, 1H), 3.80 (s, 3H), 1.85 (brs, 1H), 1.64 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 158.7, 145.2, 138.7, 126.6, 113.7, 112.2, 74.6, 55.4, 29.4.

**GC-MS** (Method B, $t_R$ = 10.7 min): *m/z* (%) 178 ($M^+$, 33), 163 (47), 151 (10), 145 (13), 135 (22), 121 (100), 108 (22), 91 (12), 77 (15), 55 (50), 43 (55).

**IR**: $\tilde{\nu}$ = 3381 (w), 2976 (w), 2932 (w), 2835 (w), 1609 (m), 1510 (s), 1463 (w), 1413 (w), 1367 (w), 1300 (m), 1248 (s), 1177 (s), 1103 (w), 1032 (s), 921 (m), 832 (s).

**1-(Buta-1,3-dien-2-yl)-4-methoxybenzene (90b)**



In a round bottom flask, 2-(4-methoxyphenyl)but-3-en-2-ol **93b** (551 mg, 3.09 mmol, 1.0 eq.), aniline hydrobromide (48.0 mg, 0.28 mmol, 0.09 eq.) and hydroquinone (6.90 mg, 0.06 mmol, 0.02 eq.) were dissolved in THF (5 mL) and stirred under reflux for two hours.

The reaction mixture was concentrated and purified by column chromatography (silica gel, 2 cm × 13 cm, cyclohexane) to obtain the product as a colorless liquid (190 mg, 38%).

$C_{11}H_{12}O$ (160,22 g/mol)

**TLC**: $R_f$ = 0.41 (cyclohexane, UV).

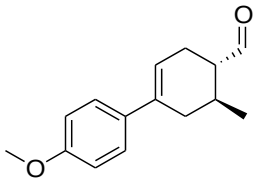
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.28 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 6.90 (d, $^3J_{HH}$ = 8.6 Hz, 2H), 6.63 (dd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 7.1 Hz, 1H), 5.25-5.18 (m, 4H), 3.83 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 159.2, 147.8, 138.5, 132.3, 129.5, 117.1, 116.1, 113.7, 55.4.

**GC-MS** (Method B, $t_R$ = 8.1 min): *m/z* (%) 161, (11), 160 ($M^+$, 100), 159 (43), 145 (41), 144 (30), 132 (12), 129 (47), 128 (25), 127 (15), 121 (13), 177 (44), 116 (16), 115 (52), 91 (24), 89 (16), 77 (10), 65 (10), 63 (13), 51 (10).

**IR**: $\tilde{\nu}$ = 3089 (w), 3003 (w), 2955 (w), 2835 (w), 1609 (m), 1509 (s), 1285 (m), 1242 (s), 1176 (m), 1032 (m), 892 (m), 833 (s), 802 (m).

**(3*S*,4*S*)-4'-Methoxy-3-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbaldehyde (102)**



To a solution of 1-(buta-1,3-dien-2-yl)-4-methoxybenzene **90b** (150 mg, 0.94 mmol, 1.0 eq.) in 1.0 mL acetonitrile/water (95/5 v/v) was added (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride **91** (47.7 mg, 0.187 mmol, 0.2 eq.) at 0 °C followed by the addition of *trans*-crotonaldehyde **92** (203 mg, 2.90 mmol, 3.1 eq.). The reaction mixture was stirred at 0 °C for 24 hours and then placed directly onto a silica gel column (2 cm × 15 cm, pentane:EtOAc = 19:1). The product was obtained as a yellow liquid (120 mg, 56%).

$C_{15}H_{18}O_2$ (230.31 mg/mol)

**TLC**: $R_f$ = 0.22 (pentane:EtOAc = 19:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.70 (d, $^3J_{HH}$ = 3.1 Hz, 1H), 7.32-7.29 (m, 2H), 6.87-6.84 (m, 2H), 6.02-5.99 (m, 1H), 3.81 (s, 3H), 2.62-2.09 (m, 6H), 1.13 (d, $^3J_{HH}$ = 6.3 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 205.2, 158.9, 135.6, 134.3, 126.2, 119.6, 113.8, 55.5, 52.4, 34.7, 28.9, 24.9, 19.9.

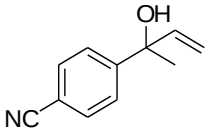
**GC-MS** (Method B, $t_R$ = 20.4 min): *m/z* (%) 230 ($M^+$, 94), 202 (100), 199 (73), 187 (37), 185 (50), 184 (22), 173 (88), 160 (31), 159 (48), 148 (29), 145 (33), 144 (20), 129 (34), 128 (32), 121 (67), 117 (20), 115 (46), 91 (34), 77 (31).

**HPLC** (ODH, *n*heptane:*i*PrOH 94:6, 1.0 mL/min, 25 °C): $t_{r(major)}$ = 17.3 min, $t_{r(minor)}$ = 20.2 min, 89% *ee*, determined for the corresponding alcohol.

**IR**: ṽ = 2955 (w), 2905 (w), 2834 (w), 1720 (s), 1607 (m), 1512 (s), 1461 (w), 1372 (w), 1249 (s), 1180 (m), 1035 (m), 831 (w).

**$[\alpha]^{20}_D$** = +34.2 (c = 1.00, $CHCl_3$).

**4-(2-Hydroxybut-3-en-2-yl)benzonitrile (93c)**




Under inert atmosphere a solution of 4-cyanoacetophenone **89c** (1.94 g, 13.3 mmol, 1.0 eq.) in absolute THF (4 mL) was added to a solution of vinylmagnesiumbromide in THF (1 M, 16.0 mL, 16.0 mmol, 1.2 eq.) via a dropping funnel and the mixture was stirred for one hour under reflux. Saturated ammonium chloride-solution (10 mL) was added and the aqueous phase was extracted with THF (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 4 cm × 15 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a yellow liquid (1.45 g, 63%).

$C_{11}H_{11}NO$ (173.21 g/mol)

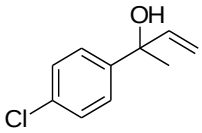
**TLC**: $R_f$ = 0.35 (cyclohexane:EtOAc = 4:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.64-7.61 (m, 2H), 7.59-7.57 (m, 2H), 6.12 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.6 Hz, 1H), 5.31 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 0.7 Hz, 1H), 5.21 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 0.7 Hz, 1H), 1.98 (brs, 1H), 1.65 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 152.1, 144.1, 132.5, 126.5, 119.3, 114.1, 111.2, 75.1, 29.8

**GC-MS** (Method B, $t_R$ = 12.2 min): *m/z* (%) 173 ($M^+$, 8), 158 (51), 146 (13), 140 (14), 131 (46), 130 (45), 116 (10), 103 (14), 102 (15), 55 (22), 43 (100).

**IR**: $\tilde{\nu}$ = 3425 (w), 2980 (w), 2931 (w), 2229 (s), 1687 (w), 1606 (m), 1501 (w), 1402 (m), 1362 (w), 1262 (w), 1067 (m), 927 (s), 840 (s), 570 (m).




**2-(4-Chlorophenyl)but-3-en-2-ol (93d)**

Under inert atmosphere a solution of 4-chloroacetophenone **89d** (2.01 g, 13.0 mmol, 1.0 eq.) in absolute THF (10 mL) was added to a solution of vinylmagnesiumbromide in THF (1 M, 15.6 mL, 15.6 mmol, 1.2 eq.) via a dropping funnel. The mixture was stirred for one hour under reflux. Saturated ammonium chloride-solution (10 mL) was added and the aqueous phase was extracted with THF (2 x 25 mL). The combined organic layers were dried over sodium sulfate and

concentrated. The crude product was purified by column chromatography (silica gel, 4 cm × 14 cm, cyclohexane:EtOAc = 19:1) to obtain the product as a yellow liquid (2.30 g, 97%).

$C_{10}H_{11}ClO$ (182.65 g/mol)

**TLC**: $R_f$ = 0.53 (cyclohexane:EtOAc = 9:1, UV).

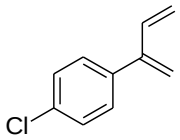
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.42-7.38 (m, 2H), 7.32-7.28 (m, 2H), 6.13 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.6 Hz, 1H), 5.29 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 0.9 Hz, 1H), 5.16 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 0.9 Hz, 1H), 1.94 (brs, 1H), 1.63 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 145.1, 144.6, 132.9, 128.4, 126.9, 113.0, 74.6, 29.5.

**GC-MS** (Method B, $t_R$ = 9.5 min): *m/z* (%) 182 ($M^+$, 17), 169 (13), 147 (41), 147 (34), 139 (24), 132 (12), 129 (11), 127 (11), 125 (23), 103 (19), 77 (14), 75 (13), 55 (38), 51 (10), 43 (100).

**IR**: ṽ = 3362 (w), 2977 (w), 2930 (w), 1590 (w), 1489 (m), 1400 (m), 1368 (m), 1217 (w), 1176 (w), 1094 (s), 1013 (s), 924 (m), 829 (m).

**1-(Buta-1,3-dien-2-yl)-4-chlorobenzene (90d)**




In a round bottom flask, 2-(4-chlorophenyl)but-3-en-2-ol **93d** (1.40 g, 7.66 mmol, 1.0 eq.), aniline hydrobromide (0.12 g, 0.69 mmol, 0.09 eq.) and hydroquinone (0.02 g, 0.15 mmol, 0.02 eq.) were heated at 100 to 150 °C for 3 hours while continuously distilling. The distillate was purified by column chromatography (silica gel, 2 cm × 14 cm, cyclohexane) to obtain the product as a colorless liquid (0.15 g, 12%).

$C_{10}H_9Cl$ (164.63 g/mol)

**TLC**: $R_f$ = 0.67 (cyclohexane, UV).

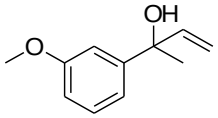
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.32-7.28 (m, 2H), 7.24-7.21 (m, 2H), 6.58 (ddd, $^2J_{HH}$ = 17.4 Hz, $^3J_{HH}$ = 10.7 Hz, $^3J_{HH}$ = 0.7 Hz, 1H), 5.29-5.28 (m, 1H), 5.22-5.19 (m, 1H) 5.17-5.16 (m, 1H), 5.15-5.11 (m, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 147.3, 138.3, 138.0, 133.5, 129.8, 128.5, 117.5, 117.4.

**GC-MS** (Method B, $t_R$ = 6.7 min): *m/z* (%) 164 ($M^+$, 14), 130 (10), 129 (100), 128 (52), 127 (26), 51 (11).

**IR**: $\tilde{\nu}$ = 2914 (w), 2878 (w), 1638 (w), 1490 (m), 1090 (m), 1012 (m), 916 (m), 829 (s), 806 (s), 528 (m).

**2-(3-Methoxyphenyl)but-3-en-2-ol (93e)**




Under inert atmosphere a solution of 3-methoxyacetophenone **89e** (1.03 g, 6.66 mmol, 1.0 eq.) in absolute THF (4 mL) was added to a solution of vinylmagnesiumbromide in absolute THF (1 M, 8.0 mL, 8.0 mmol, 1.2 eq.) via a dropping funnel. The mixture was stirred for two hours under reflux. After cooling to room temperature, saturated ammonium chloride-solution (5 mL) was added and the aqueous phase was extracted with THF (2 x 15 mL). The combined organic layers were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 14 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a yellow liquid (0.97 g, 82%).

$C_{11}H_{14}O_2$ (178.23 g/mol)

**TLC**: $R_f$ = 0.24 (cyclohexane:EtOAc = 9:1, UV).

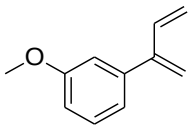
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.26 (dd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 7.7 Hz, 1H), 7.06-6.87 (m, 2H), 6.20-6.13 (m, 1H), 6.17 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.6 Hz, 1H), 5.31 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 1.0 Hz, 1H), 5.15 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 1.0 Hz, 1H), 3.82 (s, 3H), 1.86 (brs, 1H), 1.65 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 159.7, 148.4, 144.8, 129.4, 117.7, 112.5, 112.4, 111.3, 74.9, 55.4, 29.5.

**GC-MS** (Method B, $t_R$ = 10.3 min): *m/z* (%) 178 ($M^+$, 26), 163 (20), 136 (10), 135 (100), 105 (12), 91 (10), 77 (13), 55 (55), 43 (57).

**IR**: $\tilde{\nu}$ = 3396 (w), 3083 (w), 2976 (w), 2936 (w), 2834 (w), 1599 (m), 1485 (m), 1431 (m), 1318 (m), 1287 (s), 1045 (s), 924 (m), 784 (m), 699 (m).

**1-(Buta-1,3-dien-2-yl)-3-methoxybenzene (90e)**



In a round bottom flask 2-(3-methoxyphenyl)but-3-en-2-ol **93e** (970 mg, 5.33 mmol, 1.0 eq.), aniline hydrobromide (82.5 mg, 0.48 mmol, 0.09 eq.) and hydroquinone (11.9 mg, 0.11 mmol, 0.02 eq.) were dissolved in THF (10 mL) and stirred at 130 °C for 15 hours. The reaction mixture was concentrated and purified by column chromatography (silica gel, 2 cm × 13 cm, cyclohexane) to obtain the product as a colorless liquid (120 mg, 14%).

$C_{11}H_{12}O$ (160.22 g/mol)

**TLC**: $R_f$ = 0.30 (cyclohexane, UV).

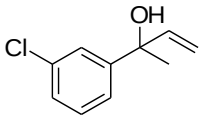
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.29-7.24 (m, 1H), 6.93-6.91 (m, 1H), 6.88-6.85 (m, 2H), 6.64-6.57 (m, 1H), 5.30-5.29 (m, 1H), 5.25-5.23 (m, 1H), 5.22-5.21 (m, 2H), 3.82 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 159.5, 148.2, 141.3, 138.1, 129.2, 120.9, 117.4, 117.0, 114.1, 113.1, 55.4.

**GC-MS** (Method B, $t_R$ = 7.7 min): *m/z* (%) 161 (12), 160 ($M^+$, 100), 159 (53), 145 (30), 144 (33), 130 (10), 129 (78), 128 (37), 127 (22), 117 (25), 116 (17), 115 (54), 102 (12), 91 (22), 89 (11), 77 (10).

**IR**: $\tilde{\nu}$ = 3086 (w), 3000 (w), 2935 (w), 2833 (w), 1575 (s), 1485 (m), 1429 (m), 1321 (m), 1283 (m), 1228 (s), 1049 (s), 901 (m), 784 (m), 715 (m).

**2-(3-Chlorophenyl)but-3-en-2-ol (93f)**



Under inert atmosphere a solution of 3-chloroacetophenone **89f** (515 mg, 3.33 mmol, 1.0 eq.) in absolute THF (2 mL) was added to a solution of vinylmagnesiumbromide in THF (1 M, 4.0 mL, 4.00 mmol, 1.2 eq.) via a dropping funnel and the mixture was stirred for two hours under reflux. Saturated ammonium chloride-solution (5 mL) was added and the aqueous phase was extracted with THF (2 x 15 mL). The combined organic layers were dried over sodium sulfate and concentrated.

The crude product was separated by column chromatography (silica gel, 3 cm × 13 cm, cyclohexane:EtOAc = 19:1) to obtain the product as a pale yellow liquid (330 mg, 54%).

$C_{10}H_{11}ClO$ (182.65 g/mol)

**TLC**: $R_f$ = 0.53 (cyclohexane:EtOAc = 9:1, UV).

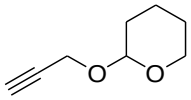
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.47-7.46 (m, 1H), 7.34-7.31 (m, 1H), 7.28-7.24 (m, 1H), 7.23-7.20 (m, 1H), 6.13 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 10.6 Hz, 1H), 5.30 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HH}$ = 0.9 Hz, 1H), 5.17 (dd, $^3J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 0.9 Hz, 1H), 1.91 (brs, 1H), 1.63 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 148.7, 144.3, 134.3, 129.6, 127.2, 125.7, 123.6, 113.2, 74.6, 29.5.

**GC-MS** (Method B, $t_R$ = 9.4 min): *m/z* (%) 182 ($M^+$, 18), 167 (31), 147 (23), 141 (13), 139 (38), 132 (10), 103 (19), 77 (14), 75 (11), 55 (38), 51 (12), 43 (100).

**IR**: ṽ = 3357 (w), 3068 (w), 2980 (w), 2930 (w), 1595 (m), 1474 (m), 1416 (s), 1368 (m), 1214 (m), 1122 (m), 1068 (m), 996 (m), 926 (s), 893 (m), 787 (s), 766 (s), 708 (m).

**2-(Prop-2-yn-1-yloxy)tetrahydro-2H-pyran (99)**




In round bottom flask, a solution of propargyl alcohol **98** (2.10 g, 37.8 mmol, 1.0 eq.), dihydropyrane (5.01 g, 60.0 mmol, 1.6 eq.) and *p*-toluenesulfonic acid (0.95 g, 5.00 mmol, 0.13 eq.) were dissolved in ether (75 mL) and stirred for three hours at room temperature. The reaction mixture was washed with saturated $NaHCO_3$-solution (50 mL) and the phases were separated. The aqueous phase was extracted with ether (2 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried over sodium sulfate and concentrated. The crude product was separated by column chromatography (silica gel, 4 cm × 15 cm, cyclohexane: EtOAc = 49:1) to obtain the product as a colorless liquid (4.37 g, 83%).

$C_8H_{12}O_2$ (140.18 g/mol)

**TLC**: $R_f$ = 0.46 (cyclohexane:EtOAc = 19:1, $KMnO_4$).

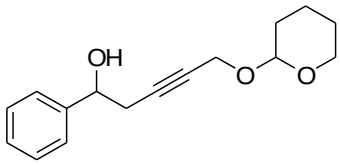
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.82 (t, $^3J_{HH}$ = 3.3 Hz, 1H), 4.32-4.21 (m, 2H), 3.86-3.81 (m, 1H), 3.55-3.52 (m, 1H), 2.41 (t, $^4J_{HH}$ = 2.4 Hz, 1H), 1.84-1.71 (m, 2H), 1.66-1.52 (m, 4H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 97.0, 79.9, 74.1, 62.1, 54.1, 30.4, 25.5, 19.1.

**GC-MS** (Method C, $t_R$ = 5.1 min): *m/z* (%) 139 ([$M^+$−1], 8), 85 (100), 83 (10), 82 (12), 67 (10), 57 (24), 56 (46), 55 (29), 53 (11), 43 (15), 41 (50).

**IR**: $\tilde{\nu}$ = 3288 (w), 2942 (m), 2869 (w), 1441 (w), 1345 (w), 1323 (w), 1264 (m), 1119 (s), 1026 (s), 901 (m), 663 (w).

