Synthesis of new phosphino-oxazoline ligands for asymmetric catalysis

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Enantioselective catalysis – Introduction

1. Enantioselective catalysis - Introduction

During the past two decades, asymmetric catalysis has become a very rapidly developing area of organic synthesis. The reason lies in the constantly increasing demand from the chemical industry for enantiomerically pure compounds. The main area where the requirement for enantiomerically pure compounds is the greatest is in the pharmaceutical industry. This need is hence a driving force for developing new methods for the production of biologically active substances in their enantiomerically pure forms. The development of asymmetric synthesis from the late 1960s is illustrated in *Figure 1*.

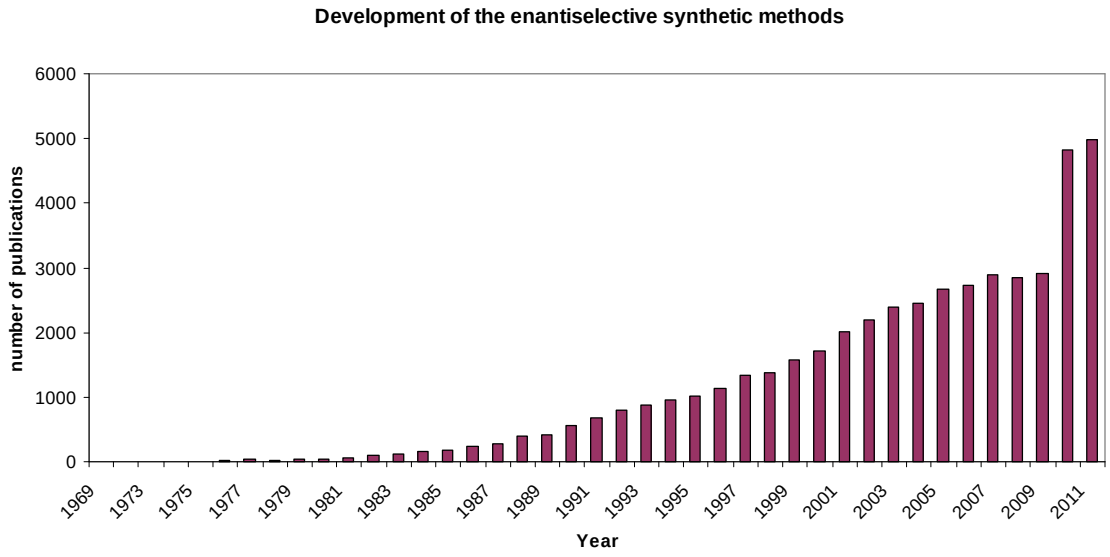


Figure 1: Development of the stereoselective synthesis from the 1970's until present.

The main impulse for research in this new area of chemical synthesis was the fact that in drugs containing stereogenic centers, each enantiomer can have a different effect on the patient. This implies that if the drug were to be used in its racemic form (containing both enantiomers), in the better case scenario, only one of the enantiomers would be biologically active and therefore only 50% of the active ingredient would be used effectively. In the worst case scenario the second enantiomer would have a completely different effect from that of the first enantiomer, either suppressing the desired effect of the first one or even causing undesirable side effects. The differences in various biological effects of each enantiomer can be explained by the pharmacon-receptor interaction, whenever only one of the enantiomers fits into the biological receptor.

An example of the second enantiomer of a drug having an undesired effect is exemplified by the case of Thalidomide in the late 1950s. The development of the drug as a racemic mixture was initiated during the Second World War and was first described in 1953 by the Swiss pharmaceutical company Ciba, which subsequently discontinued its development. Then in 1957 the German pharmaceutical company Grünenthal introduced Thalidomide on the market as Contergan.[1] The drug was subsequently distributed in many European countries and also in Canada, USA and Australia and prescribed mainly as an analog of the structurally related barbiturates (*Figure 2*) which were at that time known for their relatively low toxicity in adults.

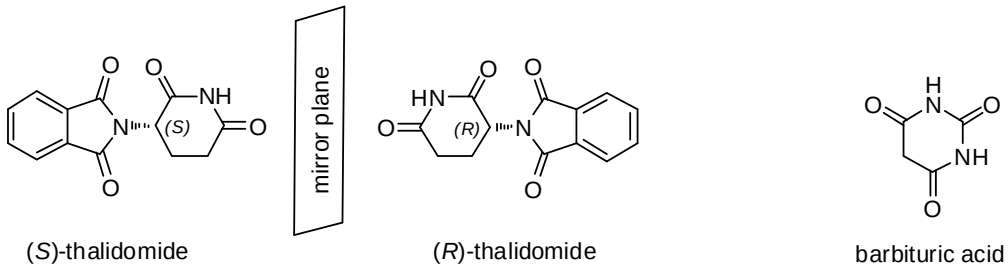


Figure 2: Enantiomers of Thalidomide, an analog of barbituric acid.

The indication was therefore similar and Thalidomide was used as a sedative and tranquilizer for treating insomnia. Because it was also found to have an antiemetic effect, the drug was prescribed to pregnant women in their first three months of pregnancy to treat morning sickness. After the introduction of the drug on the market, a large number of birth defects were observed, such as amelia (absence of limbs), different limbs malformations, bone hypoplasticity and also congenital defects of internal organs. It was found that the occurrence of these defects was related to the drug Thalidomide, which was therefore withdrawn from the market in 1961 for its teratogenic and neurophatic effects. During its few years on the market, Thalidomide produced a worldwide tragedy claiming over 10.000 victims.[2] At that time, it was thought that no exogenous agent can cross the placental barrier and therefore the side effects of the drugs were not specifically tested in this regard. (*R*)-thalidomide was found to be non-toxic whereas the (*S*)-enantiomer was discovered to be responsible for the adverse effects of *rac*-thalidomide. This observation was also a motivation for the development of new methods for preparing enantiomerically pure pharmaceuticals, although it later materialised that the Thalidomide tragedy could not have been avoided by supplying just the pure (*R*)-enantiomer. The reason being, that enantiopure Thalidomide racemizes under *in vivo* conditions.[3]

The teratogenicity of the *rac*-thalidomide then started a new period of drug development with respect to safety and it has opened a new area of chemical research, namely the preparation of enantiomerically pure compounds (*Figure 1*).

Asymmetric transformations can be either achieved using stochiometric amounts of chiral reagents[4] or, more effectively by using a chiral catalyst ensuring an enantioselective outcome for the reaction. Our current work also deals with the preparation of chiral catalytic systems. This thesis will focus on the preparation of chiral ligands which can control the enantioselectivity of metal-catalyzed reactions in order to prepare pure enantiomers.

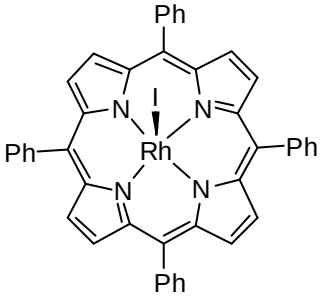
Chapter 2

Chiral bis(oxazoline) ligands in asymmetric catalysis

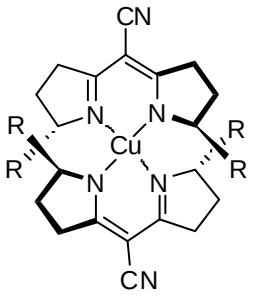
2. Chiral bis(oxazoline) ligands in asymmetric catalysis

2.1 Semicorrin ligands

In 1977 Mansuy et al. reported the first example of a metalloporphyrin carbene complex [Fe^{II}(tetraphenylporphin)(CCl_2)], which was formed by the reaction of [(TPP)Fe^{II}] with carbon tetrachloride in the presence of an excess of a reducing agent.[5] This result was in analogy to the previously reported abilities of cytochrome P-450 to reduce various polyhalogenated compounds. Three years later, Callot found that rhodium (III) porphyrins (*Figure 3*) can catalyze the cyclopropanation of alkenes with ethyl diazoacetate to form cyclopropyl esters with a favorable *cis*–selectivity.[6] This result can be rationalized by a metal-catalyzed mechanism involving a rhodium porphyrin carbene as an active species in the catalytic cycle. Porphinoid metal complexes of this type inspired the development of related catalysts including chiral complexes for asymmetric catalysis.