**1-Phenyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-3-yn-1-ol (101)** [77]




In a 100 mL round bottom flask at −78 °C, *n*-butyllithium (1.6 mol/L in hexanes, 11.0 mL, 17.6 mmol, 1.5 eq.) was slowly added to a solution of 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran **99** (2.46 g, 17.6 mmol, 1.5 eq.) in absolute THF (50 mL) and the reaction mixture was stirred for 30 min. A solution of styrene oxide **100** (1.41 g, 11.7 mmol, 1.0 eq.) in absolute THF (10 mL) was slowly added followed by boron trifluoride diethyl etherate (2.49 g, 17.6 mmol, 1.5 eq.) and the mixture was stirred for 18 hours at room temperature. The reaction was quenched with saturated ammonium chloride-solution (50 mL). The phases were separated and the aqueous phase extracted with ether (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 15 cm, cyclohexane:EtOAc = 6:1) to obtain the product as a colorless liquid (0.48 g, 16%).

$C_{16}H_{20}O_3$ (260.33 g/mol)

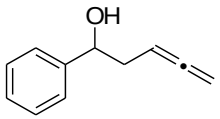
**TLC**: $R_f$ = 0.23 (petroleum ether:EtOAc = 4:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.40-7.26 (m, 5H), 4.89-4.85 (m, 1H), 4.75 (t, $^3J_{HH}$ = 3.5 Hz, 1H), 4.32-4.19 (m, 2H), 3.87-3.80 (m, 1H), 3.54-3.49 (m, 1H), 2.69-2.67 (m, 2H), 2.50 (dd, $^3J_{HH}$ = 3.5 Hz, $^3J_{HH}$ = 11.0 Hz, 1H), 1.86-1.78 (m, 1H), 1.75-1.68 (m, 1H), 1.64-1.49 (m, 4H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 142.8, 128.6, 128.0, 125.9, 97.1, 82.8, 79.0, 72.6, 62.2, 54.8, 30.5, 30.2, 25.5, 19.3.

**IR**: $\tilde{\nu}$ = 3359 (w), 2939 (w), 2868 (w), 1453 (w), 1345 (w), 1201 (w), 1116 (m), 1021 (s), 902 (w), 753 (w), 701 (m).

**1-Phenylpenta-3,4-dien-1-ol (94)** [77]




Under inert atmosphere a solution of 1-phenyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-3-yn-1-ol **101** (1.10 g, 4.23 mmol, 1.0 eq.) in absolute ether (2 mL) was added to a slurry of lithium aluminium hydride (0.18 g, 4.65 mmol, 1.1 eq.) in absolute ether (10 mL) a round bottom flask and stirred under reflux for 4.5 hours. The reaction mixture was quenched with a small amount of water and filtrated. The solid was washed with ether (3 x 10 mL) and the filtrate was dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 15 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a colorless liquid (0.05 g, 7%).

$C_{11}H_{12}O$ (160.22 g/mol)

**TLC**: $R_f$ = 0.24 (cyclohexane:EtOAc = 9:1, $KMnO_4$).

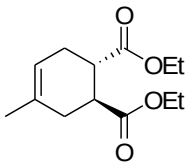
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.38-7.33 (m, 4H), 7.32-7.27 (m, 1H), 5.15-5.08 (m, 1H), 4.78-4.75 (m, 1H), 4.73-4.70 (m, 2H), 2.49-2.44 (m, 2H), 2.24 (d, $^3J_{HH}$ = 44.1 Hz, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 209.6, 143.8, 128.6, 127.7, 126.0, 86.3, 75.2, 73.8, 38.6.

**GC-MS** (Method B, $t_R$ = 10.0 min): *m/z* (%) 142 ([$M^+$–18], 6), 118 (10), 107 (100), 105 (18), 79 (93), 77 (49), 54 (11), 51 (16).

**IR**: $\tilde{\nu}$ = 3351 (w), 3061 (w), 2917 (w), 2871 (w), 1955 (m), 1453 (m), 1054 (m), 1026 (m), 844 (m), 758 (m), 700 (s).

**Diethyl (1*R*,2*R*)-4-methylcyclohex-4-ene-1,2-dicarboxylate (103)** [68c]




In the glove box a solution of oxazaborolidine **68** (0.5 M in toluene, 0.38 mL, 0.19 mmol, 0.05 eq.) was weighed in a Schlenk tube. Outside the glove box, aluminium bromide (40.0 mg, 0.15 mmol, 0.04 eq.) was added to the solution at −40 °C and stirred for 30 min. Then, the temperature was increased to −20 °C and isoprene **81** (1.13 mL, 11.3 mmol, 3.0 eq.) and diethyl fumarate **106** (0.62 mL, 3.75 mmol, 1.0 eq.) were added and the reaction mixture was stirred at this temperature for 72 hours, then 48 hours at room temperature.

The reaction was quenched with triethylamine (0.6 mL) and the solvent was removed. The crude product was purified by column chromatography (silica gel, 3 cm × 15 cm, cyclohexane:EtOAc = 99:1) to obtain the product as a colorless liquid (480 mg, 53%).

$C_{13}H_{20}O_4$ (240.30 g/mol)

**TLC**: $R_f$ = 0.18 (cyclohexane:EtOAc = 19:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.38-5.37 (m, 1H), 4.21-4.08 (m, 4H), 2.90-2.83 (m, 1H), 2.80-2.73 (m, 1H), 2.42-2.36 (m, 1H), 2.30-2.24 (m, 1H), 2.18-2.08 (m, 2H), 1.67 (s, 3H), 1.27-1.22 (m, 6H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 175.2, 175.0, 132.4, 119.2, 60.7, 60.7, 42.0, 41.4, 32.8, 28.3, 23.2, 14.3.

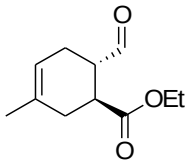
**GC-MS** (Method B, $t_R$ = 13.5 min): *m/z* (%) 195 ([$M^+$–45], 17), 194 (14), 166 (32), 94 (11), 93 (100), 92 (32), 91 (13), 79 (11), 77 (14).

**HPLC** (OJ, *n*heptane:*i*PrOH 99:1, 1.0 mL/min, 25 °C): $t_{r(major)}$ = 8.4 min, $t_{r(minor)}$ = 9.2 min, 96% *ee*.

**IR**: $\tilde{\nu}$ = 2979 (w), 2933 (w), 2846 (w), 1731 (s), 1445 (w), 1372 (w), 1308 (m), 1253 (m), 1180 (m), 1158 (m), 1035 (m).

**$[\alpha]^{20}_D$** = +95.8 (c = 1.03, $CHCl_3$).

**Ethyl (1*S*,6*S*)-6-formyl-3-methylcyclohex-3-ene-1-carboxylate (104)** [69c]




At 0 °C isoprene **81** (1.61 g, 23.4 mmol, 3.0 eq.) was added to a mixture of (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)pyrrolidinium perchlorate **109** (0.27 g, 0.39 mmol, 0.05 eq.) and ethyl (*Z*)-4-oxobut-2-enoate **108** (1.00 g, 7.80 mmol, 1.0 eq.) in water (4 mL) and was stirred at 0 °C for 18 hours. Saturated $NaHCO_3$-solution (10 mL) and EtOAc (15 mL) were added. The aqueous phase was extracted with EtOAc (2 x 15 mL), the combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 19 cm, cyclohexane:EtOAc = 19:1) to obtain the product as a colorless liquid (0.86 g, 56%).

$C_{11}H_{16}O_3$ (196.25 g/mol)

**TLC**: $R_f$ = 0.42 (cyclohexane:EtOAc = 19:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.71 (d, $^3J_{HH}$ = 1.1 Hz, 1H), 5.42-5.39 (m, 1H), 4.16 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 2.95-2.75 (m, 2H), 2.36-2.06 (m, 4H), 1.67 (s, 3H), 1.26 (t, $^3J_{HH}$ = 7.2 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 202.9, 174.6, 133.1, 118.4, 61.0, 47.4, 39.9, 31.6, 24.3, 23.3, 14.3.

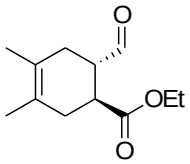
**GC-MS** (Method B, $t_R$ = 10.6 min): *m/z* (%) 196 ($M^+$, 2), 151 (18), 150 (30), 122 (20), 107 (25), 106 (15), 105 (64), 95 (23), 94 (20), 93 (100), 91 (29), 79 (24), 77 (28), 67 (12), 55 (10), 41 (11).

**HPLC** (ADH, *n*heptane:*i*PrOH 99:1, 1.0 mL/min, 25 °C): $t_{r(major)}$ = 19.5 min, $t_{r(minor)}$ = 22.6 min, 93% *ee*.

**IR**: $\tilde{\nu}$ = 2966 (w), 2915 (w), 2847 (w), 2720 (w), 1725 (s), 1444 (w), 1376 (w), 1280 (m), 1179 (m), 1032 (m).

**$[\alpha]^{20}_D$** = +24.5 (c = 0.95, $CHCl_3$).

**Ethyl (1*S*,6*S*)-6-formyl-3,4-dimethylcyclohex-3-ene-1-carboxylate (105)** [69c]




At 4 °C 2,3-dimethyl-1,3-butadiene **107** (0.94 g, 11.5 mmol, 2.3 eq.) was added to a mixture of bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)pyrrolidinium perchlorate **109** (0.17 g, 0.25 mmol, 0.05 eq.) and ethyl (*Z*)-4-oxobut-2-enoate **108** (0.64 g, 5.00 mmol, 1.0 eq.) in water (2.5 mL) and was stirred at this temperature for 20 hours. Saturated $NaHCO_3$-solution (10 mL) and EtOAc (15 mL) were added. The aqueous phase was extracted with EtOAc (2 x 15 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 22 cm, cyclohexane:EtOAc = 19:1) to obtain the product as a yellow liquid (0.53 g, 50%).

$C_{12}H_{18}O_3$ (210.27 g/mol)

**TLC**: $R_f$ = 0.45 (cyclohexane:EtOAc = 19:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.70 (d, $^3J_{HH}$ = 1.4 Hz, 1H), 4.16 (q, $^3J_{HH}$ = 7.2 Hz, 2H), 2.91-2.84 (m, 1H), 2.84-2.78 (m, 1H), 2.25-2.18 (m, 3H), 2.10-2.03 (m, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 1.26 (t, $^3J_{HH}$ = 7.2 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 202.8, 174.7, 124.7, 123.4, 60.9, 48.4, 40.2, 33.3, 30.4, 19.0, 18.9, 14.3.

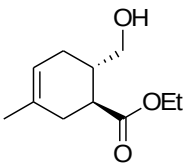
**GC-MS** (Method B, $t_R$ = 12.4 min): *m/z* (%) 210 ($M^+$, 5), 165 (11), 164 (22), 136 (26), 121 (24), 120 (11), 119 (59), 109 (11), 108 (20), 107 (100), 105 (14), 93 (23), 91 (34), 79 (13), 77 (13), 67 (10), 41 (14).

**HPLC** (ADH, *n*heptane:*i*PrOH 99:1, 1.0 mL/min, 25 °C): $t_{r(major)}$ = 17.5 min, $t_{r(minor)}$ = 20.8 min, 85% *ee*.

**IR**: $\tilde{\nu}$ = 2981 (w), 2910 (w), 2838 (w), 2719 (w), 1725 (s), 1442 (w), 1374 (w), 1309 (w), 1217 (m), 1180 (m), 1032 (m).

**$[\alpha]^{20}_D$** = +38.5 (c = 1.06, $CHCl_3$).

**Ethyl (1*S*,6*S*)-6-(hydroxymethyl)-3-methylcyclohex-3-ene-1-carboxylate (110)**




Sodium borohydride (38.5 mg, 1.02 mmol, 1.0 eq.) was added slowly to a solution of ethyl (1*S*,6*S*)-6-formyl-3-methylcyclohex-3-ene-1-carboxylate **104** (200 mg, 1.02 mmol, 1.0 eq.) in methanol (8 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 2.5 hours. Then, 2 M HCl-solution (10 mL) was added and stirred for a few minutes. It was extracted with ether (4 x 10 mL). The combined organic phases were washed with saturated $NaHCO_3$-solution (10 mL) and water (10 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 16 cm, cyclohexane:EtOAc = 4:1) to obtain the alcohol as a colorless liquid (130 mg, 64%).

$C_{11}H_{18}O_3$ (198.26 g/mol)

**TLC**: $R_f$ = 0.21 (cyclohexane:EtOAc = 4:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.38-5.37 (m, 1H), 4.17 (qd, $^3J_{HH}$ = 7.2 Hz, $^5J_{HH}$ = 0.9 Hz, 2H), 3.61-3.58 (m, 2H), 2.55-2.49 (m, 1H), 2.34-2.26 (m, 1H), 2.14-2.08 (m, 2H), 2.02-1.90 (m, 2H), 1.70 (t, $^3J_{HH}$ = 6.2 Hz, 1H) 1.67 (s, 3H), 1.28 (t, $^3J_{HH}$ = 7.2 Hz, 3H).

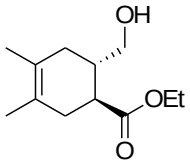
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 176.2, 132.0, 119.9, 65.7, 60.7, 42.8, 38.3, 32.8, 27.9, 23.3, 14.4.

**GC-MS** (Method B, $t_R$ = 12.0 min): *m/z* (%) 180 ($M^+$–18, 14), 152 (10), 107 (100), 106 (47), 105 (13), 93 (34), 91 (40), 80 (10), 79 (34), 77 (18), 41 (11).

**IR**: $\tilde{\nu}$ = 3408 (w), 2963 (w), 2925 (m), 2846 (w), 1729 (s), 1440 (m), 1377 (m), 1299 (m), 1253 (m), 1177 (s), 1035 (s).

**$[\alpha]^{20}_D$** = +39.9 (c = 1.02, $CHCl_3$).

**Ethyl (1*S*,6*S*)-6-(hydroxymethyl)-3,4-dimethylcyclohex-3-ene-1-carboxylate (111)**




Sodium borohydride (48 mg, 1.27 mmol, 1.0 eq.) was added slowly to a solution of ethyl (1*S*,6*S*)-6-formyl-3,4-dimethylcyclohex-3-ene-1-carboxylate **105** (266 mg, 1.27 mmol, 1.0 eq.) in methanol (8 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for one hour. 2 M HCl-solution (10 mL) was added to the reaction mixture, stirred for a few minutes and then extracted with ether (4 x 10 mL). The combined organic phases were washed with saturated $NaHCO_3$-solution (10 mL) and water (10 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 16 cm, cyclohexane:EtOAc = 4:1) to obtain the alcohol as a colorless liquid (185 mg, 69%).

$C_{12}H_{20}O_3$ (212.29 g/mol)

**TLC**: $R_f$ = 0.24 (cyclohexane:EtOAc = 4:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.16 (qd, $^3J_{HH}$ = 7.1 Hz, $^5J_{HH}$ = 1.0 Hz, 2H), 3.62-3.52 (m, 2H), 2.49-2.42 (m, 1H), 2.35-2.28 (m, 1H), 2.14-2.09 (m, 1H), 2.05-1.93 (m, 3H), 1.76 (t, $^3J_{HH}$ = 6.1 Hz, 1H) 1.61 (s, 2x3H), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3H).

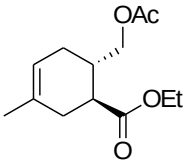
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 176.3, 124.6, 123.7, 65.8, 60.6, 43.3, 39.2, 34.7, 34.4, 18.9, 18.7, 14.4.

**GC-MS** (Method B, $t_R$ = 13.7 min): *m/z* (%) 212 ($M^+$, 2), 194 (10), 122 (10), 121 (100), 120 (25), 107 (43), 105 (26), 93 (22), 81 (22), 79 (16), 77 (11), 41 (12).

**IR**: $\tilde{\nu}$ = 3343 (w), 2980 (w), 2903 (w), 2881 (w), 2837 (w), 1716 (s), 1374 (m), 1307 (m), 1257 (m), 1177 (s), 1050 (s), 994 (m), 664 (w).

**$[\alpha]^{20}_D$** = +35.1 (c = 1.02, $CHCl_3$).

**Ethyl (1*S*,6*S*)-6-(acetoxymethyl)-3-methylcyclohex-3-ene-1-carboxylate (112)**




Acetic anhydride (505 mg, 4.95 mmol, 1.05 eq.) was added to a solution of ethyl (1*S*,6*S*)-6-(hydroxymethyl)-3-methylcyclohex-3-ene-1-carboxylate **110** (933 mg, 4.71 mmol 1.0 eq.) in pyridine (3.5 mL) at 0 °C. After addition, the mixture was stirred for seven hours at room temperature. The reaction mixture was concentrated and the crude product was purified by column chromatography (silica gel, 3 cm × 18 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a colorless liquid (490 mg, 43%).

$C_{13}H_{20}O_4$ (240.30 g/mol)

**TLC**: $R_f$ = 0.57 (cyclohexane:EtOAc = 4:1, $KMnO_4$).

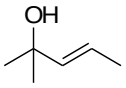
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.36-5.34 (m, 1H), 4.15 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.07 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.7 Hz, 1H), 3.98 (dd, $^2J_{HH}$ = 11.1 Hz, $^3J_{HH}$ = 5.3 Hz, 1H), 2.54-2.48 (m, 1H), 2.32-2.08 (m, 4H), 2.03 (s, 3H), 1.91-1.82 (m, 1H), 1.66 (s, 3H), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 175.3, 171.1, 132.1, 119.3, 66.7, 60.6, 42.5, 34.6, 32.5, 27.6, 23.3, 21.0, 14.4.

**GC-MS** (Method B, $t_R$ = 14.0 min): *m/z* (%) 195 ($M^+$–45, 1), 180 (19), 153 (19), 152 (10), 107 (100), 106 (54), 105 (12), 93 (13), 91 (32), 79 (20), 77 (10), 43 (35).

**IR**: $\tilde{\nu}$ = 2964 (w), 2906 (w), 2846 (w), 1731 (s), 1442 (w), 1366 (m), 1232 (s), 1176 (m), 1035 (m).

**$[\alpha]^{20}_D$** = +33.4 (c = 1.04, $CHCl_3$).




**(*E*)-2-Methylpent-3-en-2-ol (118)** [83]

A solution of (*E*)-methyl-crotonate **119** (1.00 g, 10.0 mmol, 1.0 eq.) in absolute ether (7 mL) was added dropwise to a solution of methyllithium in ether (1.6 M, 13.8 mL, 22.0 mmol, 2.2 eq.) at –78 °C over 5 minutes. The mixture was warmed to room temperature during one hour and was stirred for another 20 hours at this temperature. The reaction mixture was quenched with saturated

ammonium chloride-solution (60 mL). The aqueous phase was extracted with ether (3 x 70 mL) and the combined organic phases were washed with brine (50 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 14 cm, pentane:ether = 4:1) to obtain the product as a pale yellow liquid (0.60 g, 60%).

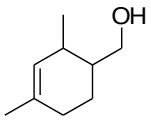
$C_6H_{12}O$ (100.16 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.68-5.58 (m, 2H), 1.68-1.67 (m, 3H), 1.44 (brs, 1H), 1.29 (s, 2x3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 139.2, 122.1, 70.8, 29.9, 17.8.

**IR**: $\tilde{\nu}$ = 3352 (w), 2970 (m), 2920 (w), 2859 (w), 1450 (w), 1375 (m), 1146 (m), 967 (s), 895 (m).

**(2,4-Dimethylcyclohex-3-en-1-yl)methanol (124)**




Sodium borohydride (0.41 g, 10.9 mmol, 1.5 eq.) was added slowly to a solution of 2,4-dimethylcyclohex-3-ene-1-carbaldehyde **115** (1.00 g, 7.24 mmol, 1.0 eq.) in methanol (50 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for one hour. Then, 2 M HCl-solution (20 mL) was added and stirred for a few minutes. The reaction mixture was extracted with ether (4 x 40 mL). The combined organic phases were washed with saturated $NaHCO_3$-solution (40 mL) and water (40 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 13 cm, pentane:ether = 4:1) to obtain the alcohol as a yellow liquid (0.88 g, 87%). The product was obtained as a mixture of the *cis*- and *trans*-product (3:1 in favour of the *trans*).

$C_9H_{16}O$ (140.23 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.36-5.33 (m, 1H), 3.61 (dd, $^2J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 7.4 Hz, 1H), 3.54-3.49 (m, 1H), 2.35-2.30 (m, 1H), 2.02-1.92 (m, 2H), 1.90-1.78 (m, 1H), 1.64 (s, 3H), 1.60-1.53 (m, 1H), 1.46-1.35 (m, 1H), 1.34-1.25 (m, 1H), 0.85 (d, $^3J_{HH}$ = 7.1 Hz, 3H), all *trans*.
5.18-5.17 (m, 1H), 3.74 (dd, $^2J_{HH}$ = 10.6 Hz, $^3J_{HH}$ = 4.2 Hz), 3.54-3.49 (m, 1H), 2.35-2.30 (m, 1H), 2.02-1.92 (m, 2H), 1.90-1.78 (m, 1H), 1.64 (s, 3H), 1.60-1.53 (m, 1H), 1.46-1.35 (m, 1H), 1.34-1.25 (m, 1H), 1.00 (d, $^3J_{HH}$ = 6.9 Hz, 3H), all *cis*.

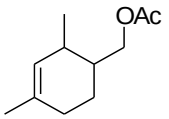
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 133.3, 127.3, 65.2, 39.7, 30.6, 30.0, 23.7, 21.2, 15.5, all *trans*.

133.3, 127.2, 65.9, 43.2, 31.9, 29.3, 24.9, 20.8, 15.5, all *cis*.

**GC-MS** (Method B, $t_R$ = 5.7 min (*cis*), 6.1 min (*trans*)): *m/z* (%) 140 ($M^+$, 11), 122 (39), 109 (37), 108 (10), 107 (100), 94 (15), 93 (22), 91 (24), 82 (28), 81 (22), 79 (30), 77 (14), 67 (70), 55 (17), 43 (14), 41 (25), all *trans*.

**IR**: ṽ = 3307 (w), 2959 (m), 2923 (s), 2870 (m), 2833 (m), 1450 (m), 1377 (m), 1077 (m), 1034 (m), 1013 (m), 842 (w).

**(2,4-Dimethylcyclohex-3-en-1-yl)methyl acetate (125)**




Acetic anhydride (0.15 g, 1.50 mmol, 1.05 eq.) was added to a solution of (2,4-dimethylcyclohex-3-en-1-yl)methanol **124** (0.20 g, 1.43 mmol, 1.0 eq.) in pyridine (1 mL) at 0 °C. After addition, the mixture was stirred for seven hours at room temperature. The reaction mixture was concentrated and purified by column chromatography (silica gel, 2 cm × 15 cm, cyclohexane:EtOAc = 49:1) to obtain the product as a colorless liquid (0.19 g, 71%). The product was obtained as a mixture of the *cis*- and *trans*-product (3:1 in favour of the *trans*).

$C_{11}H_{18}O_2$ (182.26 g/mol)

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.33-5.30 (m, 1H), 3.98 (d, $^3J_{HH}$ = 7.6 Hz, 2H), 2.33-2.28 (m, 1H), 2.05 (s, 3H), 2.01-1.90 (m, 3H), 1.64 (s, 3H), 1.58-1.52 (m, 1H), 1.49-1.39 (m, 1H), 0.85 (d, $^3J_{HH}$ = 7.1 Hz, 3H) all *trans.*

5.17-5.16 (m, 1H), 4.14 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 4.3 Hz, 1H), 3.97-3.93 (m, 1H), 2.33-2.28 (m, 1H), 2.05 (s, 3H), 2.01-1.90 (m, 3H), 1.64 (s, 3H), 1.58-1.52 (m, 1H), 1.49-1.39 (m, 1H), 1.00 (d, $^3J_{HH}$ = 6.9 Hz, 3H) all *cis*.

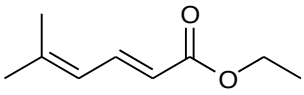
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 171.5, 133.1, 126.9, 66.5, 36.1, 30.8, 29.6, 23.6, 21.4, 21.2, 15.7 *trans.*

171.5, 133.2, 126.8, 67.4, 39.9, 32.2, 29.0, 25.1, 23.6, 21.2, 20.7 all *cis.*

**GC-MS** (Method B, $t_R$ = 8.0 min (*cis*), 8.5 min (*trans*)): *m/z* (%) 122 ([$M^+$–60], 44), 107 (100), 94 (19), 93 (31), 91 (17), 82 (14), 79 (22), 67 (26), 43 (43), 41 (13) all *trans*.

**IR**: $\tilde{\nu}$ = 2958 (w), 2913 (w), 2873 (w), 2834 (w), 1740 (s), 1451 (w), 1366 (m), 1232 (s), 1034 (m).

**Ethyl (*E*)-5-methylhexa-2,4-dienoate (130)**



Under inert atmosphere (carbethoxymethylene)triphenylphosphorane **129** (2.43 g, 6.99 mmol, 1.0 eq.) was added to a solution 3-methyl-2-butenal **128** (0.58 g, 6.85 mmol, 1.0 eq.) in absolute toluene (16 mL) and the solution was stirred under reflux for five hours. Water (20 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with ether (3 x 20 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was obtained as a 6:1 mixture of the *E*- and the *Z*-isomer with the desired *E*-isomer as the major product. The isomers could be purified by column chromatography (silica gel, 3 cm × 15 cm, cyclohexane:EtOAc=49:1) to obtain the *E*-isomer as a colorless liquid (0.78 g, 75%).

$C_9H_{14}O_2$ (154.21 g/mol)

Analytical data for the *E*-isomer:

**TLC**: $R_f$ = 0.34 (cyclohexane:EtOAc = 19:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.56 (dd, $^3J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 11.6 Hz, 1H), 5.99-5.96 (m, 1H), 5.75 (d, $^3J_{HH}$ = 15.1 Hz, 1H), 4.20 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 1.89 (s, 3H), 1.87 (s, 3H), 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 167.9, 146.4, 141.1, 123.8, 118.7, 60.2, 26.7, 19.1, 14.5.

**GC-MS** (Method B, $t_R$ = 6.6 min): *m/z* (%) 154 ($M^+$, 32), 139 (22), 111 (50), 109 (36), 81 (100), 80 (29), 79 (38), 53 (15), 41 (22).

**IR**: $\tilde{\nu}$ = 2978 (w), 2908 (w), 1709 (s), 1637 (s), 1444 (w), 1366 (m), 1275 (s), 1212 (m), 1138 (s), 991 (m), 968 (m), 880 (w).

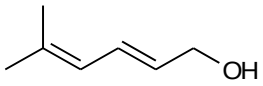
Analytical data for the *Z*-isomer:

**TLC**: $R_f$ = 0.43 (cyclohexane:EtOAc = 19:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.21-7.16 (m, 1H), 6.85 (t, $^3J_{HH}$ = 11.7 Hz, 1H), 5.55 (d, $^3J_{HH}$ = 11.7 Hz, 1H), 4.18 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 1.91 (s, 3H), 1.85 (s, 3H), 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 167.0, 146.8, 140.7, 122.1, 114.8, 59.9, 27.0, 18.4, 14.5.
**GC-MS** (Method B, $t_R$ = 6.2 min): *m/z* (%) 154 ($M^+$, 32), 139 (23), 111 (54), 109 (36), 81 (100), 80 (29), 79 (40), 53 (15), 41 (23).
**IR**: $\tilde{\nu}$ = 2979 (w), 2908 (w), 1710 (s), 1634 (s), 1595 (m), 1419 (m), 1203 (s), 1163 (s), 1043 (m), 820 (m).

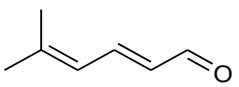
**(*E*)-5-Methylhexa-2,4-dien-1-ol**




Under inert atmosphere, DIBALH (1 M in toluene, 8.6 mL, 8.60 mmol, 2.2 eq.) was added to a solution of ethyl (*E*)-5-methylhexa-2,4-dienoate **130** (0.60 g, 3.89 mmol, 1.0 eq.) in absolute toluene (40 mL) at −78 °C and stirred for one hour at room temperature. Saturated ammonium chloride-solution (20 mL) was added and the reaction mixture was filtrated over celite. The aqueous phase was separated and extracted with methylene chloride (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried over sodium sulfate and the solvent was removed to obtain the product as a colorless liquid (0.38 g, 87%).

$C_7H_{12}O$ (112.17 g/mol)
**TLC**: $R_f$ = 0.24 (cyclohexane:EtOAc = 4:1, UV).
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 6.46 (ddt, $^3J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 10.9 Hz, $^4J_{HH}$ = 1.3 Hz, 1H), 5.84 (d, $^3J_{HH}$ = 10.9 Hz, 1H), 5.71 (dt, $^3J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 6.1 Hz, 1H), 4.18 (d, $^3J_{HH}$ = 5.5 Hz, 2H), 1.78 (s, 3H), 1.76 (s, 3H), 1.35 (brs, 1H).
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 136.5, 129.1, 128.6, 124.3, 64.0, 26.2, 18.4

**(*E*)-5-Methylhexa-2,4-dienal (131)** [69f]




Dess-Martin-periodinane (11.2 g, 25.7 mmol, 1.3 eq.) was added to a solution of (*E*)-5-methylhexa-2,4-dien-1-ol (2.20 g, 19.6 mmol, 1.0 eq.) in DMSO (50 mL) and the reaction mixture was stirred overnight at room temperature. Saturated ammonium chloride-solution (150 mL) was added and the reaction mixture was filtrated over celite. The aqueous phase was separated and extracted with

methylene chloride (3 x 120 mL). The combined organic phases were washed with brine (150 mL), dried over sodium sulfate and the solvent was removed. The crude product was purified by column chromatography (silica gel, 4 cm × 15 cm, pentane:ether = 9:1) to obtain the product as a yellow liquid (1.46 g, 68%).

$C_7H_{10}O$ (110.16 g/mol)

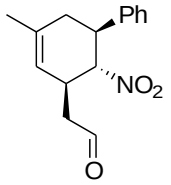
**TLC**: $R_f$ = 0.49 (cyclohexane:EtOAc = 4:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.56 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.38 (dd, $^3J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 11.5 Hz, 1H), 6.16-6.12 (m, 1H), 6.06 (dd, $^3J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 8.0 Hz, 1H), 1.94 (s, 3H), 1.93 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 194.3, 149.6, 148.8, 129.8, 124.4, 27.0, 19.3.

**GC-MS** (Method A, $t_R$ = 9.2 min): *m/z* (%) 110 ($M^+$, 21), 95 (100), 79 (16), 77 (10), 67 (30), 53 (12), 41 (33).

**IR**: ṽ = 2975 (w), 2911 (w), 2810 (w), 2714 (w), 1675 (s), 1626 (s), 1441 (m), 1378 (m), 1250 (m), 1179 (m), 1126 (s), 982 (m), 877 (m), 623 (m).




**2-((1*S*,2*R*,3*S*)-5-Methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)acetaldehyde (126)** [69f]

*trans-β*-Nitrostyrene **132** (257 mg, 1.72 mmol, 1.0 eq.), *ortho*-fluorobenzoic acid (48.2 mg, 0.34 mmol, 0.2 eq.) and (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **71** (112 mg, 0.34 mmol, 0.2 eq.) were added to a solution of (*E*)-5-methylhexa-2,4-dienal **131** (380 mg, 3.45 mmol, 2.0 eq.) in chloroform (10 mL) and stirred for three hours at 55 °C under inert atmosphere. The reaction mixture was concentrated and purified by column chromatography (silica gel, 2 cm × 17 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a yellow liquid (340 mg, 76%).

$C_{15}H_{17}NO_3$ (259.31 g/mol)

**TLC**: $R_f$ = 0.37 (cyclohexane:EtOAc = 4:1, UV).

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.77 (s, 1H), 7.34-7.20 (m, 5H), 5.26 (s, 1H), 4.74 (dd, $^{3}J_{HH}$ = 11.6 Hz, $^{3}J_{HH}$ = 10.1 Hz, 1H), 3.53-3.45 (m, 2H), 2.67 (ddd, $^{2}J_{HH}$ = 17.8 Hz, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{HH}$ = 1.7 Hz, 1H), 2.54 (ddd, $^{2}J_{HH}$ = 17.8 Hz, $^{3}J_{HH}$ = 3.6 Hz, $^{4}J_{HH}$ = 0.9 Hz, 1H), 2.38-2.35 (m, 2H), 1.72 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 199.4, 139.5, 135.0, 129.0, 127.9, 127.5, 120.7, 92.4, 46.3, 45.4, 38.4, 36.8, 22.8.

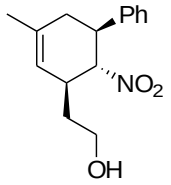
**GC-MS** (Method B, $t_R$ = 21.2 min): *m/z* (%) 212 ([$M^+$–47], 45), 194 (47), 183 (10), 181 (10), 179 (16), 170 (14), 169 (80), 168 (34), 167 (13), 155 (15), 154 (18), 153 (14), 141 (19), 129 (14), 128 (19), 115 (19), 105 (10), 91 (100), 77 (21), 65 (12), 41 (11).

**HPLC** (IC, *n*heptane:*i*PrOH 80:20, 1.0 mL/min, 25 °C): $t_{r(major)}$ = 25.3 min, $t_{r(minor)}$ = 24.0 min, 93% *ee*, determined for the corresponding alcohol.

**IR**: ṽ = 3031 (w), 2924 (w), 2851 (w), 1720 (w), 1547 (s), 1376 (m), 763 (m), 699 (s), 533 (w).

**$[\alpha]^{20}_{D}$** = +40.8 (c = 0.98, $CHCl_3$).

**2-((1*S*,2*R*,3*S*)-5-Methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)ethan-1-ol (136)**




Sodium borohydride (53.5 mg, 1.41 mmol, 1.1 eq.) was added slowly to a solution of 2-((1*S*,2*R*,3*S*)-5-methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)acetaldehyde **126** (340 mg, 1.31 mmol, 1.0 eq.) in methanol (10 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for three hours. Then, 2 M HCl-solution (10 mL) was added and stirred for a few minutes. The reaction mixture was extracted with ether (4 x 15 mL). The combined organic phases were washed with saturated $NaHCO_3$-solution (15 mL) and water (15 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 15 cm, cyclohexane:EtOAc = 4:1) to obtain the product as a yellow solid (300 mg, 88%).

$C_{15}H_{19}NO_3$ (261.32 g/mol)

**TLC**: $R_f$ = 0.33 (cyclohexane:EtOAc = 4:1, UV).

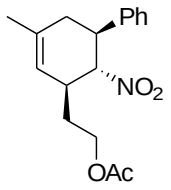
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.33-7.29 (m, 2H), 7.26-7.20 (m, 3H), 5.38 (s, 1H), 4.77 (dd, $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 10.1 Hz, 1H), 3.82-3.71 (m, 2H), 3.44 (dt, $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 8.7 Hz, 1H), 3.11 (brs, 1H), 2.35 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 1.81-1.75 (m, 1H), 1.74 (s, 3H), 1.68-1.61 (m, 1H), 1.35 (brs, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 139.8, 134.3, 129.0, 127.8, 127.5, 121.5, 93.4, 59.8, 45.8, 39.2, 38.5, 35.2, 22.9.

**IR**: $\tilde{\nu}$ = 3359 (w), 3035 (w), 2918 (w), 2864 (w), 1542 (s), 1455 (w), 1370 (m), 1049 (m), 760 (m), 696 (m), 545 (m).

**$[\alpha]^{20}_D$** = +9.0 (c = 0.91, $CHCl_3$).

**2-((1*S*,2*R*,3*S*)-5-Methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)ethyl acetate (138)**




Acetic anhydride (123 mg, 1.21 mmol, 1.05 eq.) was added to a solution of 2-((1*S*,2*R*,3*S*)-5-methyl-2-nitro-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl)ethan-1-ol **136** (300 mg, 1.15 mmol 1.0 eq.) in pyridine (1.0 mL) in a round bottom flask at 0 °C. After addition the mixture was stirred for 72 hours at room temperature. The reaction mixture was concentrated and the crude product was purified by column chromatography (silica gel, 2 cm × 18 cm, cyclohexane:EtOAc = 19:1) to obtain the product as a colorless oil (150 mg, 43%).

$C_{17}H_{21}NO_4$ (303.36 g/mol)

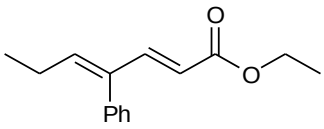
**TLC**: $R_f$ = 0.34 (cyclohexane:EtOAc = 4:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.33-7.30 (m, 2H), 7.27-7.20 (m, 3H), 5.35 (s, 1H), 4.71 (dd, $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 10.1 Hz, 1H), 4.26-4.12 (m, 2H), 3.44 (dt, $^3J_{HH}$ = 11.6 Hz, $^3J_{HH}$ = 8.7 Hz, 1H), 3.07 (brs, 1H), 2.34 (d, $^3J_{HH}$ = 8.7 Hz, 2H), 2.06 (s, 3H), 1.91-1.83 (m, 1H), 1.74 (s, 3H), 1.72-1.63 (m, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 171.2, 139.6, 134.7, 129.0, 127.9, 127.5, 120.8, 92.9, 61.0, 45.7, 39.2, 38.4, 31.2, 27.1, 21.1.

**GC-MS** (Method D, $t_R$ = 12.1 min): *m/z* (%) 256 ([$M^+$–47], 1), 197 (25,), 196 (100), 182 (12), 181 (75), 169 (31), 168 (17), 167 (12), 155 (16), 154 (10), 141 (15), 129 (11), 128 (11), 115 (11), 105 (14), 91 (73), 77 (11), 43 (42).