RhTPPI

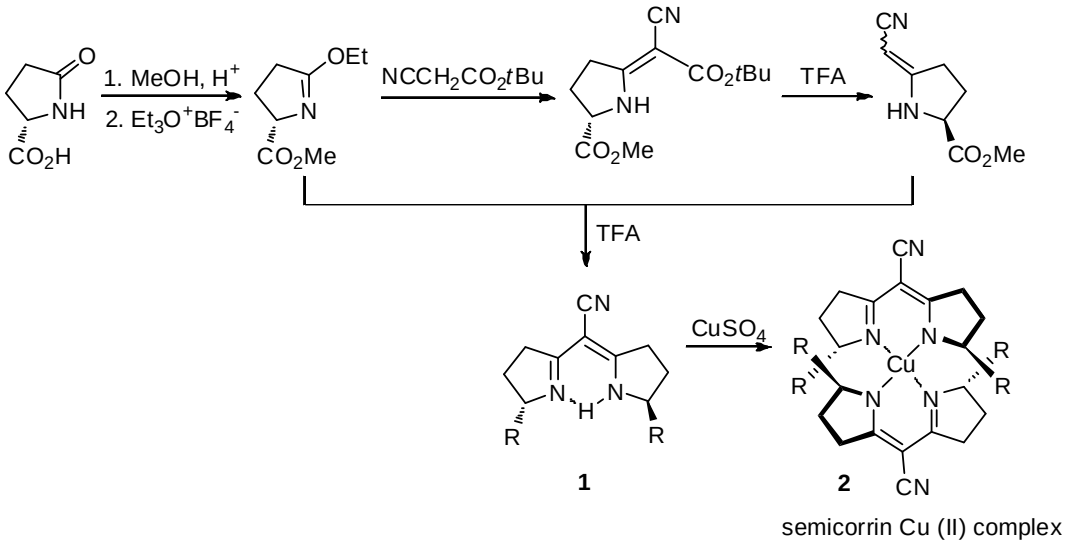


semicorrin Cu (II) complex

Figure 3: Comparison of the rhodium porphyrin and copper semicorrin.

The C_2-symmetric bidentate nitrogen ligands called semicorrins,[7] developed by Pfaltz and co-workers in 1986, were specifically designed for enantioselective catalysis. They were derived from the porphyrin structural motif of known compounds called corrinoids and hydroporphonoids.[8] These semicorrin ligands consist of two chiral moieties, which are bridged via a vinyl system. They can be readily prepared from the natural amino acid pool as enantiomerically pure compounds in both enantiomeric forms (*Scheme 1*).[7, 9] The vinyl sp^2 bridge makes the ligand scaffold more rigid, which is reflected in better stereocontrol of a

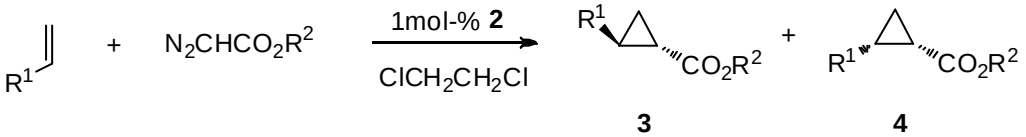
metal-catalyzed reaction. Steric hindrance around the metal center can be further tuned by modifying the R groups, which are generated by derivatization of the ester functional groups.



***Scheme 1*:** Semicorrin ligand synthesis.

Semicorrins ligands **1** were then complexed with copper (II) to obtain homoleptic metal complexes. These were further investigated in the asymmetric copper-catalyzed cyclopropanation reaction of olefins. This reaction has its origin in the pioneering work of Nozaki, and consists of the formation of a metal-carbene species from the corresponding diazoacetate, which then undergoes reaction with the double bond of an olefin.[10]

Table 1: Enantioselective cyclopropanation catalyzed by copper-semicorrin complex **2**.

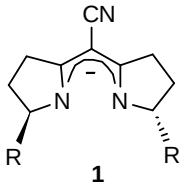


R^1	R^2	Yields of	Stereoselectivity		
		3 + 4 [%]	**3** [% *ee*]	**4** [% ee]	**3 : 4**
Ph	Et	65	85	68	78 : 22
Ph	*t*Bu	60	93	92	84 : 16
Ph	*L*-menthyl	65-75	91	90	85 : 15
Ph	*D*-menthyl	60-70	97	95	82 : 18
$CH=CH_2$	*D*-menthyl	60	97	95	63 : 37
n-pentyl	*D*-menthyl	25-30	92	92	82 : 18

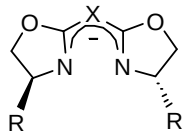
In the asymmetric copper-semicorrin-catalyzed cyclopropanation reaction of olefins with diazoesters, these catalysts exhibited hight enantioselectivities. The results obtained were impressive and better than those of previously reported asymmetric cyclopropanation reactions, which reached a maximum of about 80 % *ee*.[11] Since this time, the scope of the semicorrins ligands application has been broadened further; for example, the cobalt-catalyzed enantioselective reduction of α,β-unsaturated carboxylates[12] or carboxamide[13] by $NaBH_4$ and also an intramolecular version of the copper-catalyzed cyclopropanation.[14]

2.2 Bisoxazolines in asymmetric catalysis

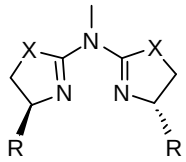
Several new types of C_2-symmetrical ligands derived from the semicorrins were developed over time, and they have found different applications in asymmetric catalysis. Representative examples, which were inspired by the negatively charged structural motif of the semicorrins **1**, are methylene bisoxazolines **2** or their aza-derivatives **3**.



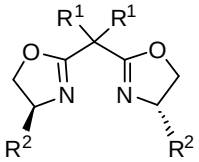
1



2: X = CH
3: X = N



4: X = CH_2
5: X = O



6

These ligands bear a characteristic π-conjugated system, which bridges the two chiral moieties and is partially responsible for the rigidity of the backbone, which remains planar during the catalytic process. At the same time, the π-electrons of the system are donated to the electrophilic metal center. A decrease in the electrophilicity of the system is not always desirable. Therefore, neutral variants of the ligands were also designed [9] called 5-azasemicorrins (**4**) or 5-azaoxazolines (**5**), both of which have a planar nitrogen bridging

atom. Another class is the bisoxazoline ligands (**6**; BOX) where the connection between two oxazolines is made through an sp^3 carbon bridge. They were introduced by Masamune et al.[15] in 1990 and by David Evans[16] in 1991, respectively.

The oxazoline structural motif has turned out to be one of the most popular ligands for use in enantioselective catalysis. There was enormous growth in the use of bis(oxazoline) ligands in the field of asymmetric catalysis after their introduction in 1990, as can be seen in *Figure 4*.

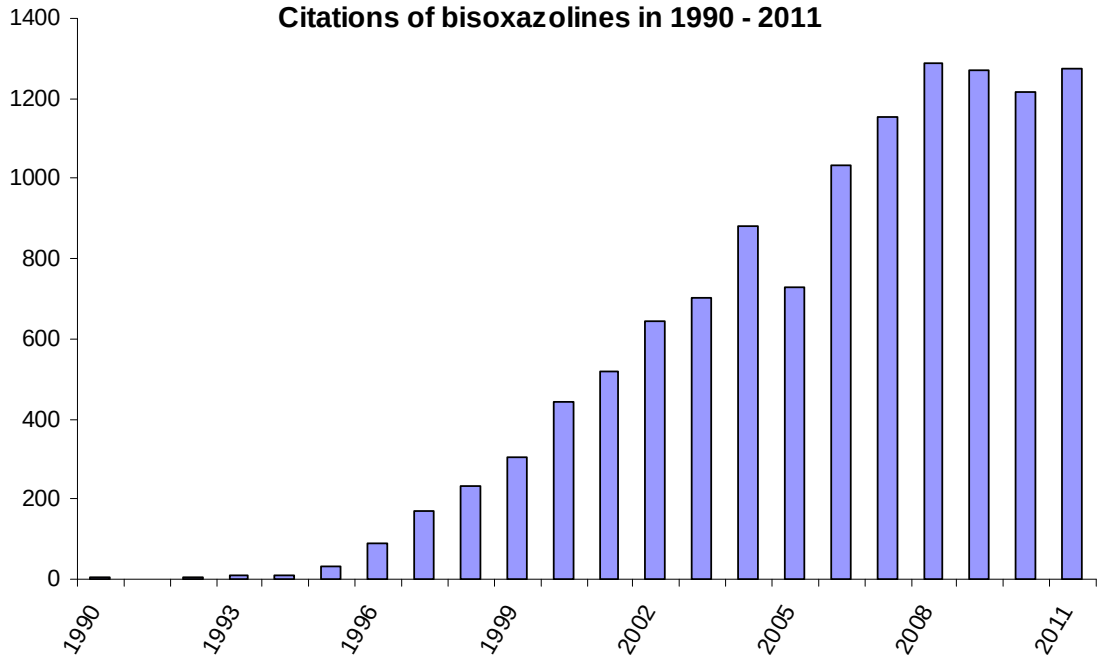
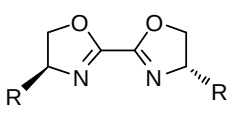


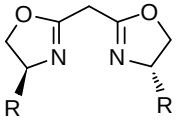
Figure 4: Number of citations containing the keyword "bis(oxazoline)" in the years 1990 – 2011.