**Ethyl (2*E*,4*Z*)-4-phenylhepta-2,4-dienoate (134)**




Under inert atmosphere (carbethoxymethylene)triphenylphosphorane **129** (6.75 g, 19.4 mmol, 1.0 eq.) was added to a solution of (*E*)-2-phenylpent-2-enal **133** (3.00 g, 18.2 mmol, 1.0 eq.) in absolute toluene (45 mL) and the solution was stirred under reflux for five hours. Water (60 mL) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted with ether (3 x 60 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was redissolved in hot cyclohexane (20 mL) and cooled to room temperature. The precipitate was filtered off and the filtrate was concentrated. The remaining crude product was purified by column chromatography (silica gel, 4 cm × 17 cm, cyclohexane:EtOAc = 49:1) to obtain the product as a colorless liquid (3.30 g, 79%).

$C_{15}H_{18}O_2$ (230.31 g/mol)

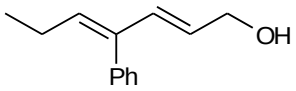
**TLC**: $R_f$ = 0.52 (cyclohexane:EtOAc = 19:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.50 (d, $^3J_{HH}$ = 15.6 Hz, 1H), 7.40-7.36 (m, 2H), 7.34-7.29 (m, 1H), 7.10-7.08 (m, 2H), 6.12 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 5.38 (d, $^3J_{HH}$ = 15.6 Hz, 1H), 4.16 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 2.01 (quint, $^3J_{HH}$ = 7.5 Hz, 2H), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 0.97 (t, $^3J_{HH}$ = 7.5 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 167.6, 148.8, 144.3, 139.7, 136.7, 129.4, 128.6, 127.5, 118.9, 60.3, 23.2, 14.4, 13.9.

**GC-MS** (Method B, $t_R$ = 16.3 min): *m/z* (%) 230 ($M^+$, 30), 201 (17), 185 (20), 173 (19), 158 (14), 157 (100), 156 (60), 155 (31), 142 (35), 141 (57), 129 (72), 128 (31), 127 (11), 115 (53), 91 (21), 77 (17).

**(2*E*,4*Z*)-4-Phenylhepta-2,4-dien-1-ol**




Under inert atmosphere, DIBALH (1 M in toluene, 31.5 mL, 31.5 mmol, 2.2 eq.) was added to a solution of ethyl (2*E*,4*Z*)-4-phenylhepta-2,4-dienoate **134** (3.30 g, 14.3 mmol, 1.0 eq.) in absolute toluene (150 mL) at −78 °C and stirred for 16 hours at room temperature. Saturated ammonium chloride-solution (90 mL) was added and the reaction mixture was filtrated over celite. The aqueous phase was separated and extracted with methylene chloride (3 x 90 mL). The combined organic phases were washed with brine (120 mL), dried over sodium sulfate and the solvent was removed to obtain the product as a colorless liquid (2.26 g, 84%).

$C_{13}H_{16}O$ (188.27 g/mol)

**TLC**: $R_f$ = 0.23 (cyclohexane:EtOAc = 9:1, UV).

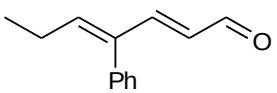
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.39-7.34 (m, 2H), 7.31-7.27 (m, 1H), 7.13-7.10 (m, 2H), 6.45 (d, $^3J_{HH}$ = 15.5 Hz, 1H), 5.72 (t, $^3J_{HH}$ = 7.5 Hz, 1H), 5.30 (dt, $^3J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 5.8 Hz, 1H), 4.15 (d, $^3J_{HH}$ = 5.8 Hz, 2H), 1.93 (quint, $^3J_{HH}$ = 7.5 Hz, 2H), 1.26 (brs, 1H), 0.93 (t, $^3J_{HH}$ = 7.5 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 140.0, 138.3, 135.9, 135.8, 129.6, 129.0, 128.3, 127.0, 63.8, 22.6, 14.4.

**GC-MS** (Method D, $t_R$ = 7.3 min): *m/z* (%) 188 ($M^+$, 25), 170 (10), 157 (63), 155 (28), 144 (21), 143 (10), 142 (21), 140 (42), 131 (25), 130 (13), 129 (100), 128 (42), 127 (14), 118 (21), 117 (28), 116 (13), 115 (47), 91 (48), 77 (19).

**IR**: $\tilde{\nu}$ = 3309 (w), 3054 (w), 3021 (w), 2963 (m), 2930 (m), 2871 (m), 1670 (w), 1493 (m), 1441 (m), 969 (m), 770 (w), 703 (s).

**(2*E*,4*Z*)-4-Phenylhepta-2,4-dienal (135)** [69f]




Dess-Martin-periodinane (8.74 g, 20.0 mmol, 1.8 eq.) was added to a solution of (2*E*,4*Z*)-4-phenylhepta-2,4-dien-1-ol (2.09 g, 11.1 mmol, 1.0 eq.) in DMSO (30 mL) and the reaction mixture was stirred overnight at room temperature. Saturated ammonium chloride-solution (90 mL) was

added and the reaction mixture was filtrated over celite. The aqueous phase was extracted with methylene chloride (3 x 90 mL). The combined organic phases were washed with brine (120 mL), dried over sodium sulfate and the solvent was removed. The crude product was purified by column chromatography (silica gel, 3 cm × 15 cm, pentane:ether = 19:1) to obtain the product as a yellow liquid (1.19 g, 58%).

$C_{13}H_{14}O$ (186.25 g/mol)

**TLC**: $R_f$ = 0.24 (pentane:ether = 19:1, UV).

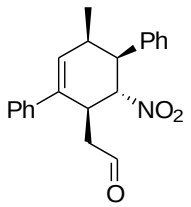
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.58 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.41-7.31 (m, 3H), 7.29 (d, $^3J_{HH}$ = 15.5 Hz, 1H), 7.10-7.08 (m, 2H), 6.25 (t, $^3J_{HH}$ = 7.6 Hz, 1H), 5.71 (dd, $^3J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 7.9 Hz, 1H), 2.07 (quint, $^3J_{HH}$ = 7.5 Hz, 2H), 1.01 (t, $^3J_{HH}$ = 7.5 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 194.0, 156.7, 146.7, 140.2, 136.1, 129.8, 129.2, 128.7, 127.8 23.5, 13.7.

**GC-MS** (Method B, $t_R$ = 13.4 min): *m/z* (%) 186 ($M^+$, 18), 158 (14), 157 (100), 142 (15), 141 (15), 130 (15), 129 (47), 128 (43), 127 (13), 115 (40), 91 (14), 77 (13).

**IR**: $\tilde{\nu}$ = 2967 (w), 2932 (w), 2873 (w), 2812 (w), 2724 (w), 1676 (s), 1618 (m), 1119 (m), 972 (m), 704 (m).

**2-((2'*S*,3'*R*,4'*S*,5'*R*)-5'-Methyl-3'-nitro-2',3',4',5'-tetrahydro-[1,1':4',1''-terphenyl]-2'-yl)acetaldehyde (127)** [69f]




*trans-β*-Nitrostyrene **132** (0.48 g, 3.20 mmol, 1.0 eq.), *ortho*-fluorobenzoic acid (0.09 g, 0.64 mmol, 0.2 eq.) and (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **71** (0.21 g, 0.64 mmol, 0.2 eq.) were added to a solution of (2*E*,4*Z*)-4-phenylhepta-2,4-dienal **135** (1.19 g, 6.39 mmol, 2.0 eq.) in chloroform (16 mL) and stirred for 2 hours at 55 °C under inert atmosphere. The reaction mixture was concentrated and purified by column chromatography (silica gel, 3 cm × 17 cm, cyclohexane:EtOAc = 49:1) to obtain the product as a yellow liquid (0.68 g, 63%).

$C_{21}H_{21}NO_3$ (335.40 g/mol)

**TLC**: $R_f$ = 0.23 (cyclohexane:EtOAc = 49:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.49 (s, 1H), 7.36-7.27 (m, 6H), 7.24-7.20 (m, 4H), 5.98 (dd, $^3J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 2.4 Hz, 1H), 5.53 (dd, $^3J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 9.4 Hz, 1H), 3.82 (dd, $^3J_{HH}$ = 12.3 Hz, $^3J_{HH}$ = 5.7 Hz, 1H), 3.80-3.75 (m, 1H), 2.80-2.70 (m, 2H), 2.56 (dd, $^2J_{HH}$ = 18.8 Hz, $^3J_{HH}$ = 3.7 Hz, 1H), 0.99 (d, $^3J_{HH}$ = 7.2 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 199.1, 140.1, 138.1, 136.1, 132.7, 128.8, 128.7, 128.1, 127.8, 127.6, 127.2, 87.7, 47.9, 43.4, 39.9, 36.5, 15.7.

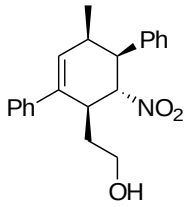
**GC-MS** (Method D, $t_R$ = 18.1 min): *m/z* (%) 305 ([$M^+$–30], 4), 270 (24), 269 (84), 261 (22), 255 (14), 254 (24), 245 (38), 244 (60), 230 (16), 229 (17), 215 (18), 169 (11), 167 (13), 165 (14), 155 (13), 153 (12), 152 (13), 141 (15), 129 (23), 128 (27), 115 (38), 105 (38), 103 (10), 91 (100), 77 (17).

**HPLC** (IC, *n*heptane:*i*PrOH 80:20, 1.0 mL/min, 25 °C): $t_{r(major)}$ = 16.5 min, $t_{r(minor)}$ = 12.3 min, 93% *ee*, determined for the corresponding alcohol.

**IR**: ṽ = 3027 (w), 2957 (w), 2903 (w), 2876 (w), 2735 (w), 1725 (m), 1543 (s), 1370 (w), 749 (m), 697 (s), 522 (w).

**[α]$^{20}_D$** = +11.2 (c = 0.87, $CHCl_3$).

**2-((2'*S*,3'*R*,4'*S*,5'*R*)-5'-Methyl-3'-nitro-2',3',4',5'-tetrahydro-[1,1':4',1''-terphenyl]-2'-yl)ethan-1-ol (137)**




Sodium borohydride (72.4 mg, 1.91 mmol, 1.4 eq.) was added slowly to a solution of **2-**((2'*S*,3'*R*,4'*S*,5'*R*)-5'-methyl-3'-nitro-2',3',4',5'-tetrahydro-[1,1':4',1''-terphenyl]-2'-yl)acetaldehyde **127** (450 mg, 1.34 mmol, 1.0 eq.) in methanol (15 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 16 hours. Then, 2 M HCl-solution (15 mL) was added and stirred for a few minutes. The aqueous phase was extracted with ether (4 x 20 mL). The combined organic phases were washed with saturated $NaHCO_3$-solution (20 mL) and water (20 mL), dried over sodium sulfate and concentrated. The product was obtained as a yellow solid (400 mg, 89%).

$C_{21}H_{23}NO_3$ (337.42 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.38-7.23 (m, 10H), 6.08 (dd, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 2.1 Hz, 1H), 5.75 (dd, $^3J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 9.1 Hz, 1H), 3.75 (dd, $^3J_{HH}$ = 12.5 Hz, $^3J_{HH}$ = 5.2 Hz, 1H), 3.69-3.65 (m, 1H), 3.62-3.58 (m, 1H), 3.56-3.51 (m, 1H), 2.70-2.63 (m, 1H), 1.83-1.79 (m, 2H), 1.23 (brs, 1H), 0.93 (d, $^3J_{HH}$ = 7.2 Hz, 3H).

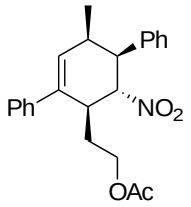
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 140.5, 138.2, 137.1, 133.4, 128.7, 128.7, 128.3, 127.6, 127.5, 126.8, 87.8, 59.6, 48.2, 41.8, 36.5, 32.1, 16.1.

**GC-MS** (Method D, $t_R$ = 18.1 min): *m/z* (%) 289 ([$M^+$–48], 13), 288 (52), 274 (23), 273 (100), 240 (12), 239 (11), 115 (11).

**IR**: $\tilde{\nu}$ = 3418 (w), 3029 (w), 2961 (w), 2928 (w), 2876 (w), 1544 (s), 1372 (w), 1095 (w), 751 (m), 702 (s), 522 (w).

**$[\alpha]^{20}_D$** = +2.1 (c = 0.68, $CHCl_3$).

**2-((2'*S*,3'*R*,4'*S*,5'*R*)-5'-Methyl-3'-nitro-2',3',4',5'-tetrahydro-[1,1':4',1''-terphenyl]-2'-yl)ethyl acetate (139)**




Acetic anhydride (89.0 mg, 0.87 mmol, 1.05 eq.) was added to a solution of 2-((2'*S*,3'*R*,4'*S*,5'*R*)-5'-methyl-3'-nitro-2',3',4',5'-tetrahydro-[1,1':4',1''-terphenyl]-2'-yl)ethan-1-ol **137** (280 mg, 0.83 mmol 1.0 eq.) in pyridine (0.5 mL) in a round bottom flask at 0 °C. After addition the mixture was stirred for 16 hours at room temperature. The reaction mixture was concentrated and the crude product was purified by column chromatography (silica gel, 3 cm × 18 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a colorless oil (250 mg, 79%).

$C_{23}H_{25}NO_4$ (379.46 g/mol)

**TLC**: $R_f$ = 0.33 (cyclohexane:EtOAc = 9:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.38-7.21 (m, 10H), 6.07 (dd, $^3J_{HH}$ = 6.0 Hz, $^3J_{HH}$ = 2.0 Hz, 1H), 5.51 (dd, $^3J_{HH}$ = 12.4 Hz, $^3J_{HH}$ = 9.3 Hz, 1H), 3.98-3.92 (m, 2H), 3.75 (dd, $^3J_{HH}$ = 12.4 Hz,

$^{3}J_{HH}$ = 5.2 Hz, 1H), 3.69 (brs, 1H), 2.72-2.64 (m, 1H), 2.06 (s, 3H), 1.97-1.89 (m, 1H), 1.88-1.80 (m, 1H), 0.92 (d, $^{3}J_{HH}$ = 7.2 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 170.8, 140.1, 138.0, 136.7, 133.6, 128.8, 128.7, 128.2, 127.7, 127.6, 126.8, 87.4, 60.9, 48.1, 41.7, 36.4, 28.4, 21.2, 16.1.

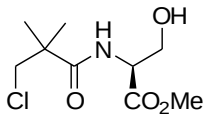
**GC-MS** (Method D, $t_R$ = 22.3 min): *m/z* (%) 332 ([$M^+$–47], 1), 289 (12), 272 (34), 271 (100), 257 (23), 256 (13), 245 (20), 244 (25), 243 (12), 215 (11), 181 (23), 167 (13), 165 (13), 155 (12), 153 (10), 141 (13), 129 (19), 128 (18), 117 (11), 115 (21), 105 (30), 91 (62), 43 (47).

**IR**: $\tilde{\nu}$ = 3031 (w), 2967 (w), 2953 (w), 2924 (w), 2876 (w), 1740 (s), 1552 (s), 1377 (m), 1220 (s), 1056 (m), 763 (m), 696 (s), 534 (w).

**$[\alpha]^{20}_D$** = +9.8 (c = 1.31, $CHCl_3$).

## 5.5 Synthesis of NeoPHOX catalysts

### Methyl (3-chloro-2,2-dimethylpropanoyl)-*L*-serinate (158) [70]




Serine methylester hydrochloride **157** (5.00 g, 32.1 mmol, 1.0 eq.) was dissolved in methylene chloride (50 mL) and triethylamine (9.74 g, 96.3 mmol, 3.0 eq.) was added at 0 °C followed by slow addition of 3-chloropivaloyl chloride **156** (4.98 g, 32.1 mmol, 1.0 eq.). The reaction mixture was stirred for 18 hours at room temperature. Saturated $NaHCO_3$-solution (10 mL) was added to the mixture and the phases were separated. The aqueous phase was extracted with ether (3 x 30 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 7 cm × 15 cm, EtOAc) to obtain the product as a pale yellow oil (6.85 g, 90%).

$C_9H_{16}ClNO_4$ (237.68 g/mol)

**TLC**: $R_f$ = 0.70 (EtOAc, $KMnO_4$).

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 6.71 (d, $^{3}J_{HH}$ = 5.0 Hz, 1H), 4.66 (dt, $^{3}J_{HH}$ = 7.0 Hz, $^{3}J_{HH}$ = 3.5 Hz, 1H), 4.02-3.93 (m, 2H), 3.80 (s, 3H), 3.68 (d, $^{2}J_{HH}$ = 10.7 Hz, 1H), 3.57 (d, $^{2}J_{HH}$ = 10.7 Hz, 1H), 2.48 (t, $^{3}J_{HH}$ = 6.0 Hz, 1H), 1.35 (s, 3H), 1.33 (s, 3H).

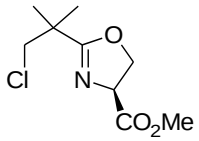
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 175.4, 171.0, 63.4, 55.1, 53.0, 52.9, 44.5, 23.7, 23.2.

**GC-MS** (Method B, $t_R$ = 14.9 min): *m/z* (%) 220 ([$M^+$–18], 1), 207 (15), 180 (10), 178 (33), 177 (10), 175 (31), 160 (20), 136 (23), 121 (14), 119 (45), 118 (10), 93 (31), 91 (100), 88 (25), 86 (17), 60 (16), 57 (10), 56 (47), 55 (55), 42 (21), 41 (31).

**IR**: $\tilde{\nu}$ = 3359 (w), 2954 (w), 2884 (w), 1739 (s), 1645 (s), 1519 (s), 1438 (m), 1209 (s), 1078 (m).

**$[\alpha]^{20}_D$** = +14.5 (c = 1.04, $CHCl_3$).

**Methyl (*S*)-2-(1-chloro-2-methylpropan-2-yl)-4,5-dihydrooxazole-4-carboxylate (159)** [70]




Under inert atmosphere methyl (3-chloro-2,2-dimethylpropanoyl)-*L*-serinate **158** (6.60 g, 27.8 mmol, 1.0 eq.) was dissolved in absolute methylene chloride (130 mL). DAST (4.93 g, 30.6 mmol, 1.1 eq.) was added dropwise at −78 °C and the reaction mixture was stirred at this temperature for one hour. Anhydrous potassium carbonate (5.76 g, 41.7 mmol, 1.5 eq.) was added and the mixture was warmed to room temperature. The reaction mixture was poured into saturated $NaHCO_3$-solution (140 mL) and the phases were separated. The aqueous phase was extracted with methylene chloride (3 x 140 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The product was obtained as a yellow oil (6.00 g, 98%) and was used without further purification.