2.3 Preparation of bis(oxazoline) ligands

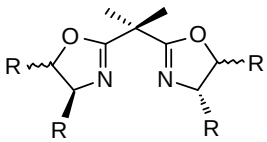
Inspired by the initial successful semicorrin structural backbone, the library of new chiral bis(oxazoline ligands) was quickly broadened . Bisoxazoline ligands were developed that are either bridged directly over the oxazoline sp^2 carbon (examples **7**-**10**), or via the substituted methylene bridge (examples **11**-**18**).



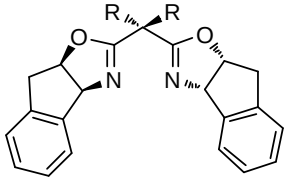
7 R = Ph
8 R = CH_2Ph
9 R = *t*Bu
10 R = *i*Pr



11 R = Ph
12 R = CH_2Ph
13 R = *t*Bu
14 R = *i*Pr

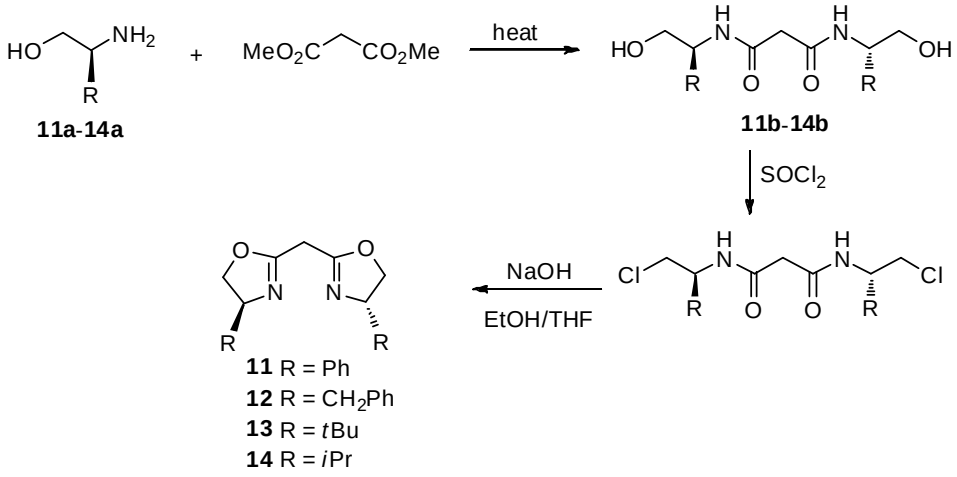


15 R = Ph (*R*, *R*)
16 R = Ph (*S*, *S*)



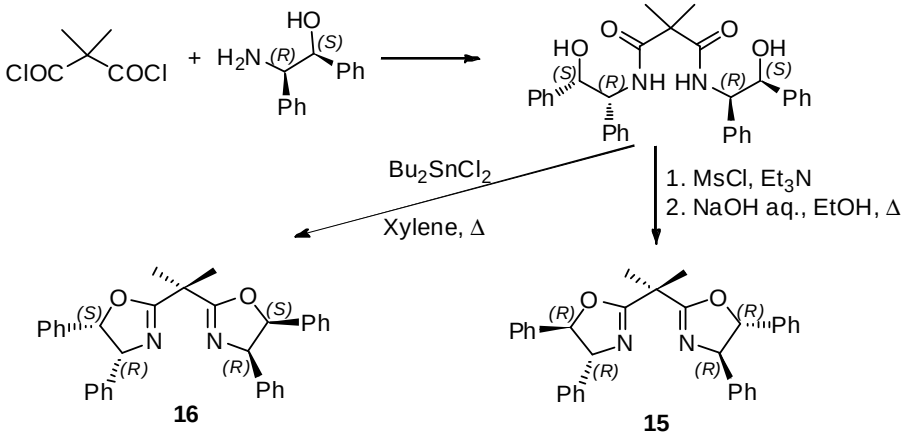
17 R = H (1*S*, 2*R*)
18 R = CH_3 (1*S*, 2*R*)

They all have of the potential for different substitution patterns, allowing for their sterical and electronic properties to also be tuned. The previously mentioned bridged bis(oxazolines) can be readily prepared, starting either from dimethylcarboxylate or dimethylmalonate and various chiral aminoalcohols (**11a** – **14a**) to form the corresponding bis(hydroxy)amides (**11b** – **14b**). Those are subsequently converted into the bis(oxazolines) via a cyclization reaction (*Scheme 2*).[17] The dimethyl substituted bridge in **11**-**18** could be formed by the reaction of dimethylmalonyl chloride with the corresponding aminoalcohol in the presence of a base, followed by the same oxazoline closing protocol as in the other examples.[18]



Scheme 2: Synthesis of methylene-bridged bis(oxazolines).

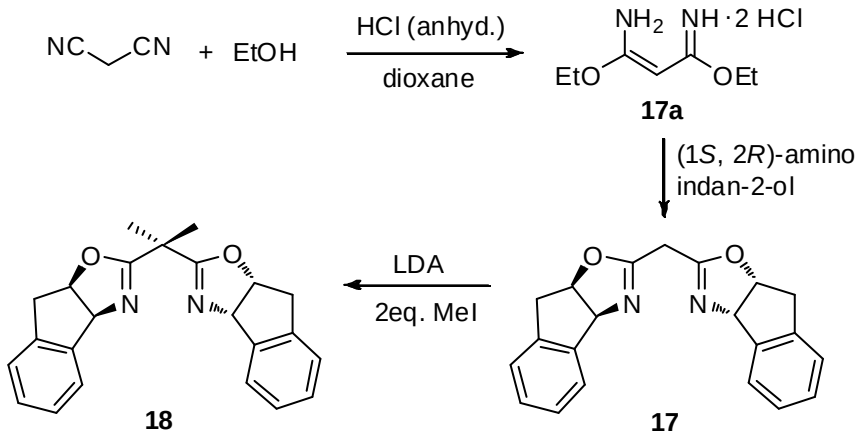
Different methods were employed for the oxazoline closure using a wide range of reagents, such as CH_3SO_3H,[19] Me_2SnCl_2, [15, 20] $ZnCl_2$,[21] DAST,[22] or CF_3SO_3H and $BF_3.Et_2O$.[23] The selection of a proper cyclization method to close the oxazoline ring can be used to control the absolute configuration of the final oxazoline, as was done by Desimoni et al. for the synthesis of 4,5-disubstituted chiral bis(oxazolines) **15** and **16,** as shown in *Scheme 3*.[24]



Scheme 3: Stereodivergent synthesis of chiral 4,5-disubstituted bis(oxazolines).

The cyclization of bis(hydroxy)amide in the presence of Bu_2SnCl_2 proceeds with retention of configuration at C5, while cyclization using mesylate as a leaving group leads to inversion of configuration to yield oxazoline **15**.

The indane-derived BOX ligands **17** and **18** can be obtained by the reaction of (*1S, 2R*)-aminoindan-2-ol with imidate salt **17a** (*Scheme 4*)[25], which is easily accessible via the treatment of malonitrile with anhydrous HCl in ethanol.



Scheme 4: Synthesis of (1*S*, 2*R*)-inda-box.

After the cyclization reaction, either ligand **17** can be obtained directly, or the acidic malonate protons can be readily deprotonated by lithium diisopropylimide, followed by alkylation with two equivalents of the methyliodide to deliver bis(oxazoline) ligand **18**. When alkylation on the bridging carbon is performed with a diiodoalkane, the spirocyclic inda-boxes are produced instead.[26]

2.4 Bis(oxazoline)-metal complexes

Bis(oxazoline) ligands are chiral C_2-symmetric ligands that readily forms stable five-membered (for example, with ligands **7**–**10**), or, more frequently, six-membered metallacycles with various metals, such as Cd^{2+}, Co^{2+}, Cu^{2+}, Mn^{2+}, Ni^{2+}, Pd^{2+}, Ru^{4+}, Ti^{2+}, and Zn^{2+} (*Figure 5*). During their development, after successful complexation with certain metals, the structural elucidation of the newly prepared complexes is undertaken. The argument in favor of this is that knowledge of the three dimensional structure can allow more sophisticated design of new

ligands, but furthermore, with knowledge of the metal complex structure, the transition state for certain transformations can be proposed. The ligand-metal complexation can be done by direct in situ mixing of both components in the proper ratio, to form either homoleptic or heteroleptic complexes, depending on the ligand structure and the reactivity of the corresponding metal. Alternatively, they can be precomplexed and isolated prior to use. The presence of a C_2-symmetric axis in these ligands minimizes the number of possible transition states for certain transformations, which can have a beneficial effect on selectivity.[27] Also, the presence of lateral bulky groups on the oxazoline rings constrains the space around the metal center and in this way can favour one direction for substrate access. The bulky groups either come directly from the pool of natural/unnatural amino acids or from further chemical transformation of the reactive functional groups on the oxazoline.

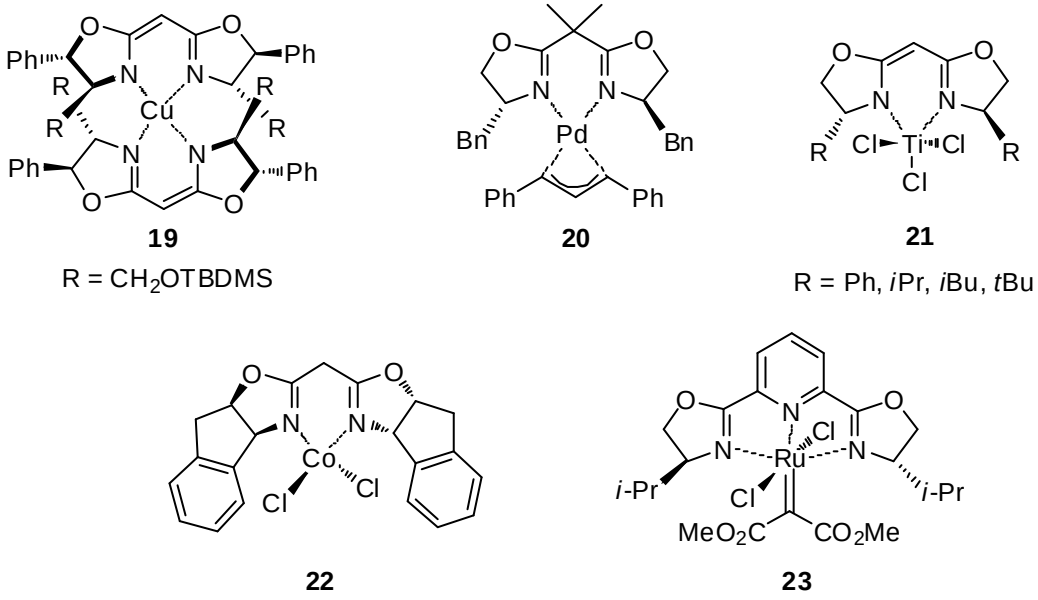


Figure 5: Diversity in the box metal complexes.

The bis(oxazoline)-Cu(II) (2:1) complex **19** was isolated and X-ray analysis showed a tetrahedral coordination geometry. Lehn et al. thought of incorporating such ligands into oligomeric bipyridyl strands, which should lead to strained double helicatal complexes capable of asymmetric induction.[28] The other example is Pd(II)-allyl complex **20**, reported by Pfaltz et al. Based on the crystal structure and NMR measurements of the chiral metal complexes, the mechanism for the asymmetric palladium-catalyzed allylic substitution was elucidated.[29] Box-titanium (IV) complexes **21**, prepared by the reaction of different bis(oxazolines) ligands with $TiCl_4$ in toluene, were shown to have a trigonal bipyramidal

structure, with the two nitrogen binding sites in the equatorial position.[30] The authors were not able to obtain crystal structures of these metal complexes, because of their instability during the crystallization process. Ghosh and co-workers were successful in preparing crystalline cobalt (II) complex **22**, which showed tetrahedral geometry at the metal center, using an (1*S*, 2*R*)-inda-box ligand.[31] Most of the common bisoxazoline ligands are bidentate, but there also exist several types of tridentate bis(oxazolines), which also readily form metal complexes, such as **23** where a (*S*,*S*-*i*Pr_2)-Py-BOX ligand is complexed with ruthenium (IV).[32]

The bis(oxazoline) ligands were also research topic of our group. They were used for the asymmetric catalysis deploying mainly their copper and palladium metal complexes.[12-14] The next chapter will be focused on their analogs bearing a negatively charged boron atom within the bis(oxazoline) backbone.

Chapter 3

Boron-bridged bis(oxazoline) ligands

3. Boron-bridged bis(oxazoline) ligands

3.1 Introduction

Phosphine ligands are widely used in inorganic and organic synthesis. Their bidentate versions are also frequently used in asymmetric catalysis.[33] In 2003, a new family of these ligands was developed by Peters et al.[34] by incorporating the boron atom into the bridging backbone of the bis(phosphine) scaffold. The boron atom in those ligands bears a negative charge because it is four-substituted (*Figure 6*); hence, these ligands could be expected to have new properties.

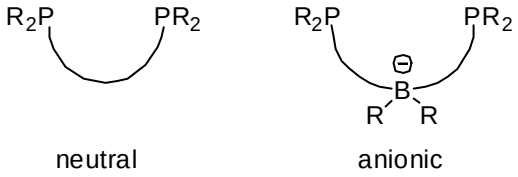
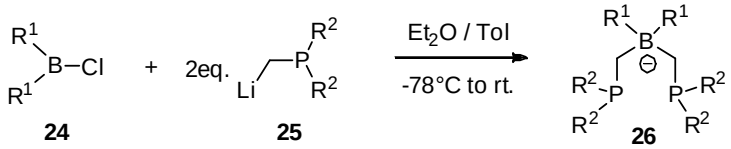


Figure 6: bis(phosphine) ligands vs. bis(phosphino)borates.

In these species, the anionic bis(phosphino)borate ligands keep the coordination properties of their neutral analogs towards the metal, while being anionic at the same time. The negative charge can also influence the electronic properties of the complex by electron donation to the phosphine, thus affecting the electron charge on the metal center. The synthesis of metal borate complexes is not a well developed area, even though it has been studied, for example by the group of Riordan (*Scheme 5*).[35]



R^1 = Ph, Cy, *p*-CH_3-C_6H_5, 3,5-$(CH_3)_2$-C_6H_4, *p*-*t*Bu-C_6H_5, *p*-MeO-C_6H_5, *p*-CF_3-C_6H_5

R^2 = *t*Bu, Ph, *p*-*t*Bu-C_6H_5, *p*-*i*Pr-C_6H_5, *p*-CF_3-C_6H_5

Scheme 5: Synthesis of anionic bis(phosphino)borate ligands

The preparation of these anionic ligands starts from a diarylchloroborane **24** that, after the nucleophilic attack by a lithium diarylphosphine salt **25**, forms boron ate-complex **26** as the product. Although the synthesis of those ligands looks very simple, the reaction proceeds cleanly only under the optimized conditions (Et_2O / Tol, -78 °C to room temperature).

The anionic bidentate ligands were isolated as lithium salts, which were then crystallized and the X-ray structure was obtained. The lithium salts can be further modified by a simple cation exchange, for example with Me_2PtCOD or $Tl(NO_3)_3$. The tantalum complex was subjected to crystallographic analysis and the structure is depicted in *Figure 7*.[34]

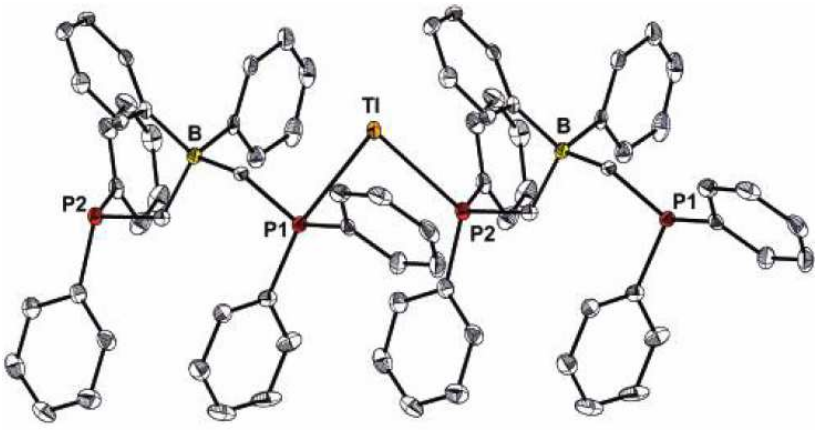


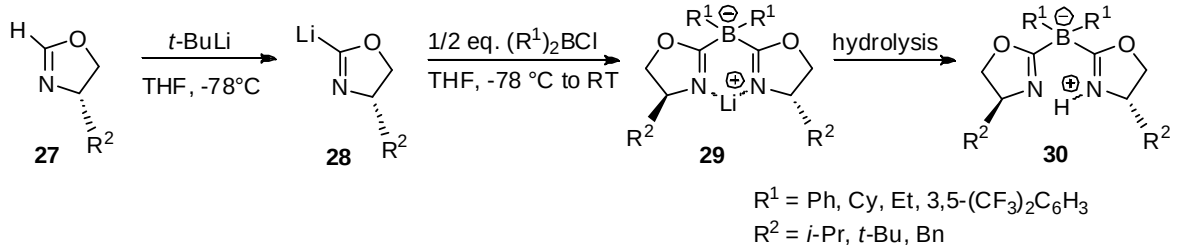
Figure 7: X-ray structure of dimeric bis(phosphino)borate tantalum (III)

The influence of different substituents on the boron or phosphorous in the bis(phosphino)borate dimethylplatinum (II) complexes was also studied. CO gas was used to exchange one of the methyl ligands on the platinum, and the resulting change in the stretching band of the CO was observable by infrared spectroscopy. However, the difference between the different substituents was rather small. For example, the difference between electron-donating *para* substituents CH_3O and electron-withdrawing CF_3 groups on the phenyl group of boron was only 3 cm^{-1}, although the difference between *para* substituents *t*Bu and CF_3 on the phenyl group of phosphorous was already 14 cm^{-1}.