$C_9H_{14}ClNO_3$ (219.66 g/mol)

**TLC**: $R_f$ = 0.20 (cyclohexane:EtOAc = 4:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.75 (dd, $^3J_{HH}$ = 10.5 Hz, $^3J_{HH}$ = 7.7 Hz, 1H), 4.51 (dd, $^2J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 7.7 Hz, 1H), 4.41 (dd, $^3J_{HH}$ = 10.5 Hz, $^2J_{HH}$ = 8.7 Hz, 1H), 3.78 (s, 3H), 3.65 (d, $^2J_{HH}$ = 10.8 Hz, 1H), 3.60 (d, $^2J_{HH}$ = 10.8 Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H).

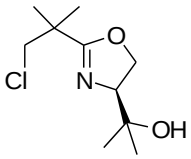
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 173.4, 171.7, 69.8, 68.3, 52.8, 52.4, 39.2, 23.9, 23.8.

**GC-MS** (Method B, $t_R$ = 10.8 min): *m/z* (%) 184 ([$M^+$–35], 11), 162 (32), 160 (100), 132 (17), 70 (67), 55 (26), 42 (18), 41 (13).

**IR**: $\tilde{\nu}$ = 2977 (w), 2954 (w), 1741 (s), 1651 (s), 1437 (m), 1206 (s), 1180 (s), 1118 (m), 982 (m) 751 (w).

**$[\alpha]^{20}_D$** = +108.4 (c = 0.95, $CHCl_3$).

**(*S*)-2-(2-(1-Chloro-2-methylpropan-2-yl)-4,5-dihydrooxazol-4-yl)propan-2-ol (160)** [70]




Under inert atmosphere methyl (*S*)-2-(1-chloro-2-methylpropan-2-yl)-4,5-dihydrooxazole-4-carboxylate **159** (785 g, 3.57 mmol, 1.0 eq.) was dissolved in absolute THF (15 mL) and a solution of methylmagnesium chloride in THF (3 M, 2.4 mL, 7.14 mmol, 2.0 eq.) was added dropwise at 0 °C and the reaction mixture was stirred for 1.5 hours at this temperature. Saturated ammonium chloride-solution (20 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 x 20 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 18 cm, cyclohexane:EtOAc = 4:1) to obtain the product as a colorless liquid (500 mg, 64%).

$C_{10}H_{18}ClNO_2$ (219.71 g/mol)

**TLC**: $R_f$ = 0.20 (cyclohexane:EtOAc = 3:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.27-4.20 (m, 2H), 4.03 (dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 7.7 Hz, 1H), 3.64 (d, $^2J_{HH}$ = 10.7 Hz, 1H), 3.60 (d, $^2J_{HH}$ = 10.7 Hz, 1H), 1.85 (s, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.12 (s, 3H).

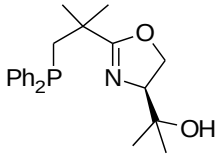
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 171.7, 75.3, 71.5, 69.1, 52.9, 39.2, 27.0, 24.9, 24.1, 23.9.

**GC-MS** (Method B, $t_R$ = 9.9 min): *m/z* (%) 204 ([$M^+$–15], 5), 163 (13), 161 (40), 126 (22), 121 (17), 119 (51), 93 (32), 91 (100), 59 (35), 56 (10), 55 (34), 43 (40), 42 (10), 41 (19).

**IR**: $\tilde{\nu}$ = 3255 (w), 2981 (m), 2965 (w), 2929 (w), 1649 (s), 1470 (m), 1362 (m), 1183 (s), 1145 (s), 1118 (s), 978 (s), 928 (m), 870 (m), 755 (m), 524 (m), 465 (m).

**$[\alpha]^{20}_D$** = +52.2 (c = 1.04, $CHCl_3$).

**(*S*)-2-(2-(1-(Diphenylphosphanyl)-2-methylpropan-2-yl)-4,5-dihydrooxazol-4-yl)propan-2-ol (L12)** [70]




Under inert atmosphere (*S*)-2-(2-(1-chloro-2-methylpropan-2-yl)-4,5-dihydrooxazol-4-yl)propan-2-ol **160** (520 mg, 2.37 mmol, 1.0 eq.) was dissolved in absolute THF (25 mL) and a solution of *n*-butyllithium in THF (1.6 M, 1.48 mL, 2.37 mmol, 1.0 eq.) was added at 0 °C followed by a solution of potassium diphenylphosphide in THF (0.5 M, 4.74 mL, 2.37 mmol, 1.0 eq.). The reaction mixture was warmed to room temperature and stirred under reflux for 16 hours. The solvent was evaporated and the residue redissolved in ether (75 mL) and saturated ammonium chloride-solution (15 mL). The phases were separated and the aqueous phase was extracted with ether (3 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 16 cm, cyclohexane:EtOAc = 4:1) to obtain the product as a colorless liquid (400 mg, 46%).

$C_{22}H_{28}NO_2P$ (369.44 g/mol)

**TLC**: $R_f$ = 0.33 (cyclohexane:EtOAc = 2:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.52-7.47 (m, 2H), 7.43-7.39 (m, 2H), 7.35-7.27 (m, 6H), 4.25 (dd, $^2J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 7.0 Hz, 1H), 4.03 (dd, $^3J_{HH}$ = 10.0 Hz, $^2J_{HH}$ = 8.1 Hz, 1H), 3.93 (dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 7.0 Hz, 1H), 2.59-2.54 (m, 2H), 2.37 (dd, $^2J_{HH}$ = 14.1 Hz, $^2J_{HP}$ = 3.5 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H), 1.11 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 173.9 (d, $^3J_{CP}$ = 1.8 Hz), 139.3 (d, $^1J_{CP}$ = 9.5 Hz), 138.8 (d, $^1J_{CP}$ = 10.2 Hz), 133.3 (d, $^2J_{CP}$ = 19.4 Hz), 132.9 (d, $^2J_{CP}$ = 19.2 Hz), 128.8, 128.6, 128.6, 128.5, 75.1, 71.7, 68.7, 41.4 (d, $^1J_{CP}$ = 14.0 Hz), 37.4 (d, $^2J_{CP}$ = 17.6 Hz), 28.1 (d, $^3J_{CP}$ = 7.4 Hz), 27.6, 27.5 (d, $^3J_{CP}$ = 9.2 Hz), 25.1.

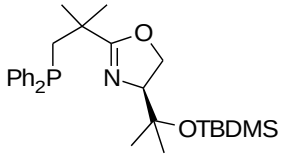
**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = –21.4.

**GC-MS** (Method D, $t_R$ = 16.4 min): *m/z* (%) 368 ([$M^+$–1], 2), 311 (37), 310 (100), 292 (26), 228 (14), 227 (91), 202 (14), 199 (12), 185 (11), 184 (13), 183 (37), 121 (35), 108 (15), 59 (12).

**IR**: ṽ = 3370 (w), 3060 (w), 2974 (w), 2929 (w), 1641 (m), 1433 (m), 1370 (w), 1185 (m), 1130 (m), 969 (m), 747 (m), 697 (s), 505 (m).

**$[\alpha]^{20}_D$** = +29.2 (c = 1.09, $CHCl_3$).

**(*S*)-4-(2-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-4,5-dihydrooxazole (L13)** [70]




Under inert atmosphere (*S*)-2-(2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-4,5-dihydrooxazol-4-yl)propan-2-ol **L12** (300 mg, 0.81 mmol, 1.0 eq.) was dissolved in absolute methylene chloride (15 mL) and 2,6-lutidine (435 mg, 4.06 mmol, 5.0 eq.) was added dropwise. Then *tert*-butyldimethylsilyl trifluoromethanesulfonate (429 mg, 1.62 mmol, 2.0 eq.) was added and the mixture was stirred for three hours at room temperature. The solvent was removed under high vacuum and the residue was redissolved in ether (10 mL). The precipitate was removed and the filtrate concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 17 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a colorless liquid (322 mg, 82%).

$C_{28}H_{42}NO_2PSi$ (483.71 g/mol)

**TLC**: $R_f$ = 0.56 (cyclohexane:EtOAc = 9:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.47-7.43 (m, 4H), 7.34-7.27 (m, 6H), 4.17 (dd, $^2J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 5.7 Hz, 1H), 3.77-3.68 (m, 2H), 2.50 (dd, $^2J_{HH}$ = 14.3 Hz, $^2J_{HP}$ = 3.8 Hz, 1H), 2.40 (dd, $^2J_{HH}$ = 14.3 Hz, $^2J_{HP}$ = 3.3 Hz, 1H), 1.33 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 1.12 (s, 3H), 0.81 (s, 9H), 0.06 (s, 6H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 173.1 (d, $^3J_{CP}$ = 3.3 Hz), 139.9 (d, $^1J_{CP}$ = 13.0 Hz), 139.7 (d, $^1J_{CP}$ = 12.5 Hz), 133.3 (d, $^2J_{CP}$ = 19.9 Hz), 132.9 (d, $^2J_{CP}$ = 19.5 Hz), 128.5-128.4 (m), 76.1, 74.8, 68.7, 41.2 (d, $^1J_{CP}$ = 16.8 Hz), 36.7 (d, $^2J_{CP}$ = 16.8 Hz), 28.9, 27.7 (d, $^3J_{CP}$ = 9.3 Hz), 27.2 (d, $^3J_{CP}$ = 10.7 Hz), 25.9, 24.6, 18.2,–2.0, –2.1.

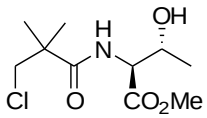
**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = –23.3.

**GC-MS** (Method D, $t_R$ = 27.9 min): *m/z* (%) 483 ([$M^+$–1], 1), 426 (29), 406, (32), 311 (23), 310 (73), 274 (13), 227 (51), 199 (24), 183 (19), 173 (100), 121 (38), 115 (21), 75 (20), 73 (76).

**IR**: $\tilde{\nu}$ = 3054 (w), 2955 (s), 2927 (s), 2897 (m), 2855 (s), 1657 (s), 1471 (m), 1433 (m), 1381 (m), 1253 (s), 1162 (s), 1053 (s), 907 (w), 835 (s), 774 (s), 742 (m), 696 (s).

**$[\alpha]^{20}_D$** = +12.5 (c = 1.05, $CHCl_3$).

**Methyl (3-chloro-2,2-dimethylpropanoyl)-*L*-threoninate[70]**




Threonine methylester hydrochloride **161** (5.10 g, 30.1 mmol, 1.0 eq.) was dissolved in methylene chloride (50 mL) and triethylamine (9.14 g, 90.3 mmol, 3.0 eq.) was added at 0 °C followed by slow addition of 3-chloropivaloyl chloride **156** (4.67 g, 30.1 mmol, 1.0 eq.). The reaction mixture was stirred for 18 hours at room temperature. Saturated $NaHCO_3$-solution (10 mL) was added to the mixture and the phases were separated. The aqueous phase was extracted with ether (3 x 30 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude mixture was purified by column chromatography (silica gel, 7 cm × 15 cm, EtOAc) to obtain the product as a pale yellow oil (6.80 g, 90%).

$C_{10}H_{18}ClNO_4$ (251.71 g/mol)

**TLC**: $R_f$ = 0.77 (EtOAc, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 6.53 (d, $^3J_{HH}$ = 8.3 Hz, 1H), 4.61 (dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 2.4 Hz, 1H), 4.40-4.34 (m, 1H), 3.77 (s, 3H), 3.71 (d, $^2J_{HH}$ = 10.8 Hz, 1H), 3.57 (d, $^2J_{HH}$ = 10.8 Hz, 1H), 2.34 (d, $^3J_{HH}$ = 4.8 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 3H), 1.22 (d, $^3J_{HH}$ = 6.4 Hz, 3H).

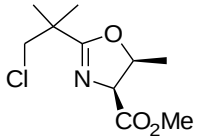
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 175.5, 171.6, 68.1, 57.3, 52.7, 44.6, 27.0, 23.8, 23.3, 20.2

**GC-MS** (Method B, $t_R$ = 15.2 min): *m/z* (%) 209 ([$M^+$–42], 12), 207 (35), 192 (11), 177 (32), 175 (100), 126 (33), 121 (12), 120 (10), 119 (35), 93 (28), 88 (59), 83 (11), 74 (12), 57 (10), 56 (41), 55 (48), 45 (15), 41 (24).

**IR**: $\tilde{\nu}$ = 3391 (m), 2975 (m), 1740 (s), 1648 (s), 1521 (s), 1438 (m), 1288 (m), 1209 (s), 1084 (m), 1020 (m), 731 (w).

**$[\alpha]^{20}_D$** = –8.5 (c = 1.16, $CHCl_3$).

**Methyl (4*S*,5*S*)-2-(1-chloro-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (162)** [70]




Under inert atmosphere methyl (3-chloro-2,2-dimethylpropanoyl)-*L*-threoninate (5.51 g, 21.9 mmol, 1.0 eq.) was dissolved in absolute methylene chloride (100 mL). DAST (4.24 g, 26.3 mmol, 1.2 eq.) was added dropwise at −78 °C and the reaction mixture was stirred at this temperature for one hour. Anhydrous potassium carbonate (4.54 g, 32.8 mmol, 1.5 eq.) was added and the reaction mixture was warmed to room temperature. The reaction mixture was poured into saturated $NaHCO_3$-solution (100 mL) and the phases were separated. The aqueous phase was extracted with methylene chloride (3 x 100 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 4 cm × 18 cm, cyclohexane:EtOAc = 4:1) to obtain the product as a colorless liquid (4.48 g, 88%).

$C_{10}H_{16}ClNO_3$ (233.69 g/mol)

**TLC**: $R_f$ = 0.20 (cyclohexane:EtOAc = 4:1, $KMnO_4$).

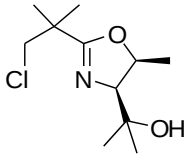
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.92-4.85 (m, 1H), 4.78 (d, $^3J_{HH}$ = 10.0 Hz, 1H), 3.74 (s, 3H), 3.65 (d, $^2J_{HH}$ = 10.8 Hz, 1H), 3.62 (d, $^2J_{HH}$ = 10.8 Hz, 1H), 1.34 (s, 3H), 1.34 (s, 3H), 1.27 (d, $^3J_{HH}$ = 6.4 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 173.3, 170.4, 77.9, 71.4, 52.4, 52.1, 39.1, 23.7, 23.7, 16.1.

**GC-MS** (Method B, $t_R$ = 11.5 min): *m/z* (%) 198 ([$M^+$–35], 13), 176 (31), 174 (97), 140 (12), 84 (100), 57 (21), 55 (23), 41 (11).

**$[\alpha]^{20}_D$** = +51,7 (c = 1.12, $CHCl_3$).

**2-((4*S*,5*S*)-2-(1-Chloro-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-ol (163)** [70]




Under inert atmosphere methyl (4*S*,5*S*)-2-(1-chloro-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate **162** (337 mg, 1.44 mmol, 1.0 eq.) was dissolved in absolute THF (5 mL) and a solution of methylmagnesium chloride in THF (3 M, 0.96 mL, 2.88 mmol, 2.0 eq.) was added dropwise at −78 °C. The reaction mixture was stirred overnight while slowly warming up to room temperature in the cooling bath. Saturated ammonium chloride-solution (10 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (silica gel, 2 cm × 17 cm, cyclohexane:EtOAc = 3:1) to obtain the product as a yellow liquid (235 mg, 70%).

$C_{11}H_{20}ClNO_2$ (233.74 g/mol)

**TLC**: $R_f$ = 0.20 (cyclohexane:EtOAc = 3:1, $KMnO_4$).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.79-4.71 (m, 1H), 3.89 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 3.63 (d, $J_{HH}$ = 1.7 Hz, 2H), 2.25 (s, 1H), 1.46 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H).

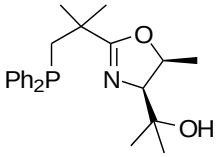
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 171.1, 79.5, 76.1, 72.0, 52.7, 39.1, 28.5, 26.4, 23.9, 23.8, 16.2.

**GC-MS** (Method B, $t_R$ = 11.0 min): *m/z* (%) 218 ([$M^+$−15], 3), 177 (12), 175 (34), 162 (10), 160 (33), 119 (29), 93 (31), 91 (100), 84 (15), 83 (11), 59 (29), 57 (26), 56 (17), 55 (31), 43 (19), 41 (17).

**IR**: $\tilde{\nu}$ = 3427 (w), 2976 (m), 2934 (m), 2873 (w), 1656 (s), 1459 (w), 1385 (s), 1338 (m), 1117 (s), 1023 (m), 945 (m), 830 (m), 751 (w).

**$[\alpha]^{20}_D$** = +14.3 (c = 1.02, $CHCl_3$).

**2-((4*S*,5*S*)-2-(1-(Diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-ol (L14)** [70]




Under inert atmosphere 2-((4*S*,5*S*)-2-(1-chloro-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-ol **163** (514 mg, 2.20 mmol, 1.0 eq.) was dissolved in absolute THF (25 mL) and a solution of *n*-butyllithium in THF (1.6 M, 1.38 mL, 2.20 mmol, 1.0 eq.) was added at 0 °C followed by a solution of potassium diphenylphosphide in THF (0.5 M, 4.4 mL, 2.20 mmol, 1.0 eq.). The reaction mixture was warmed to room temperature and stirred under reflux for 16 hours. The solvent was evaporated and the residue was purified by column chromatography (silica gel, 3 cm × 16 cm, cyclohexane:EtOAc = 1:1) to obtain the product as a colorless liquid (480 mg, 57%).

$C_{23}H_{30}NO_2P$ (383.47 g/mol)

**TLC**: $R_f$ = 0.18 (cyclohexane:EtOAc = 3:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.52-7.48 (m, 2H), 7.43-7.39 (m, 2H), 7.34-7.25 (m, 6H), 4.55-4.48 (m, 1H), 3.74 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 2.69 (brs, 1H), 2.56 (dd, $^2J_{HH}$ = 14.3 Hz, $^2J_{HP}$ = 4.9 Hz, 1H), 2.38 (dd, $^2J_{HH}$ = 14.3 Hz, $^2J_{HP}$ = 3.4 Hz, 1H), 1.48 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 173.2 (d, $^3J_{CP}$ = 2.2 Hz), 139.7 (d, $^1J_{CP}$ = 10.6 Hz), 139.0 (d, $^1J_{CP}$ = 11.1 Hz), 133.3 (d, $^2J_{CP}$ = 19.7 Hz), 132.8 (d, $^2J_{CP}$ = 19.1 Hz), 128.7, 128.5, 128.4, 128.4, 79.3, 75.6 72.2 41.1 (d, $^1J_{CP}$ = 15.0 Hz), 37.2 (d, $^2J_{CP}$ = 17.7 Hz), 29.0, 27.7 (d, $^3J_{CP}$ = 8.2 Hz), 27.4 (d, $^3J_{CP}$ = 9.7 Hz), 26.3, 16.2.