The authors of this article also disclosed problems which they faced during the ligand synthesis, for example, when they attempted to prepare the less strained ligand $[Ph_2B(CH_2PMe_2)_2]$. Another problem was in the preparation of the simple phosphine carbanion, but this problem was circumvented by BH_3 protection of the phosphine. However this protection could cause problems of its own in the subsequent deprotection step.

3.2 Borabox ligand synthesis

Two years later, after the invention of the bis(phosphino)borate by Peters et al., the synthesis of a new ligand class bearing both tetravalent boron and two chiral oxazoline moieties was developed in the Pfaltz group.[36] These ligands are also anionic and in combination with the metal they can produce a neutral species, called a zwitterionic metal complex (*Scheme 6*).



Scheme 6: Borabox ligand synthesis.

The synthesis of the borabox ligands is very straightforward. It starts from readily available oxazolines **27** by the deprotonation of the acidic proton with a sterically hindered base, such as *t*-BuLi, to obtain the corresponding lithiated oxazoline **28**. This product is then treated with a dialykyl or diaryl chloroborane (0.5 equiv) at low temperature and the reaction mixture is allowed to warm to room temperature, resulting in the desired product **29** in good to moderate yield, depending on the nature of the boron substituent. This product could be isolated as either a highly hygroscopic white powder, by crystallization from apolar solvents, or it can be converted into its protonated form **30** by hydrolysis. The hydrolysis usually spontaneously occurs during column chromatography on silica gel with EtOAc/Hex/Et_3N (9:1:0.5) as eluent. Thus, the protonation happens during the purification of the reaction mixture and the additional step is not necessary. The lithium salts can be regenerated from their protonated forms by using one molar equivalent of *n*-butyllithium in diethylether at room temperature.

A number of ligands, which differ sterically and electronically, could be prepared through this short series of reactions. The substituents on the oxazoline ring are mainly intended to vary the steric environment that will be close to the reaction center in the catalyzed reaction. By variation of the substituents of the chloroborane from alkyl to aryl to aryl with electron-withdrawing substituents, the electronic properties of the final metal complex are also modified.

3.3 Borabox Metal complexes

3.3.1 Complexes with copper (II)

The borabox complexes readily form metal complexes with various transition metals, such as Cu(II), Zn(II), Pd(II), Rh(I), and Ir(I), either by directly using the protonated ligand in the presence of a base such as K_2CO_3, or just by ion exchange of the lithium salts with the transition metal. In *Figure 8* two related metal complexes are shown. The first one is a homoleptic [Cu(II)(borabox)$_2$], which shows slightly distorted tetrahedral geometry. For comparison, the second structure is [Cu(II)(box)Cl_2], which also has tetrahedral geometry but is heteroleptic.

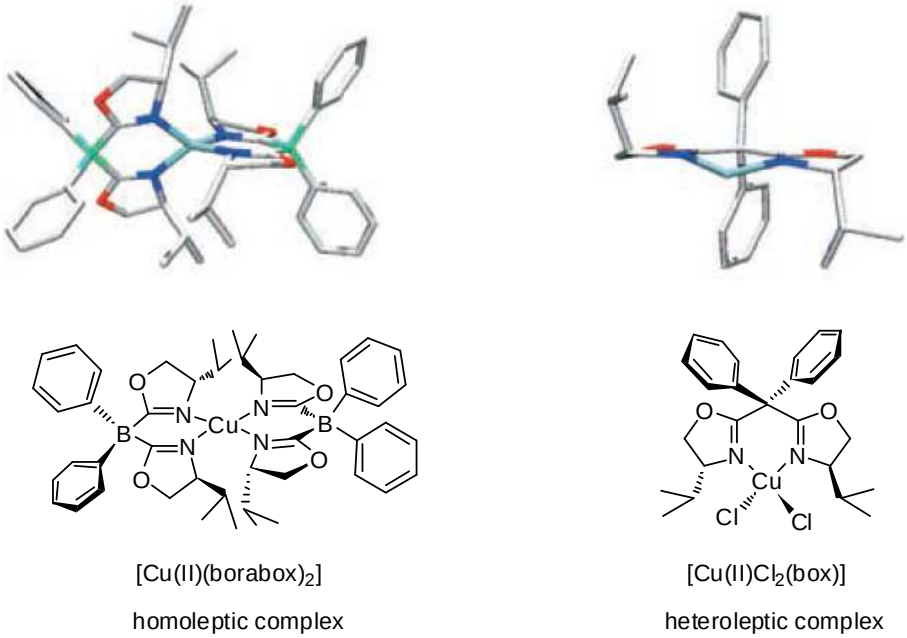


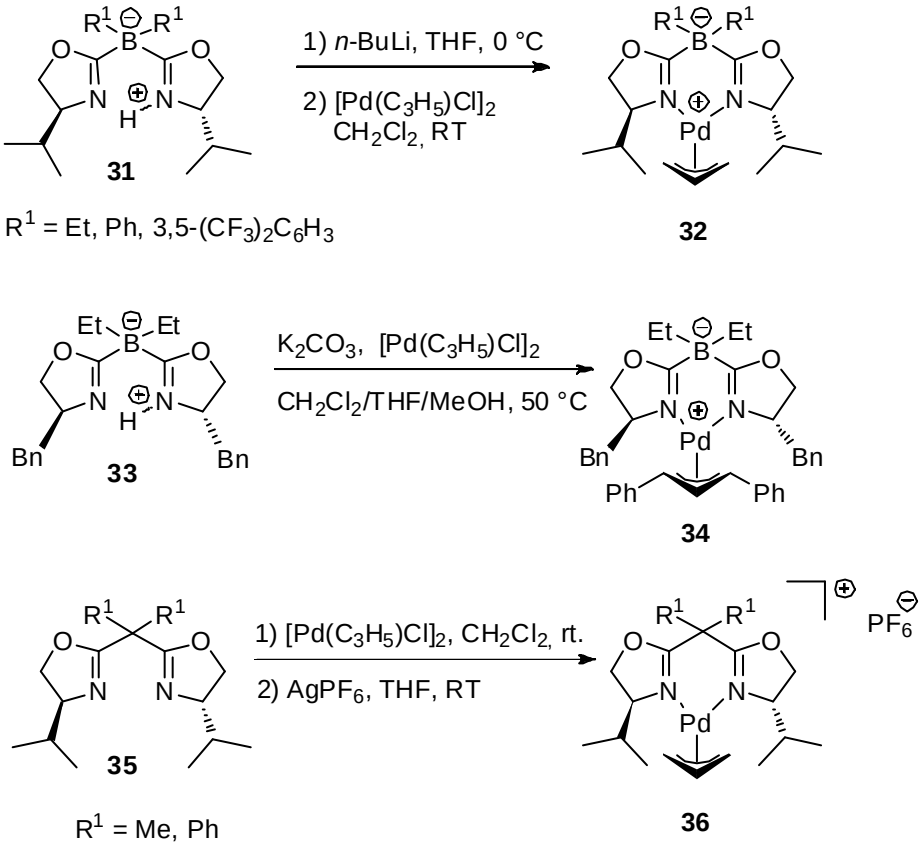
Figure 8: Crystal structures of the Cu(II) complexes of borabox and the related box complex. Hydrogen and chorine atoms were omitted for clarity.