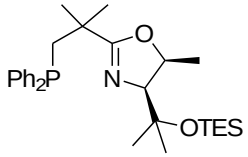
**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = –21.8.

**GC-MS** (Method D, $t_R$ = 17.4 min): *m/z* (%) 368 ([$M^+$–15], 3), 325 (13), 324 (59), 306 (11), 284 (45), 228 (15), 227 (100), 202 (19), 185 (11), 184 (10), 183 (30), 121 (25), 108 (12), 59 (10).

**IR**: $\tilde{\nu}$ = 3424 (w), 3053 (w), 2971 (w), 2928 (w), 1651 (m), 1434 (m), 1383 (m), 1168 (m), 1126 (m), 1093 (m), 1023 (m), 741 (m), 695 (s), 508 (m).

**$[\alpha]^{20}_D$** = +28.4 (c = 0.95, $CHCl_3$).

**(4*S*,5*S*)-2-(1-(Diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4-(2-((triethylsilyl)oxy)propan-2-yl)-4,5-dihydrooxazole (L15)** [70]




Under inert atmosphere 2-((4*S*,5*S*)-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-ol **L14** (70.0 mg, 0.18 mmol, 1.0 eq.) was dissolved in absolute methylene chloride (4 mL) and 2,6-lutidine (98.1 mg, 0.92 mmol, 5.0 eq.) was added dropwise. Then, triethylsilyl trifluoromethanesulfonate (96.7 mg, 0.37 mmol, 2.0 eq.) was added and the reaction mixture was stirred for three hours at room temperature. The solvent was removed under high vacuum and the residue was redissolved in ether (5 mL). The precipitate was removed and the filtrate concentrated. The crude product was purified by column chromatography (silica gel, 2 cm ×17 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a colorless liquid (77.0 mg, 85%).

$C_{29}H_{44}NO_2PSi$ (497.73 g/mol)

**TLC**: $R_f$ = 0.52 (cyclohexane:EtOAc = 9:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.48-7.43 (m, 4H), 7.33-7.27 (m, 6H), 4.36-4.29 (m, 1H), 3.62 (d, $^3J_{HH}$ = 9.2 Hz, 1H), 2.52 (dd, $^2J_{HH}$ = 14.4 Hz, $^2J_{HP}$ = 4.0 Hz, 1H), 2.40 (dd, $^2J_{HH}$ = 14.4 Hz, $^2J_{HP}$ = 3.4 Hz, 1H), 1.46 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H), 0.94 (t, $^3J_{HH}$ = 8.0 Hz, 9H), 0.58 (q, $^3J_{HH}$ = 8.0 Hz, 6H).

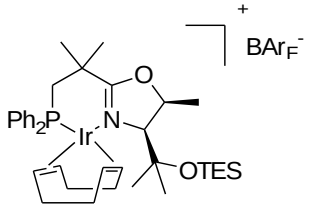
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 172.8 (d, $^3J_{CP}$ = 3.2 Hz), 140.1 (d, $^1J_{CP}$ = 12.7 Hz), 139.9 (d, $^1J_{CP}$ = 13.0 Hz), 133.3 (d, $^2J_{CP}$ = 19.8 Hz), 133.0 (d, $^2J_{CP}$ = 19.5 Hz), 128.5, 128.4, 128.4, 128.4, 79.9, 76.1, 75.7, 41.1 (d, $^1J_{CP}$ = 16.6 Hz), 36.9 (d, $^2J_{CP}$ = 17.3 Hz), 30.7, 27.5 (d, $^3J_{CP}$ = 9.4 Hz), 27.1 (d, $^3J_{CP}$ = 10.5 Hz), 26.4, 16.3, 7.2, 7.0.

**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = –23.0.

**IR**: $\tilde{\nu}$ = 3054 (w), 2956 (w), 2911 (w), 2875 (w), 1655 (w), 1433 (w), 1382 (w), 1236 (w), 1163 (m), 1037 (m), 857 (w), 738 (s), 694 (s), 506 (w).

**$[\alpha]^{20}_D$** = +8.1 (c = 1.06, $CHCl_3$).

**(4*S*,5*S*)-[1,5-Cyclooctadiene-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4-(2-((triethylsilyl)oxy)propan-2-yl)-4,5-dihydrooxazole-iridium(I)]-tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (C13)** [70]




Chloro(1,5-cyclooctadiene)iridium(I)dimer (20.2 mg, 30.0 µmol, 0.5 eq.) was added to a solution of (4*S*,5*S*)-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4-(2-((triethylsilyl)oxy)propan-2-yl)-4,5-dihydrooxazole **L15** (30.0 mg, 60.0 µmol, 1.0 eq.) in absolute methylene chloride (5 mL) and heated to reflux for 2.5 hours. After that the reaction mixture was cooled to room temperature, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (69.1 mg, 78.0 µmol, 1.3 eq.) was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was immobilized on silica gel, put on column and washed with ether (100 mL) The solvent was changed to methylene chloride and the product was eluted. The product was obtained as an orange solid (84 mg, 84%).

$C_{69}H_{68}BF_{24}IrNO_2PSi$ (1661.35 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.79-7.74 (m, 10H), 7.60-7.50 (m, 7H), 7.39-7.36 (m, 3H), 7.05-7.00 (m, 2H), 4.88-4.81 (m, 1H), 4.78 (m, 2H), 3.58-3.56 (m, 2H), 2.64-2.46 (m, 5H), 2.29-2.27 (m, 2H), 2.19 (s, 3H), 2.12-2.05 (m, 1H), 1.90-1.81 (m, 1H), 1.74 (d, $^3J_{HH}$ = 7.0 Hz, 3H), 1.63-1.59 (m, 1H), 1.42 (d, $^4J_{HH}$ = 2.8 Hz, 3H), 1.42 (s, 3H), 1.39-1.34 (m, 1H), 0.84-0.80 (m, 12H), 0.48-0.33 (m, 6H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 180.6 (d, $^3J_{CP}$ = 3.5 Hz), 161.9 (q, $^2J_{CF}$ = 49.9 Hz), 135.1 (d, $J_{CP}$ = 12.6 Hz), 135.0, 132.8, 132.7. 131.3, 131.2, 129.7 (d, $J_{CP}$ = 10.6 Hz), 129.2 (d, $J_{CP}$ = 10.2 Hz), 128.8 (q, $^3J_{CF}$ = 31.8 Hz), 128.8 (q, $^1J_{CF}$ = 272 Hz), 117.6, 94.3 (d, $J_{CP}$ = 10.5 Hz), 93.2 (d, $J_{CP}$ = 13.1 Hz), 84.7, 74.4, 74.2, 63.2, 60.0, 39.0, 39.0, 36.5, 36.4, 33.5 (d, $J_{CP}$ = 6.3 Hz), 33.3 (d, $J_{CP}$ = 33.0 Hz), 32.3, 32.3, 30.1, 28.5, 28.5, 27.1 (d, $J_{CP}$ = 12.2 Hz), 26.2, 26.0, 26.0, 15.3, 7.0, 6.6.

**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = 8.3.

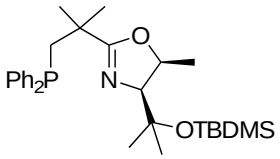
**$^{11}$B-NMR** (128 MHz, $CDCl_3$): δ (ppm) = –6.6.

**$^{19}$F-NMR** (376 MHz, $CDCl_3$): δ (ppm) = –62.4.

**IR**: $\tilde{\nu}$ = 2957 (w), 1353 (m), 1275 (s), 1163 (m), 1121 (s), 1027 (w), 887 (m), 838 (w), 744 (m), 733 (m), 696 (m), 682 (m).

$[\alpha]^{20}_D$ = –17.0 (c = 1.05, $CHCl_3$).

**(4*S*,5*S*)-4-(2-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazole (L16)** [70]




Under inert atmosphere 2-((4*S*,5*S*)-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-ol **L14** (300 mg, 0.81 mmol, 1.0 eq.) was dissolved in absolute methylene chloride (15 mL) and 2,6-lutidine (435 mg, 4.06 mmol, 5.0 eq.) was added dropwise. Then *tert*-butyldimethylsilyl trifluoromethanesulfonate (429 mg, 1.62 mmol, 2.0 eq.) was added and the mixture was stirred for three hours at room temperature. The solvent was removed under high vacuum and the residue was redissolved in ether (10 mL). The precipitate was removed and the filtrate concentrated. The crude product was purified by column chromatography (silica gel, 3 cm × 17 cm, cyclohexane:EtOAc = 9:1) to obtain the product as a colorless liquid (322 mg, 82%).

$C_{29}H_{44}NO_2PSi$ (497.73 g/mol)

**TLC**: $R_f$ = 0.39 (cyclohexane:EtOAc = 9:1, UV).

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.48-7.42 (m, 4H), 7.33-7.27 (m, 6H), 4.38-4.31 (m, 1H), 3.60 (d, $^3J_{HH}$ = 9.3 Hz, 1H), 2.51 (dd, $^2J_{HH}$ = 14.4 Hz, $^2J_{HP}$ = 4.1 Hz, 1H), 2.40 (dd, $^2J_{HH}$ = 14.4 Hz, $^2J_{HP}$ = 3.4 Hz, 1H), 1.45 (d, $^3J_{HH}$ = 6.8 Hz, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 0.85 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 172.6 (d, $^3J_{CP}$ = 3.4 Hz), 140.1 (d, $^1J_{CP}$ = 12.7 Hz), 139.9 (d, $^1J_{CP}$ = 13.1 Hz), 133.3 (d, $^2J_{CP}$ = 19.8 Hz), 133.0 (d, $^2J_{CP}$ = 19.4 Hz), 128.5-128.3 (m), 79.7, 76.2, 76.0, 41.1 (d, $^1J_{CP}$ = 16.5 Hz), 36.8 (d, $^2J_{CP}$ = 17.2 Hz), 30.7, 27.5 (d, $^3J_{CP}$ = 9.3 Hz), 27.2 (d, $^3J_{CP}$ = 10.4 Hz), 26.4, 26.1, 18.3, 16.5, –1.7, –1.7.

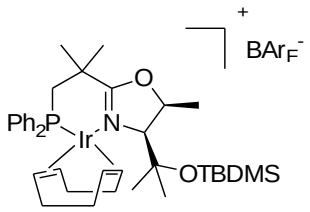
**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = –22.9.

**GC-MS** (Method D, $t_R$ = 31.5 min): *m/z* (%) 483 ([$M^+$–1], 1), 440 (47), 421 (10), 420 (22), 325 (16), 324 (87), 288 (11), 284 (27), 228 (10), 227 (100), 199 (23), 185 (20), 184 (11), 183 (23), 174 (10), 173 (79), 121 (31), 115 (19), 108 (11), 75 (14), 73 (60).

**IR**: $\tilde{\nu}$ = 3054 (w), 2956 (w), 2929 (w), 2856 (w), 1656 (w), 1434 (w), 1383 (w), 1252 (m), 1162 (s), 1029 (s), 834 (s), 772 (s), 740 (s), 694 (s), 507 (w).

**$[\alpha]^{20}_D$** = +6.8 (c = 0.99, $CHCl_3$).

**(4*S*,5*S*)-[1,5-Cyclooctadiene-4-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazole-iridium(I)]-tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate (C14)** [70]




Chloro(1,5-cyclooctadiene)iridium(I)dimer (20.2 mg, 30.0 µmol, 0.5 eq.) was added to a solution of (4*S*,5*S*)-4-(2-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-2-(1-(diphenylphosphanyl)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazole **L15** (30.0 mg, 60.0 µmol, 1.0 eq.) in absolute methylene chloride (5 mL) and heated to reflux for 2.5 hours. After that the reaction mixture was cooled to room temperature, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (69.1 mg, 78.0 µmol, 1.3 eq.) was added and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was immobilized on silica, put on column and washed with ether (100 mL) The solvent was changed to methylene chloride and the product was eluted. The product was obtained as a orange solid (73 mg, 73%).

$C_{69}H_{68}BF_{24}IrNO_2PSi$ (1661.35 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.77-7.75 (m, 2H), 7.73-7.70 (m, 8H), 7.62-7.58 (m, 1H), 7.55-7.50 (m, 6H), 7.42-7.35 (m, 3H), 7.04-6.98 (m, 2H), 4.87-4.80 (m, 1H), 4.76-4.72 (m, 2H), 3.57-3.52 (m, 2H), 2.65-2.56 (m, H), 2.49-2.42 (m, 1H), 2.29-2.26 (m, 2H), 2.19 (s, 3H), 2.11-2.04 (m, 1H), 1.88-1.79 (m, 1H), 1.77 (d, $^3J_{HH}$ = 7.0 Hz, 3H), 1.65-1.59 (m, 1H), 1.52 (d, $^4J_{HH}$ = 3.0 Hz, 3H), 1.40 (s, 3H), 1.38-1.33 (m, 1H), 0.92 (s, 3H), 0.72 (s, 9H), 0.03 (s, 3H), –0.30 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 180.6 (d, $^3J_{CP}$ = 3.5 Hz), 161.77 (q, $^2J_{CF}$ = 49.9 Hz), 135.2 (d, $J_{CP}$ = 12.6 Hz), 134.8, 132.6 (d, $J_{CP}$ = 2.0 Hz), 132.2 (d, $J_{CP}$ = 55.0 Hz), 131.2, 131.1, 129.6 (d, $J_{CP}$ = 10.6 Hz), 129.0 (d, $J_{CP}$ = 10.2 Hz), 128.9 (q, $^3J_{CF}$ = 31.8 Hz), 128.8 (d, $J_{CP}$ = 54.0 Hz), 124.6 (q, $^1J_{CF}$ = 272 Hz), 117.5, 94.2 (d, $J_{CP}$ = 10.5 Hz), 93.0 (d, $J_{CP}$ = 13.1 Hz), 84.5, 74.4, 74.3, 62.8, 59.7, 38.9 (d, $J_{CP}$ = 2.1 Hz), 36.4 (d, $J_{CP}$ = 4.8 Hz), 33.7 (d, $J_{CP}$ = 6.3 Hz), 33.0 (d, $J_{CP}$ = 33.0 Hz), 32.2, 29.7 28.3, 26.8 (d, $J_{CP}$ = 12.2 Hz), 26.1, 25.7, 25.7, 17.8, 15.0, –2.0, –2.4.

**$^{31}$P{$^1$H}-NMR** (162 MHz, $CDCl_3$): δ (ppm) = 8.5.

**$^{11}$B-NMR** (128 MHz, $CDCl_3$): δ (ppm) = –6.6.

**$^{19}$F-NMR** (376 MHz, $CDCl_3$): δ (ppm) = –62.4.

**IR**: $\tilde{\nu}$ = 2957 (w), 1353 (m), 1275 (s), 1163 (m), 1121 (s), 1027 (w), 887 (m), 838 (w), 744 (m), 733 (m), 696 (m), 682 (m).

**$[\alpha]^{20}_D$** = –19.5 (c = 1.10, $CHCl_3$).

## 5.6 Hydrogenation of cyclohexenes and test substrates

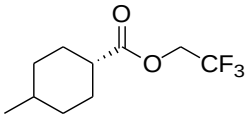
**General working procedure for hydrogenations with palladium on charcoal**

In a 2 mL vial with magnetic stirrer, palladium on charcoal (10 mass%) and the substrate (0.1 mmol) were suspended in absolute methylene chloride (0.5 mL) and the vial was put in an autoclave. The mixture was stirred for 24 hours at room temperature and 50 bar hydrogen pressure with 900 rounds per minute. The reaction mixture was concentrated, the residue redissolved in a pentane/ether mixture (4:1) and filtered through a pipette with silica gel (0.5 cm × 2 cm). The filtrate was concentrated and analyzed.

**General working procedure for hydrogenations with iridium catalysts**

In a 2 mL vial with magnetic stirrer, the substrate (0.1 mmol) and the catalyst (1 mol%) were dissolved in absolute methylene chloride (0.5 mL) and the vial was put in an autoclave. The solution was stirred for 24 hours at room temperature at 50 bar hydrogen pressure with 900 rounds per minute. The reaction mixture was concentrated, the residue redissolved in a pentane/ether mixture (4:1) and filtered through a pipette with silica gel (0.5 cm × 2 cm). The filtrate was concentrated and analyzed.

**2,2,2-Trifluoroethyl 4-methylcyclohexane-1-carboxylate (76)**



$C_{10}H_{15}F_3O_2$ (224,22 g/mol)

Analytical data for the major product of the hydrogenation with (*R*)-**C11**:

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.45 (q, $^{3}J_{HF}$ = 8.5 Hz, 2H), 2.32 (tt, $^{3}J_{HH}$ = 12.2 Hz, $^{3}J_{HH}$ = 3.6 Hz 1H), 2.01-1.96 (m, 2H), 1.79-1.75 (m, 2H), 1.51-1.40 (m, 2H), 1.39-1.31 (m, 1H), 1.00-0.92 (m, 2H), 0.90 (d, $^{3}J_{HH}$ = 6.6 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 174.7, 123.2 (q, $^{1}J_{CF}$ = 277 Hz), 60.2 (q, $^{2}J_{CF}$ = 36 Hz), 42.8, 34.2, 32.0, 29.0, 22.6 (R).

**$^{19}$F-NMR** (376 MHz, $CDCl_3$): δ (ppm) = –73.9.

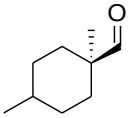
**GC-MS** (Method A, $t_R$ = 11.2 min): *m/z* (%) 224 ($M^+$, 24), 155 (22), 125 (15), 124 (31), 97 (45), 96 (14), 95 (19), 83 (26) 82 (52), 81 (57), 70 (71), 69 (16), 67 (22), 56 (10), 55 (100), 42 (12), 41 (35). 224 ($M^+$, 18), 155 (24), 135 (15), 125 (11), 124 (33), 97 (35), 96 (15), 95 (16), 83 (32), 82 (82), 81 (59), 70 (87), 69 (23), 67 (26), 56 (13), 55 (100), 54 (10), 43 (14), 42 (11), 41 (33).

Analytical data for the major product of the hydrogenation with (*S*)-**C11**:

**$^{1}$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.48 (q, $^{3}J_{HF}$ = 8.5 Hz, 2H), 2.63 (quint, $^{3}J_{HH}$ = 5.0 Hz 1H), 2.03-1.97 (m, 2H), 1.63-1.51 (m, 5H), 1.25-1.15 (m, 2H), 0.90 (d, $^{3}J_{HH}$ = 6.6 Hz, 3H).

**$^{19}$F-NMR** (376 MHz, $CDCl_3$): δ (ppm) = –73.9.

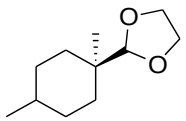
**1,4-Dimethylcyclohexane-1-carbaldehyde (78)**



$C_9H_{16}O$ (140.23 g/mol)

**GC-MS** (Method A, $t_{R(minor)}$ = 8.2 min $t_{R(major)}$ = 9.5 min): *m/z* (%) 140 ($M^+$, 4), 111 (74), 69 (100), 55 (50), 41 (28).

**2-(1,4-Dimethylcyclohexyl)-1,3-dioxolane (140)**



$C_{11}H_{20}O_2$ (184.28 g/mol)

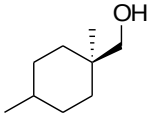
Analytical data for the main product of the hydrogenation with (*R*)-**C11**:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.90 (s, 1H, major), 4.44 (s, 1H, minor), 3.94-3.82 (m, 2H, major, 2H, minor), 1.80-1.76 (m, 1H, major, 1H, minor), 1.54-1.02 (m, 8H, major, 8H, minor), 0.90 (s, 3H, minor), 0.89 (d, $^3J_{HH}$ = 6.7 Hz, 3H, major), 0.89 (d, $^3J_{HH}$ = 6.7 Hz, 3H, minor), 0.82 (s, 3H, minor).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 111.5, 65.3, 37.1, 33.0, 32.0, 30.2, 22.8, 16.8, all major. 107.0, 65.3, 36.1, 33.3, 31.3, 30.0, 21.7, 21.5, all minor.

**GC-MS** (Method B, $t_{R(major)}$ = 8.0 min, $t_{R(minor)}$ = 8.4 min): *m/z* (%) 110 ([$M^+$–74], 3), 95 (2), 73 (100), 69 (5), 55 (5), 45 (9), 41 (5).

**(1,4-Dimethylcyclohexyl)methanol (141)**



$C_9H_{18}O$ (142.24 g/mol)

Analytical data for the main product of the hydrogenation with (*R*)-**C11**:

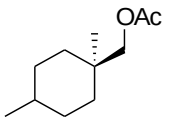
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 3.47 (s, 2H, major), 3.28 (s, 2H, minor), 1.60-1.00 (m, 9H, major, 9H, minor), 0.90 (d, $^3J_{HH}$ = 5.4 Hz, 3H, minor), 0.89 (s, 3H, major), 0.89 (s, 3H, minor), 0.88 (d, $^3J_{HH}$ = 7.2 Hz, 3H, major).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 67.8, 34.4, 34.1, 32.3, 30.6, 26.9, 22.2, all major. 75.0, 35.0, 33.8, 33.1, 30.5, 22.7, 19.6, all minor.

**GC-MS** (Method B, $t_{R(major)}$ = 4.9 min, $t_{R(minor)}$ = 5.0 min): *m/z* (%) 112 ($M^+$–30, 8), 111 (82), 110 (40), 95 (11), 69 (100), 55 (42), 41 (27).

**IR**: $\tilde{\nu}$ = 3326 (w), 2911 (s), 2852 (s), 1455 (m), 1375 (m), 1150 (w), 1045 (s), 1009 (m).

**(1,4-Dimethylcyclohexyl)methyl acetate (142)**




$C_{11}H_{20}O_2$ (184.28 g/mol)

Analytical data for the hydrogenation with (*R*)-**C11**:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 3.94 (s, 2H, major), 3.75 (s, 2H, minor), 2.05 (s, 3H, major), 2.05 (s, 3H, minor), 1.63-0.99 (m, 9H, major), 1.53-1.04 (m, 9H, minor), 0.92 (s, 3H, minor), 0.90 (s, 3H, major), 0.90 (d, $^3J_{HH}$ = 6.3 Hz, 3H, minor) 0.88 (d, $^3J_{HH}$ = 6.5 Hz, 3H, major).

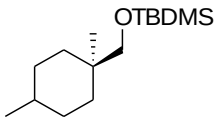
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 171.6, 68.9, 34.6, 33.0, 32.3, 30.6, 27.4, 22.2, 21.1, all major.

171.5, 75.2, 34.1, 33.6, 32.9, 30.3, 22.6, 21.1, 19.9, all minor.

**GC-MS** (Method B, $t_{R(major)}$ = 7.0 min, $t_{R(minor)}$ = 7.4 min): *m/z* (%) 124 ([$M^+$–60], 17), 111 (84), 110 (32), 109 (19), 96 (16), 95 (24), 82 (14), 81 (16), 69 (100), 68 (17), 67 (13), 55 (43), 43 (36), 41 (18).

**IR**: $\tilde{\nu}$ = 2912 (w), 2854 (w), 2839 (w), 1739 (s), 1439 (w), 1373 (m), 1240 (s), 1036 (m).

***tert*-Butyl((1,4-dimethylcyclohexyl)methoxy)dimethylsilane (143)**




$C_{15}H_{32}OSi$ (256.51 g/mol)

Analytical data for the hydrogenation with (*R*)-**C11**:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 3.37 (s, 2H, major), 3.27 (s, 2H, minor), 1.60-1.00 (m, 9H, major), 1.54-1.04 (m, 9H, minor), 0.89 (2xs, 9H, 3H, major), 0.89 (2xs, 9H, 3H, minor), 0.87 (d, $^3J_{HH}$ = 5.6 Hz, 3H, major), 0.85 (d, $^3J_{HH}$ = 5.6 Hz, 3H, minor)0.02 (s, 3H, major), 0.02 (s, 3H, minor), 0.01 (s, 3H, major), 0.01 (s, 3H, minor).

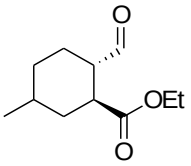
3.27 (s, 2H), 1.54-1.04 (m, 9H), 0.89 (s, 6H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 67.5, 34.6, 34.1, 32.3, 30.8, 27.4, 26.1, 22.3, 18.5, –5.3, all major.

74.5, 35.2, 34.4, 33.2, 30.7, 26.1, 22.8, 19.9, 18.5, –5.3, all minor.

**GC-MS** (Method B, $t_{R(major)}$ = 10.0 min, $t_{R(minor)}$ = 10.6 min): *m/z* (%) 241 ([$M^+$–15], 1), 200 (12), 199 (77), 123 (43), 81 (11), 75 (100), 73 (14).

**Ethyl (1*S*,2*S*)-2-formyl-5-methylcyclohexane-1-carboxylate (146)**



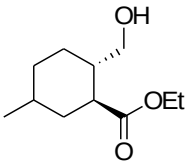

$C_{11}H_{18}O_3$ (198.26 g/mol)

Analytical data for hydrogenation with Pd/C:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.65 (s, 1H, major), 9.62 (s, 1H, minor), 4.15 (q, $^3J_{HH}$ = 7.1 Hz, 2H, minor), 4.12 (q, $^3J_{HH}$ = 7.1 Hz, 2H, major), 2.63-2.50 (m, 1H, major, minor), 2.10-2.01 (m, 2H, major, 2H, minor), 1.89-1.70 (m, 2H, major, 2H, minor), 1.46-1.36 (m, 1H, major, 1H, minor), 1.27-0.98 (m, 3H, major, 3H, minor), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H, minor), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H,major), 0.94 (d, $^3J_{HH}$ = 6.6 Hz, 3H, major), 0.90 (d, $^3J_{HH}$ = 6.8 Hz, 3H, minor).

**GC-MS** (Method B, $t_{R(minor)}$ = 10.0 min, $t_{R(major)}$ = 10.2 min): *m/z* (%) 171 ([$M^+$–17], 10), 170 (86), 155 (12), 153 (38), 142 (20), 141 (10), 127 (19), 125 (14), 124 (32), 115 (12), 107 (19), 102 (11), 101 (46), 99 (21), 97 (40), 96 (70), 95 (71), 93 (10), 67 (38), 57 (10), 55 (70), 54 (20), 53 (17), 43 (28), 41 (47).

**Ethyl (1*S*,2*S*)-2-(hydroxymethyl)-5-methylcyclohexane-1-carboxylate (147)**




$C_{11}H_{20}O_3$ (200.28 g/mol)

Analytical data for main product of hydrogenation with (*R*)-**C11**:

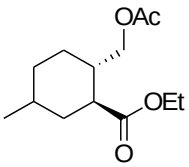
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.12 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 3.53-3.49 (m, 2H), 2.23-2.16 (m, 1H), 1.93-1.68 (m, 5H), 1.59-1.33 (m, 2H), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.20-1.09 (m, 1H), 1.03-0.93 (m, 1H), 0.91 (d, $^3J_{HH}$ = 6.5 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 176.5, 66.7, 60.5, 46.6, 41.7, 38.2, 34.1, 32.0, 28.7, 22.3, 14.4.

**GC-MS** (Method B, $t_R$ = 9.7 min): *m/z* (%) 154 ([$M^+$–46], 9), 95 (36), 82 (69), 81 (100), 79 (11), 68 (29), 67 (51), 55 (24). 54 (43), 53 (11), 41 (30).

**IR**: $\tilde{\nu}$ = 3461 (w), 2923 (m), 2852 (w), 1725 (s), 1553 (m), 1449 (m), 1375 (m), 1254 (m), 1177 (s), 1097 (m), 1030 (s), 699 (m).

**Ethyl (1*S*,2*S*)-2-(acetoxymethyl)-5-methylcyclohexane-1-carboxylate (148)**




$C_{13}H_{22}O_4$ (242.32 g/mol)

Analytical data for hydrogenation with (*R*)-**C11**:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 4.15-4.07 (m, 2H, major, 2H, minor, 4.02-3.85 (m, 2H, major, 2H, minor), 2.22-2.08 (m, 1H major, 1H, minor), 2.03 (s, 3H, minor), 2.01 (s, 3H, major), 1.94-1.34 (m, 6H, major, 6H, minor), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, major, 3H, minor), 1.19-0.96 (m, 2H, major, 2H, minor), 0.94 (d, $^3J_{HH}$ = 7.0 Hz, 3H, minor), 0.90 (d, $^3J_{HH}$ = 6.5 Hz, 3H, major).

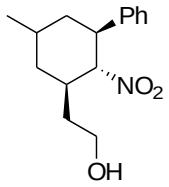
**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 175.5, 171.1, 67.6, 60.4, 46.6, 38.3, 38.2, 33.9, 31.9, 28.8, 22.3, 21.0, 14.3, all major.

175.6, 171.1, 66.9, 60.4, 41.0, 36.9, 34.1, 30.2, 27.4, 23.2, 21.0, 19.2, 14.4, all minor.

**GC-MS** (Method B, $t_{R(major)}$ = 13.5 min, $t_{R(minor)}$ = 13.6 min): *m/z* (%) 200 ([$M^+$–42], 5), 199 (39), 182 (18), 155 (56), 154 (20), 153 (100), 136 (55), 125 (17). 110 (11), 109 (59), 108 (39), 107 (23), 101 (22), 97 (17), 95 (33), 94 (13), 93 (13), 82 (11), 81 (29), 79 (14), 73 (17), 67 (33), 55 (23), 43 (92), 41 (17).

**IR**: $\tilde{\nu}$ = 2925 (w), 2855 (w), 1730 (s), 1450 (w), 1366 (w), 1232 (s), 1179 (m), 1137 (w), 1035 (m).

**2-((1*R*,2*R*,3*S*)-5-Methyl-2-nitro-3-phenylcyclohexyl)ethan-1-ol (151)**




$C_{15}H_{21}NO_3$ (263.34 g/mol)

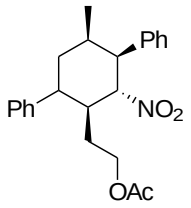
Analytical data for major product for the hydrogenation with (*S*)-**C11**:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.34-7.21 (m, 3H), 7.19-7.16 (m, 2H), 4.46 (t, $^3J_{HH}$ = 11.0 Hz, 1H), 3.76-3.62 (m, 2H), 3.24-3.17 (m, 1H), 2.39-2.29 (m, 1H), 2.07-2.02 (m, 1H), 1.99-1.93 (m, 1H), 1.81-1.74 (m, 1H), 1.67-1.59 (m, 1H), 1.53-1.45 (m, 1H), 1.41 (brs, 1H), 1.38-1.20 (m, 2H), 0.98 (d, $^3J_{HH}$ = 6.6 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 140.4, 128.9, 127.7, 127.2, 96.7, 59.8, 48.9, 41.4, 38.8, 38.5, 35.4, 31.7, 21.8.

**GC-MS** (Method D, $t_R$ = 11.3 min): *m/z* (%) 217 ([$M^+$–46], 6), 216 (34), 198 (30), 171 (39), 169 (14), 143 (35), 131 (10), 129 (28), 128 (14), 117 (20), 115 (18), 105 (13), 95 (17), 91 (100), 55 (11), 41 (14).

**2-((1*S*,2*R*,3*S*,4*R*)-4-Methyl-2-nitro-3,6-diphenylcyclohexyl)ethyl acetate (152)**




$C_{23}H_{27}NO_4$ (381.47 g/mol)

Analytical data for major product for the hydrogenation with (*R*)-**C11**:

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.38-7.21 (m, 10H), 5.43 (t, $^3J_{HH}$ = 9.4 Hz, 1H), 3.79-3.73 (m, 3H), 3.52 (q, $^3J_{HH}$ = 5.7 Hz, 1H), 2.77-2.72 (m, 1H), 2.36-2.30 (m, 1H), 2.27-2.21 (m, 1H), 2.14-2.09 (m, 1H), 1.93 (s, 3H), 1.92-1.80 (m, 1H), 1.69-1.61 (m, 1H), 0.64 (d, $^3J_{HH}$ = 7.3 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 170.9, 142.2, 138.7, 128.7, 128.6, 128.5, 127.3, 126.6, 89.7, 62.2, 49.9, 41.4, 40.6, 36.9, 33.5, 27.7, 20.9, 17.3, 14.3.

**GC-MS** (Method D, $t_R$ = 22.9 min): *m/z* (%) 292 ([$M^+$–89], 1), 274 (16), 273 (51), 195 (11), 181 (11), 171 (10), 170 (16), 169 (21), 167 (13), 157 (10), 156 (12), 155 (22), 145 (25), 143 (30), 141 (17), 131 (38), 129 (35), 128 (25), 117 (37), 115 (23), 105 (47), 91 (100), 43 (49).

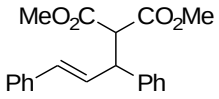
## 5.7 Palladium-catalyzed allylic substitution using 2$^{nd}$ generation of NeoPHOX ligands

**General working procedure for allylic substitution**

Under inert atmosphere, allyl-Pd chloride dimer (1.87 mg, 0.005 mmol, 0.005 eq) and the NeoPHOX ligand (9.19 mg, 0.025 mmol, 0.025 eq) were dissolved in absolute DCM (1.2 mL) in a Schlenk tube and stirred for two hours at 50 °C. In a second Schlenk tube, a solution of the substrate (1.00 mmol, 1.0 eq), dimethylmalonate (396 mg, 3.00 mmol, 3.0 eq), BSA (610 mg, 3.00 mmol, 3.0 eq) and dried potassium acetate (1.00 mg, 0.01 mmol, 0.01 eq) in absolute DCM (4 mL) was prepared and the Schlenk tube with the solution of the catalyst was added. The resulting mixture was stirred for 24 hours at room temperature. Sat. ammonium chloride-solution (20 mL) was added and the phases were separated. The aqueous phase was extracted with ether (3 x 15 mL) and the combined organic phases were dried over sodium sulfate and concentrated. The crude product was

purified by column chromatography (silica gel, 2 cm × 15 cm, cyclohexane:EtOAc = 19:1) to obtain the product as a colorless liquid.

**Dimethyl (*E*)-2-(1,3-diphenylallyl)malonate (167)**



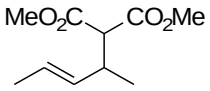

$C_{20}H_{20}O_4$ (324.14 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.34-7.18 (m, 10H), 6.48 (d, $^3J_{HH}$ =15.8 Hz, 1H), 6.33 (dd, $^3J_{HH}$ = 15.8 Hz, $^3J_{HH}$ = 8.6 Hz, 1H), 4.27 (dd, $^3J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.6 Hz, 1H), 3.96 (d, $^3J_{HH}$ = 10.8 Hz, 1H), 3.71 (s, 3H), 3.52 (s, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 168.3, 167.9, 140.3, 137.0, 132.0, 129.3, 128.9, 128.6, 128.0, 127.7, 127.3, 126.5, 57.8, 52.8, 52.6, 49.3.

**HPLC** (OJH, *n*heptane:*i*PrOH 90:10, 0.5 mL/min, 25 °C): $t_{r(major)}$ = 39.0 min, $t_{r(minor)}$ = 44.0 min, 97% *ee*.

**Dimethyl (E)-2-(pent-3-en-2-yl)malonate (169)**

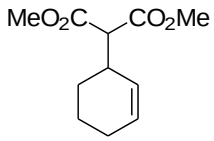



$C_{10}H_{16}O_4$ (200.23 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.52 (dqd, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 0.9 Hz, 1H), 5.34 (ddq, $^3J_{HH}$ = 15.2 Hz, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.6 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.26 (d, $^3J_{HH}$ = 9.1 Hz, 1H), 2.94-2.84 (m, 1H), 1.63 (dd, $^3J_{HH}$ = 6.4 Hz, $^3J_{HH}$ = 1.2 Hz, 3H), 1.06 (d, $^3J_{HH}$ = 7.2 Hz, 3H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 168.9, 132.4, 126.5, 58.1, 52.5, 52.4, 37.5, 18.5, 18.0.

**Dimethyl 2-(cyclohex-2-en-1-yl)malonate (171)**




$C_{11}H_{16}O_4$ (212,10 g/mol)

**$^1$H-NMR** (400 MHz, $CDCl_3$): δ (ppm) = 5.80-5.75 (m, 1H), 5.54-5.50 (m, 1H), 3.74 (s, 3H), 3.74 (s, 3H), 3.29 (d, $^3J_{HH}$ = 9.5 Hz, 1H), 2.94-2.87 (m, 1H), 2.02-1.96 (m, 2H), 1.79-1.67 (m, 2H), 1.62-1.52 (m, 1H), 1.42-1.32 (m, 1H).

**$^{13}$C-NMR** (100 MHz, $CDCl_3$): δ (ppm) = 169.1, 169.0, 129.8, 127.5, 57.0, 52.5, 52.5, 35.5, 26.8, 25.1, 21.0.

**HPLC** (OBH, *n*heptane:*i*PrOH 90:10, 0.5 mL/min, 40 °C): $t_{r(major)}$ = 11.8 min, $t_{r(minor)}$ = 14.1 min, 23% *ee*.