A number of homoleptic Cu(II)borabox complexes have been prepared, starting with variously substituted borabox ligands **30**.[37] These can be readily obtained by complexation of the corresponding borabox lithium salts in a biphasic water/CH_2Cl_2 mixture with $CuSO_4 \cdot H_2O$ (1.0 equiv.) or by treatment of the protonated borabox ligand with $Cu(OAc)_2$ (1.0 equiv.) in methanol.[38] Their crystallographic data were recorded and the structural properties of the individual ligands in their copper complexes were consequently compared. They all adopt

very similar geometries and differ only minimally. For example, the C_{oxa}-B-C_{oxa} angles are close to the ideal tetrahedral geometry in the range of 108.8°, for ethyl substituted boron and isopropyl oxazoline, to 110.4°, for the 3,5-$(CF_3)_2C_6H_3$ substituted boron and isopropyl oxazoline. The bond lengths between the oxazoline quaternary carbons and boron are within the range of 1.61 Å to 1.62 Å and the C=N bonds lengths are within the range of 1.28 Å, for *i*Pr oxazoline, to 1.30 Å, for benzyl oxazoline, both with an ethyl substituent on the boron.

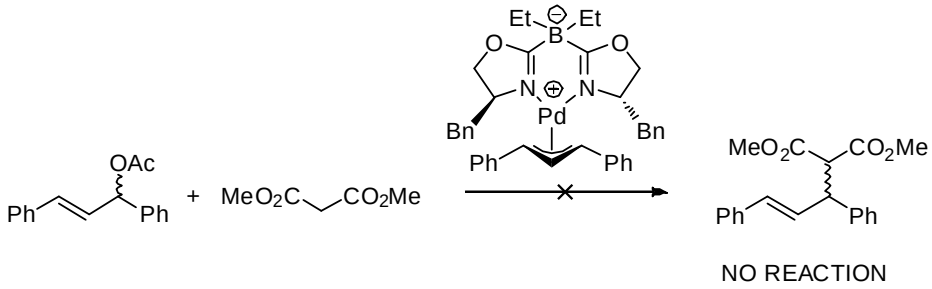
3.3.2 Complexes with palladium (II)

In analogy with already established box systems, the other transition metal that was attractive to test with the new borabox ligands was palladium. Therefore new borabox palladium (II) complexes **32** and **34** were prepared, as shown in *Scheme 7*.[37]



Scheme 7: Synthesis of borabox and box palladium complexes.

While palladium box and aza-semicorrin complexes catalyze the allylic substitution of *rac*-(*E*)-1,3-dipehnylallylacetate with dimethylmalonate very well, with excellent yields (up to 99%) and stereoselectivities (up to 97 % *ee*), the borabox ligands **31**and **33** are unreactive in this transformation.[29] Even borabox complex **34**, which is structurally very similar to box palladium complex **36**, didn't show any reaction in the corresponding allylic substitution between *rac*-(*E*)-1,3-dipehnylallylacetate and dimethylmalonate (*Scheme 8*).



Scheme 8: Palladium-catalyzed allylic substitution using borabox complex **34**.

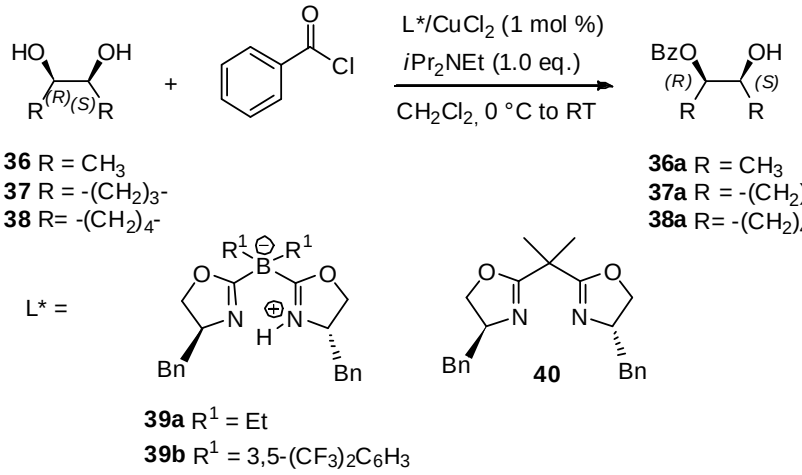
The properties of the palladium borabox complexes were further investigated in ^{13}C NMR studies, where the chemical shift of the carbon atoms within the allyl fragment should differ based on the electronic properties. The NMR studies showed that the carbon shifts of the borabox palladium complexes are further upfield than the corresponding signals in the box palladium species, which supports the expectation that the allyl moiety will be more electron-rich, owing to the delocalized negative charge of the tetrasubstituted boron. Furthermore, DFT calculations were conducted which, based on the charge distribution using natural population analysis, were in a good agreement with the results obtained by ^{13}C NMR spectroscopy.[39]

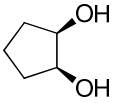
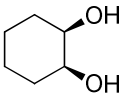
3.4 Monobenzoylation and kinetic resolution of 1,2-diols

After discovering the limitations of the borabox complexes in the palladium-catalyzed asymmetric allylic substitution reaction, further research focused on the chemistry of the more successful borabox copper complexes. Matsumura et al. published a 2003 paper about the kinetic chiral resolution of meso 1,2-diols catalyzed by Ph-box Cu(II) (5 mol %), where they obtained good to excellent enantioselectivities depending on the substrates used.[40]

This reaction (see *Scheme 9*) was then tested using the borabox Cu(II) complexes, this time catalyzed by 1 mol % of catalyst, but otherwise under the same conditions as Mastsumura. The results are summarized in *Table 2*.[36]

Table 2: Monobenzoylation of meso 1,2-diols.



Ligand	*meso* 1,2-diol	Yield [%][a]	*ee* [%][b]
39a		79	40
39b		73	76
40		70	33
39a		75	47
39b		83	90
40		74	85
39a		62	92
39b		65	94
40		68	84

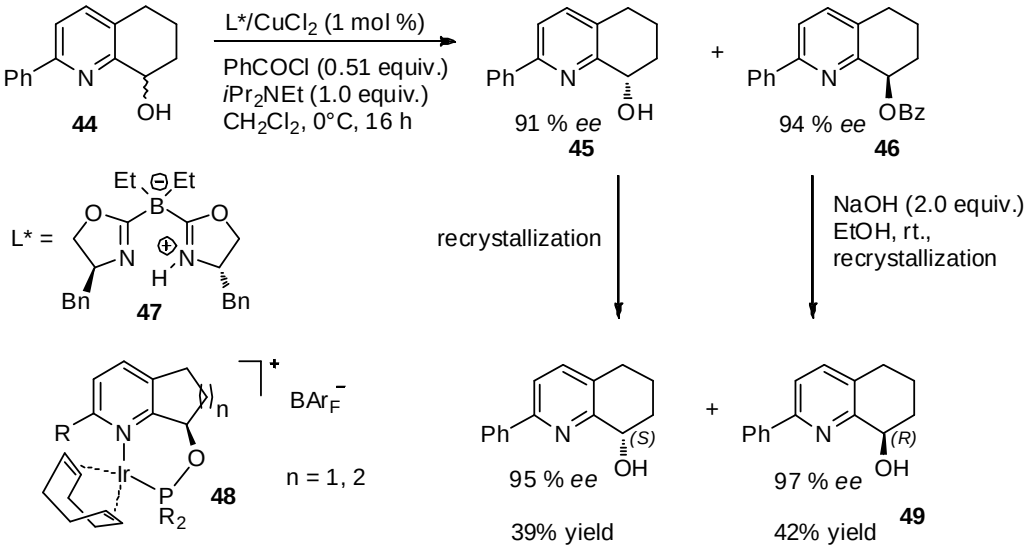
[a] Average of two runs. [b] *ee* determined by HPLC

In *Table 2* it is demonstrated that in the desymmetrization of meso 1,2-diols **36**-**38**, the boroabox copper complex can reach the same conversions as the related box copper complex and the enantiomeric excesses obtained with the borabox ligand in many cases are better than with the box ligand.

Another reaction along the same lines as the desymmetrization of the *meso* 1,2-diols is the kinetic resolution of 1,2-diols, which was also published by Matsumura using box copper(II) complexes.[40]

3.5 Kinetic resolution of pyridyl alcohols

The borabox ligands were shown to be efficient in the desymmetrization of the diols and so they were applied in the synthetically valuable kinetic resolution of pyridyl alcohols, as shown in *Scheme 9*.[41]



Scheme 9: Cu(II)-(Borabox)-catalyzed kinetic resolution of pyridyl alcohols.

Chiral pyridyl alcohols are useful precursors for the preparation of chiral P,N ligands, because their cationic iridium complexes **48** have been shown to be highly efficient catalysts in the enantioselective hydrogenation of unsubstituted olefins.[42] To date there are just a few synthetic methods to approach these chiral pyridyl alcohols. These mainly rely either on the asymmetric reduction of pyridyl ketones [43] or on enzymatic resolution.[44]

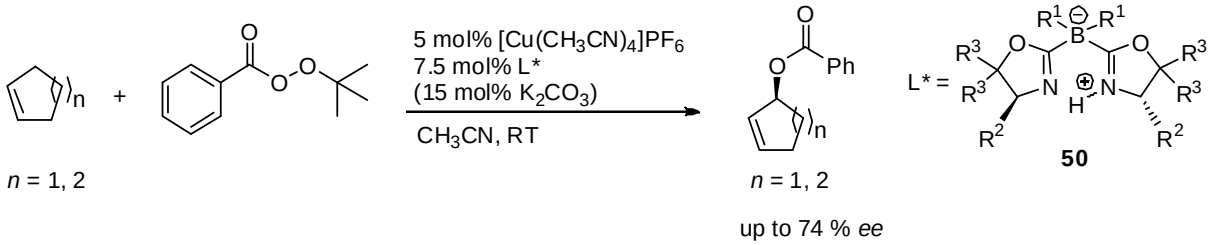
This synthesis utilizes only 1 mol % of the Cu(II) catalyst bearing chiral borabox ligand **47** and starts from racemic pyridyl alcohol **44.** After a reaction time of 16 hours under very mild conditions a mixture of chiral pyridyl alcohol **45** and benzylated alcohol **46** was obtained, which was separable by column chromatography. The chiral alcohol **45** was obtained as the *S* enantiomer in 39 % yield and 97 % enantiopurity after recrystallization. The other enantiomer of the *R* pyridyl alcohol **49** can be obtained in 42 % yield and 97 % *ee* after deprotection and recrystallization.

The enantioselectivities obtained in this kinetic resolution differ depending on the ring sizes of the pyridyl alcohols and on the pyridine R substituent, with a phenyl substituent being the

best among the substrates screened. Also, lower selectivities were obtained when using Cu(II) box as a catalyst versus the Cu(II) borabox complexes.

3.6 Copper-catalyzed allylic oxidation of cyclopentene and cyclohexene

Another reaction where the abilities of the borabox ligands were examined was the asymmetric copper-catalyzed allylic oxidation of cyclic olefins (*Scheme 10*).[37] The initial screening showed that using protonated borabox ligands **50** in combination with K_2CO_3 is more efficient in terms of enantioselectivity than using their Li(borabox) salts.

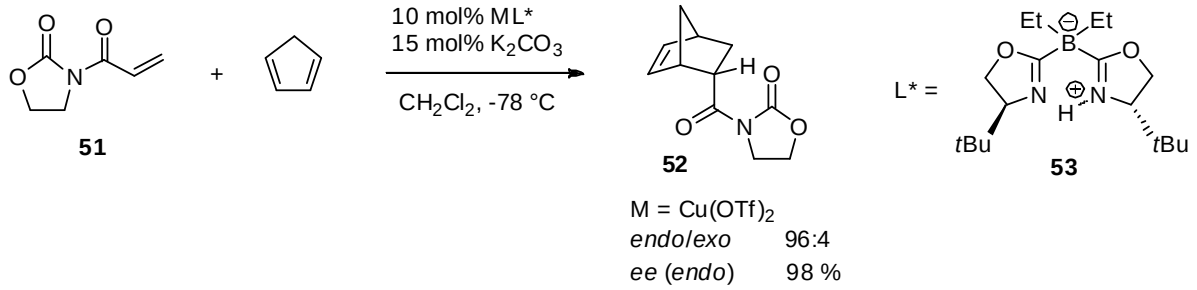


Scheme 10: Borabox Cu (II)-catalyzed allylic oxidation.

The results of this reaction were also compared with the results obtained from the analogous substitution pattern of the box ligand where R^1 was a phenyl group and R^2 was isopropyl. In the oxidation of cyclohexene, borabox ligand **50** delivered an *ee* of 74 %, whereas the box ligand only gave 48 % *ee*. A surprising observation was that the typically very effective *tert*-butyl R^2 substituent of the oxazoline completely failed in this type of reaction, delivering almost racemic products. The oxidation reaction is quite slow, usually requiring a number of days to achieve good conversions. Since the kinetic studies showed only a small dependence on temperature for the enantioselectivity, the reaction can be accelerated by heating to 80 °C, which shortens the reaction time from days to hours without significant drop in the enantioselectivity. Substitution in the C5 position of the oxazoline did not provide any significant improvement in the reaction results.

3.7 Diels-Alder reaction

An enantioselective version of the Lewis acid catalyzed Diels-Alder reaction has been successfully applied and tested with new borabox ligands. The role of the base and the source of the metal were also studied.[45] The use of a base during the formation of the zinc metal complex was shown to be crucial both for the formation of the heteroleptic borabox complex and to avoid formation of the homoleptic complex, which is unselective. A sample reaction of acyl-1,3-oxazolidin-2-one **51** with cyclopentadiene is shown in *Scheme 11*.



Scheme 11: Borabox as a chiral ligand in a Lewis acid catalyzed Diels-Alder cycloaddition.

There was a surprisingly large difference in the selectivity of chiral borabox **53,** as shown in *Scheme 11*, when the C4 substituent was changed from *t*Bu to benzyl, which lead to a completely racemic *endo* product. By employing various metal sources, such as $Zn(OTf)_2$, $MgI_2 \cdot I_2$, $FeI_3 \cdot I_2$, almost racemic *endo* product was obtained, while conversions and *endo*/*exo* ratios remained good under all conditions tested.

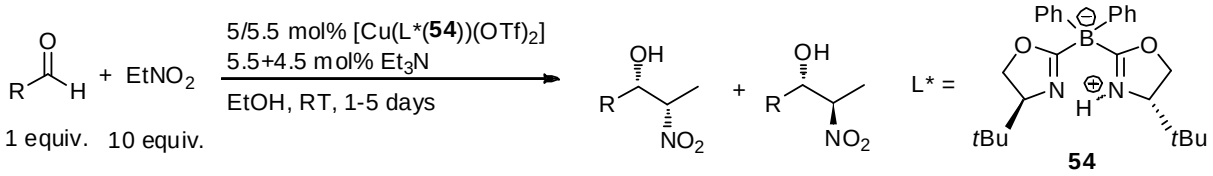
3.8 Asymmetric Henry reaction

Borabox ligands were also tested in the copper-catalyzed nitroaldol reaction, called Henry reaction, which is a base-catalyzed reaction between an aldehyde and a nitroalkane.[46] The reaction requires a base to deprotonate the nitroalkane, which then nucleophilically attacks the aldehyde. The reaction is terminated by protonation of the newly generated product, which also regenerates the base at the same time. The drawbacks of this reaction are that all of the steps in the mechanism are reversible and that the disproportionation of the aldehyde in a side

reaction when using base to deprotonate nitroalkane could affect the yield of the desired product.

Borabox ligands **54** have been shown to be effective ligands for stereoselective control of the Henry reaction. Under optimized conditions, high selectivities can be attained, especially when nitroethane or nitropropane is used in combination with the aliphatic aldehyde. The results for nitroethane are depicted in *Table 3*.

Table 3: Henry reaction with nitroethane catalyzed by a borabox Cu(II) complex.



Entry	R	Time [days]	Yield [%][a]	*syn*/*anti*[b]	*ee* (*syn*) [%][c]	*ee* (*anti*) [%][c]
1	Ph	1	80	62:38	21 (1*S*,2*S*)	15 (1*S*,2*R*)
2	Cy	5	82	90:10	90 (1*S*,2*S*)	47 (1*S*,2*R*)
3	Et	5	80	64:36	51 (1*S*,2*S*)	23 (1*S*,2*R*)

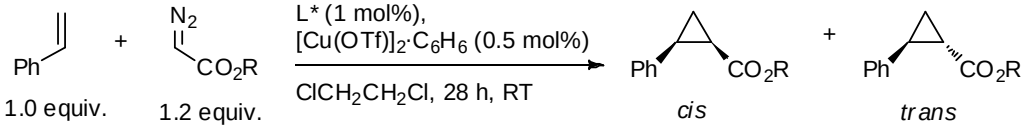
[a] Combined yield of *syn* and *anti* isomers. [b] determined by 1H NMR spectroscopy. [c] Determined by chiral HPLC analysis