# 6 Appendix

## 6.1 List of abbreviations

| | |
|---|---|
| % | percent |
| °C | degree Celsius |
| Ac | acetyl |
| AcOH | acetic acid |
| AIBN | azobisisobutyronitrile |
| Alk | alkyl |
| aq. | aqueous |
| Ar | aryl |
| atm | atmosphere |
| $BAr_F$ | tetrakis[3,5-bis(trifluoro-methyl)phenyl]borate |
| Bn | benzyl |
| br | broad |
| BSA | N,O-bis(trimethylsilyl)acetamide |
| Bz | benzoate |
| c | concentration |
| cat. | catalytic |
| Cat. | catalyst |
| COD | cyclooctadiene |
| conv. | conversion |
| Cy | cyclohexyl |
| δ (NMR) | chemical shift |
| d | doublet |
| DAST | diethylaminosulfur trifluoirde |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIBAL | diisobutylaluminium hydride |
| DMAP | 4-dinmethylaminopyridine |
| DMF | dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMPU | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone |
| DMSO | dimethyl sulfoxide |
| *dr* | diastereomeric ratio |
| *ee* | enantiomeric excess |
| EI | electron-imp |
| eq. | equivalents |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| eV | electron Volts |
| g | gram |
| GCMS | gas chromatography mass spectometry |
| h | hours |
| HMPA | hexamethylphosphoramide |
| HOMO | highest occupied molecular orbital |

| | |
|---|---|
| HPLC | high performance liquid chromatography |
| HWE | Horner-Wadsworth-Emmons |
| Hz | Hertz |
| *i*Pr | 2-propyl |
| IR | infrared |
| J | coupling constante |
| KO*t*Bu | potassium *tert*-butoxide |
| kPa | kilo Pascal |
| *l* | length |
| LUMO | lowest unoccupied molecular orbital |
| $\mu$ | micro |
| *m* | meta |
| m | multiplet (NMR) or medium (IR) |
| M | molar |
| *m*-CPBA | 3-chloroperbenzoic acid |
| Me | methyl |
| MeOH | methanol |
| min | minutes |
| mL | milliliter |
| mm | millimeter |
| mmol | millimol |
| m.p. | melting point |
| Ms | mesyl |
| MTBE | methyl *tert*-butyl ether |
| MTO | methyltrioxorhenium |
| NBS | N-bromosuccinimide |
| *n*-BuLi | *n*-butyllithium |
| n.d. | not determined |
| nm | nanometer |
| NMR | nuclear magnetic resonance |
| *n*PrOH | 1-propanol |
| OFBA | 2-fluorobenzoic acid |
| *o*-Tol | *ortho*-tolyl |
| *p* | para |
| Ph | phenyl |
| PHOX | phosphinooxazoline |
| pin | pinacol |
| ppm | parts per million |
| *p*-TsOH | p-toluenesulfonic acid |
| py | pyridine |
| q | quartet |
| quint | quintet |
| *rac* | racemic |
| $R_f$ | retention factor |
| rt | room temperature |
| s | singlet (NMR) or strong (IR) |
| sat. | saturated |
| T | temperature |

| | |
|---|---|
| t | time or triplet (NMR) |
| TBDMS | *tert*-butyldimethylsilyl |
| *t*Bu | *tert*-butyl |
| TES | triethylsilyl |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| TOF | turnover frequency |
| $t_R$ | retention time |
| w | weak |

# 7 References


[1] a) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336-345; b) E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421-431; c) M. C. Perry, K. Burgess, *Tetrahedron: Asymmetry* **2003**, *14*, 951-961; d) M. S. Taylor, N. E. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543; e) T. Mallat, E. Orglmeister, A. Baiker, *Chem. Rev.* **2007**, *107*, 4863-4890; f) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638-4660; g) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2014**, *114*, 2390-2431.

[2] a) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899; b) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614-7615; c) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008-2022; d) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029-3069; e) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402-1411; f) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513-531.

[3] a) N. B. Johnson, I. C. Lennon, P. H. Moran, J. A. Ramsden, *Acc. Chem. Res.* **2007**, *40*, 1291-1299; b) C. S. Shultz, S. W. Krska, *Acc. Chem. Res.* **2007**, *40*, 1320-1326.

[4] a) J. A. Osborn, F. H. Jardine, G. Wilkinson, *J. Chem. Soc. A* **1966**, 1711-1732; b) R. S: Coffey, *BP 1* **1965**, *121*, 642.

[5] a) W. S. Knowles, M. J. Sabacky, *Chem. Commun.* **1968**, 1445-1446; b) L. Horner, H. Siegel, H. Büthe, *Angew. Chem. Int. Ed.* **1968**, *7*, 942.

[6] H. B. Kagan, T. P. Dang, *Chem. Commun.* **1972**, 481; H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1971**, *94*, 6429-6433; c) B. D. Vineyard, W. S: Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946-5952.

[7] W. S. Knowles, *J. Chem. Educ.* **1986**, *63*, 222-225.

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

[9] a) R. Noyori, *Chem. Soc. Rev.* **1989**, *18*, 187-208; b) R. Noyori, *Science*, **1990**, *248*, 1194-1199; c) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345-350.

[10] H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, R. Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1597-1600.

[11] a) W. A. Nugent, T. V. RajanBabu, M. J. Burke, *Science* **1993**, *253*, 479-4836; b) M. J. Burk *Acc. Chem. Res.* **2000**, *33*, 363-372; c) U. Behrens, M. J. Burk, A. Gerlach, W. Hems, *Angew. Chem. Int. Ed.* 2000, *39*, 1981-1984.

[12] G. S. Forman, T. Ohkuma, W. P. Hems, R. Noyori, *Tetrahedron Lett.* **2000**, *41*, 9471-9475.

[13] a) H.-U. Blase, H.-P. Jalett, M. Müller, M. Studer, *Catalysis Today* **1997**, *37*, 441-463; b) S. Badhuri, K. R: Sharma, W. Clegg, G. M. Sheldrick, D. Stalke, *J. Chem. Soc., Dalton Trans.* **1984**, 2851-2853.

[14] a) R. D. Broene, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 12569-12570 b) N. E. Lee, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 5985-5986; c) J. Okuda, S. Verch, T. P. Spaniol, R. Stürmer, *Chem. Ber.* **1996**, *129*, 1429-1431.

[15] a) Y. Raoult, R. Choukroun, M. Basso-Bert, D. Gervais, *J. Mol. Catal.* **1992**, *72*, 47-58; b) A. H. Hoveyda, J. P. Morken, *Angew. Chem. Int. Ed.* **1996**, *35*, 1262-1284; c) M. V. Troutman, D. H. Appella, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4916-4917.

[16] A. Pfaltz *et al.*, *Adv. Synth. Catal.* **2003**, *345*, 33-43.

[17] E. Cesarotti, R. Ugo, H. B. Kagan, *Angew. Chem. Int. Ed.* **1979**, *18*, 779-780.

[18] R. H. Crabtree, H. Felkin, G. E. Morris, *J. Organomet. Chem.* **1977**, *141*, 205-215.

[19] R. H. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331-337.

[20] P. Schnider, G. Koch, R. Prétôt, G. Wang, F. M. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887-892.

[21] A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899.

[22] S. P. Smidt, A. Pfaltz, E. Martinez-Viviente, P. S. Pregosin, A. Albinati, *Organometallics* **2003**, *22*, 1000-1009.

[23] H. Nishida, N. Takada, M. Yoshimura, T. Sonada, H. Kobayashi, *Bull. Chem. Soc. Jap.* **1984**, *57*, 2600-2604.

[24] S. P. Smidt, N. Zimmermann, M. Studer, A. Pfaltz, *Chem: Eur. J.* **2004**, *10*, 4685-4693.

[25] J. Blankenstein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445-4447.

[26] F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40-44.

[27] S. P. Smidt, F. Menges, A. Pfaltz, *Org. Lett.* **2004**, *6*, 2023-2026.

[28] M. Harmata, X. Hong, *Org. Lett.* **2005**, *7*, 3581-3583.

[29] a) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem. Int. Ed.* **2006**, *45*, 5194-5197; b) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642-644.

[30] A. Ganić, A. Pfaltz, *Chem. Eur. J.* **2012**, *18*, 6724-6728.

[31] L. Pauli, R. Tannert, R. Scheil, A. Pfaltz, *Chem. Eur. J.* **2015**, *21*, 1482-1487.

[32] a) H. J. Jessen, A. Schumacher, T. Shaw, A. Pfaltz, K. Gademann, *Angew. Chem. Int. Ed.* **2011**, *50*, 4222-4226; b) T. Yoshinari, K. Ohmori, M. G. Schrems, A. Pfaltz, K. Suzuki, *Angew. Chem. Int. Ed.* **2010**, *49*, 881-885; c) M. C. Pischl, C. F. Weisse, M.-A. Müller, A.

Pfaltz, C. Schneider, *Angew. Chem. Int. Ed.* **2013**, *52*, 8968-8972.

[33] W. Bonrath, J. Medlock, J. Schütz, B. Wüstenberg, T. Netscher, Werner Bonrath, Jonathan Medlock, Jan Schütz, Bettina Wüstenberg and Thomas Netscher (2012). Hydrogenation in the Vitamins and Fine Chemicals Industry – An Overview, Hydrogenation, Prof. Iyad Karamé (Ed.), ISBN: 978-953-51-0785-9, InTech, DOI: 10.5772/48751. Available from: http://www.intechopen.com/books/hydrogenation/hydrogenation-in-the-vitamins-and-fine-chemicals-industry-an-overview

[34] M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem. Int. Ed.* **2007**, *46*, 8274-8276.

[35] J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769-1772.

[36] Q.-B. Liu, C.-B. Yu, Y.-G. Zhou, *Tetrahedron Lett.* **2006**, *47*, 4733-4736.

[37] K. Källström, I. J. Munslow, C. Hedberg, P. G. Andersson, *Adv. Synth. Catal.* **2006**, *348*, 2575-2578.

[38] M. Engmann, J. S: Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 44536-4537.

[39] P. Cheruku, S. Gohil, P. G. Andersson, *Org. Lett.* **2007**, *9*, 1659-1661.

[40] Z. Han, Z. Wang, X. Zhang, K. Ding, *Angew. Chem. Int. Ed.* **2009**, *48*, 5345-5349.

[41] S. Li, S.-F. Zhu, C.-M. Zhang, S. Song, Q. L. Zhou, *J. Am. Chem. Soc.* **2008**, *130*, 8584-8585.

[42] Y. Zhang, Z. Han, F. Li, K. Ding, A. Zhang, *Chem. Commun.* **2010**, *46*, 156-158.

[43] J. H. Xie, X.-Y. Liu, J.-B. Xie, L.-X. Wang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2011**, *50*, 7329-7332.

[44] Q.-Q. Zhang, J.-H. Xie, X.-H. Yang, J.-B. Xie, L.-X. Wang, Q.-L. Zhou, *Org. Lett.* **2012**, *14*, 6158-6161.

[45] D. H. Woodmansee, M.-A. Müller, M. Neuburger, A. Pfaltz, *Chem. Sci.* **2010**, *1*, 72-78.

[46] a) C. F. Koelsch, W. H. Gumprecht, *J. Org. Chem.* **1958**, *23*, 1603-1606; b) B. Klein, J. Berkowitz, *J. Am. Chem. Soc.* **1959**, *81*, 5160-5166; c) Z. Lotowski, E. N. Dubis, J. W. Morzicky, *Monatsh. Chem.* **2000**, *131*, 65-71; d) S. K. Das, J. Frey, *Tetrahedron Lett.* **2012**, *53*, 5869-5872.

[47] A. Ganic, *Dissertation*, University of Basel, **2012**.

[48] A. F. M. M. Rahman, B.-S. Jeong, D. H. Kim, J. K. Park, E. S. Lee, Y. Jahng, *Tetrahedron* **2007**, *63*, 2426-2431.

[49] B. R. Travis, R. S. Narayan, B. Borhan, *J. Am. Chem. Soc.* **2002**, *124*, 3824-3825.

[50] D. Yang. C. Zhang, *J. Org. Chem.* **2001**, *66*, 4814-4818.

[51] S. Yamada, H. Katsumata, *J. Org. Chem.* **1999**, *64*, 9365-9373.

[52] A. M. Daly, D. G. Gilheany, *Tetrahedron Asymmetry*, **2003**, *14*, 127-137.

[53] S. G. Gouin, J.-F. Gestin, K. Joly, A. Loussouarn, A. Reliquet, J. C. Meslin, D. Deniaud, *Tetrahedron*, **2002**, *58*, 1131-1136.

[54] H. Quast, H. Röschert, E.-M- Peters, K. Peters, H. G. v. Schnering, *Chem. Ber.* **1989**, *122*, 523-531.

[55] I. Flament, P. Sonnay, G. Ohloff, *Helv. Chim. Acta* **1973**, *56*, 610-619.

[56] I. Pérez-Castro, O. Caamaño, M. D. García, G. Gómez, F. Fernández, J. Ferreira, C. López, *Synthesis* **2007**, *17*, 2621-2626.

[57] T. Kobayashi, S. Kobayashi, *Molecules* **2005**, *5*, 1062-1067.

[58] C. Hu, X. Li, W. Wang, L. Zhang, L. Tao, X. Dong, R. Sheng, B. Yang, Y. Hu, *Bioorg. Med. Chem.* **2011**, *19*, 5454-5461.

[59] a) C. Schneider, O. Reese, *Chem. Eur. J.* **2002**, *8*, 2585-2594; b) S. H. Oh, G. S. Cortez, D. Romo, *J. Org. Chem.* **2005**, *70*, 2835-2838; c) X. Companyó, A. Zea, A-N. R. Alba, A. Mazzanti, A. Moyano, R. Rios, *Chem. Commun.* **2010**, *46*, 6953-6955.

[60] J. Marco-Contelles, C. Pozuelo, M. L. Jimeno, L. Martinez, A. Martinez-Grau, *J. Org. Chem.* **1992**, *57*, 2625-2631; b) J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519-564; c) R. K. Shrivastava, E. Maudru, G. Singh, R. H. Wightman, K. M. Morgan, *Beilstein J. Org. Chem.*, **2008**, *4*, No. 43.

[61] a) G.-L- Zhao, P. Dziedzic, F. Ullah, L. Eriksson, A. Córdova, *Tetrahedron Lett.* **2009**, *50*, 3458-3462; b) Y. Alvarez-Casao, E. Marques-Lopez, R. P. Herrera, *Symmetry*, **2011**, *3*, 220-245; c) D. Shi, Y. Xie, H. Zhou, C. Xia, H. Huang, *Angew. Chem.* **2012**, *124*, 1274-1277; d) J. I. Martínez, L. Villar, U. Uria, L. Carirllo, E. Reyes, J. L. Vicario, *Adv. Synth. Catal.* **2014**, *356*, 3627-3648.

[62] a) J. Ramharter, J. Mulzer, *Eur. J. Org. Chem.* **2012**, *77*, 2041-2053; b) M. E. Jung, T.-H. Zhang, R. M. Lui, O. Gutierrez, K. N. Houk, *J. Org. Chem.* **2010**, *75*, 6933-6940.

[63] O. Diels, K. Alder, *Justus Liebigs Annalen Der Chemie* **1928**, *460*, 98-122.

[64] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W. M. McLamore, *J. Am. Chem. Soc.* **74**, *17*, 4223-4251.

[65] K. C. Nicolau, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*

2002, *41*, 1668-1698.

[66] L. M. Joshel, L. W. Butz, *J. Am. Chem. Soc.* **1941**, *63*, 3350-3351.

[67] P. A. Grieco, K. Yoshida, P. Garner, *J. Org. Chem.* **1983**, *48*, 3137-3139.

[68] a) D. A. Evans, S. J. Miller, T. Lectka, *J. Am. Chem. Soc.*, **1993**, *115*, 6460-6461; b) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667. c) D. Liu, E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 1498-1499; d) L. C. Dias, *J. Braz. Chem. Soc.* **1997**, *8*, 289-332.

[69] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *122*, 2458-2460; c) Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 6736-6739; d) C. L. Gomez, D. C. Cruz, R. Mose, K. A. Jørgensen, *Chem. Commun.* **2014**, *50*, 6035-6038; e) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Accounts of Chemical Research* **2012**, *45*, 1491-1500; f) Z.-J. Jia, Q. Zhou, Q.-Q. Zhou, P.-Q. Chen, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8638-8641.

[70] J. Padevet, *Dissertation*, University of Basel, **2013**.

[71] R. H. Crabtree, M. W. Davis, *J. Org. Chem.* **1986**, *51*, 2655-2661.

[72] P. G. Williard, S. E. de Laszlo, *J. Org. Chem.* **1985**, *50*, 3738-3749.

[73] E. D. Sternberg, K. P. C. Vollhardt, *J. Org. Chem.* **1984**, *49*, 1574-1583.

[74] A. Bartoszewicz, M. Kalek, J. Nilsson, R. Hiresova, J. Stawinski, *Synlett* **2008**, 37-40.

[75] C. S. Marvel, R. G. Woolford, *J. Org. Chem.* **1958**, *23*, 1658-1660.

[76] C. H. Oh, S. H. Jung, S. Y. Bang, D. I. Park, *Org. Lett.* **2002**, *4*, 3325-3327.

[77] M. D. Mosher, L. G. Emmerich, K. S. Frost, B. Anderson, *J. Heterocyclic Chem.* **2006**, *43*, 535-539.

[78] G. B. Bachman, C. G. Goebel, *J. Am. Chem. Soc.* **1942**, *64*, 787-790.

[79] R. G. R. Bacon, E. H. Farmer, *J. Chem. Soc.* **1937**, 1065-1077.

[80] Z. Zhong, R. J. Hinkle, A. M. Arif, P. J. Stang, *J. Am. Chem. Soc.* **1991**, *113*, 6196-6202.

[81] L. A. Paquette, R. P. Henzel, S. E. Wilson, *J. Am. Chem. Soc.* **1972**, *94*, 7780-7788.

[82] H. M. Frey, D. C. Marshall, R. F. Skinner, *Trans. Faraday Soc.* **1965**, *61*, 861-865.

[83] M. Takahashi, M. McLaughlin, G. C. Micalizio, *Angew. Chem. Int. Ed.* **2009**, *48*, 3648-3652.

[84] Y. Wang, F. G. West, *Synthesis* **2002**, 99-103.

[85] M. G. Schrems, A. Pfaltz, *Chem. Commun.* **2009**, *45*, 6210-6212.

[86] M. G. Schrems, *Dissertation*, University of Basel, **2009**.

[87] a) A. Franzke, A. Pfaltz, *Chem. Eur. J.* **2011**, *17*, 4131-4144; b) A. Franzke, F. Voss, A. Pfaltz, *Tetrahedron* **2011**, *67*, 4358-4363.

[88] a) P. von Matt, A. Pfaltz, *Angew. Chem. Int. Ed.* **1993**, *32*, 566-568; b) G. J. Dawson, C. G. Frost. J. M. J. Williams, *Tetrahedron Lett.* **1993**, *34*, 3149-3150.

# Curriculum Vitae

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J. Padevet, M. G. Schrems, R. Scheil, A. Pfaltz, NeoPHOX – a structurally tunable ligand system for asymmetric catalysis, *Beilstein J. Org. Chem.* **2016**, *12*, 1185-1195

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