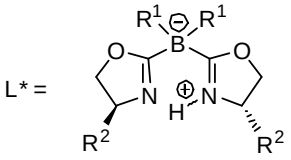
3.9 Cyclopropanation of olefins

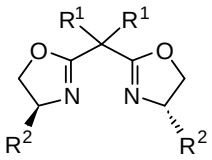
Further investigation of the borabox ligands conducted by Clément Mazet were screening experiments[36] to compare their performance with that of box complexes in cyclopropanation reactions, as previously reported by the groups of Pfaltz, Masamune, and Evans.[15-17, 47] The Cu(I) borabox complexes were prepared in situ from CuOTf and lithium salts of the corresponding borabox ligands. As a test reaction for the initial screening of the borabox ligands a typical cyclopropanation reaction using styrene and diazoacetate ester was chosen. This reaction is commonly used as a benchmark for testing selectivity of new chiral ligands. The mechanism of this Cu(I)-catalyzed cyclopropanation was investigated by Evans et al. including an X-ray structure of the catalyst.[47] The reactivities of the borabox ligands are basically the same as their box analogs (*Table 4*). Large substituents on the oxazoline ring in the C4 position have a positive influence on the enantioselectivity of the reaction, as with the box ligands, although it is not that significant (*Table 4*, **55a** and **55b** vs. **56a** and **56b**). In the reaction with ethyldiazoacetate, the selectivities obtained with borabox ligands were only

moderate (see **55a**-**55f**), but through the use of *tert*-butyl diazoacetate and 2,6-di-*tert*-butyl-4-methoxyphenyl (BHT) diazoacetate, the selectivities were significantly improved. The 3,5-bis(trifluoromethyl)phenyl group in the ligand **55f** was shown to be the best substituent for boron. To date, the best published result in terms of selectivity was obtained in the reaction of the BHT-diazoacetate and an oxazoline substituted with a *tert*-butyl group in the C4 position and an electron-withdrawing Ar_F substituent on the boron, as in ligand **55f**.

Table 4: Cyclopropanation of styrene.







55a: R^1 = Ph, R^2 = *i*Pr
55b: R^1 = Ph , R^2 = *t*Bu
55c: R^1 = Cy, R^2 = *i*Pr
55d: R^1 = Et, R^2 = *t*Bu
55e: R^1 = Cy, R^2 = *t*Bu
55f: R^1 = Ar_F, R^2 = *t*Bu

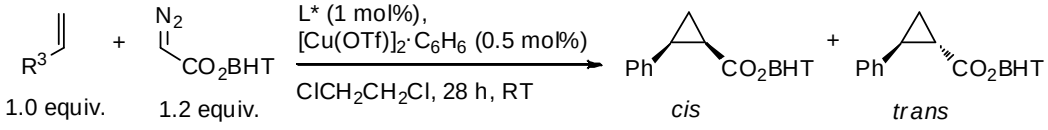
56a: R^1 = Ph, R^2 = *i*Pr
56b: R^1 = Ph, R^2 = *t*Bu
56c: R^1 = Me, R^2 = *t*Bu

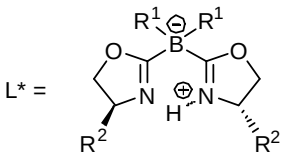
Entry	Ligand	R^1	R^2	Diazo ester (R)	*cis*/*trans*	*cis*[a] *ee* [%]	*trans*[a] *ee* [%]	Yield [%][b] (*cis*+*trans*)
1	**56a**	Ph	*i*Pr	Et	36:64	54	51	85
2	**56b**	Ph	*t*Bu	Et	33:67	91	89	72
3	**56c**	Me	*t*Bu	Et	27:73	97	99	77
4	**55a**	Ph	*i*Pr	Et	29:71	58	65	77
5	**55b**	Ph	*t*Bu	Et	30:70	66	70	84
6	**55c**	Cy	*i*Pr	Et	32:68	24	33	68
7	**55d**	Et	*t*Bu	Et	28:72	59	72	75
8	**55e**	Cy	*t*Bu	Et	28:72	78	66	79
9	**55f**	Ar_F	*t*Bu	Et	32:68	68	77	89
10	**56b**	Ph	*t*Bu	Et	21:79	93	90	70
11	**56c**	Me	*t*Bu	*t*Bu	19:81	93	96	75
12	**55b**	Ph	*t*Bu	*t*Bu	15:85	77	67	77
13	**55d**	Et	*t*Bu	*t*Bu	13:87	76	73	65
14	**55e**	Cy	*t*Bu	*t*Bu	9:91	82	73	63
15	**55f**	Ar_F	*t*Bu	*t*Bu	17:83	86	92	65
16	**56c**	Me	*t*Bu	BHT	4:96	-	99	85
17	**55f**	Ar_F	*t*Bu	BHT	1:99	-	98	89

[a] Determined by GC or HPLC analysis. [b] After chromatography [c] Determined by ^{1}H NMR spectroscopic analysis

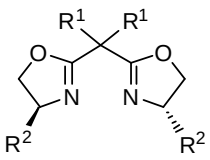
With the results from the initial screening in hand, further investigations were undertaken using additional olefins bearing substituents with different electronic properties, including electron-donating (entry 3, 4) or electron-withdrawing groups (entry 5, 6) or aromatic (entry 1, 2), as well as aliphatic substituents (entry 9, 10). Again, the best results were obtained with borabox ligand **55f**, especially in case of *p*-F-C_6H_4, which resulted in 1:99 *cis*/*trans* selectivity and 99.5 % *ee* in 91 % yield of isolated product.

Table 5: Cyclopropanation of different olefins.





55f: $R^1 = Ar_F$, $R^2 = t$Bu



56c: R^1 = Me, $R^2 = t$Bu

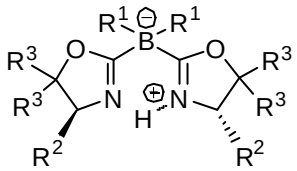
Entry	Ligand	R^1	R^2	R^3	*cis*/*trans*[a]	*trans*[b] *ee* [%]	Yield [%][c] (*cis*+*trans*)
1	**56c**	Me	*t*Bu	Ph	4:96	99	85
2	**55f**	Ar_F	*t*Bu	Ph	1:99	98	89
3	**56c**	Me	*t*Bu	*p*-$MeOC_6H_4$	4:96	96	35[d]
4	**55f**	Ar_F	*t*Bu	*p*-$MeOC_6H_5$	4:96	97	65[d]
5	**56c**	Me	*t*Bu	*p*-FC_6H_4	4:96	99.4	89
6	**55f**	Ar_F	*t*Bu	*p*-FC_6H_5	1:99	99.5	91
7	**56c**	Me	*t*Bu	$PhCH_2$	7:93	99	ng[e]
8	**55f**	Ar_F	*t*Bu	$PhCH_2$	8:92	97	66
9	**56c**	Me	*t*Bu	*n*-hexyl	2:98	99	51[d]
10	**55f**	Ar_F	*t*Bu	*n*-hexyl	1:99	95	68[d]

[a] Determined by 1H NMR spectroscopy. [b] Determined by GC or HPLC analysis. [c] After chromatography [d] Reaction time not optimized. [e] not given

3.10 C5-disubstituted borabox ligands

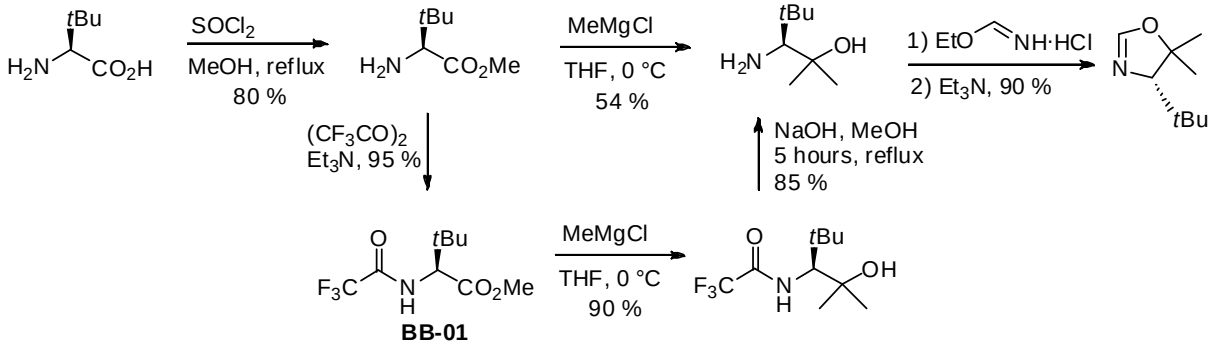
3.10.1 Preparation of C5-disubstituted borabox ligands

Directed by the results of the borabox-complex-catalyzed reactions, in particular by the cyclopropanation reactions, we proposed further modifications of the borabox scaffold in order to obtain new borabox ligands **57g** and **57h** with potentially better properties. As the steric bulk of the oxazoline substituents in the C4 position proved to be beneficial in many cases, the adjacent carbon, C5, was then a good candidate for further modification the lateral steric bulk around the metal center of the catalyst.



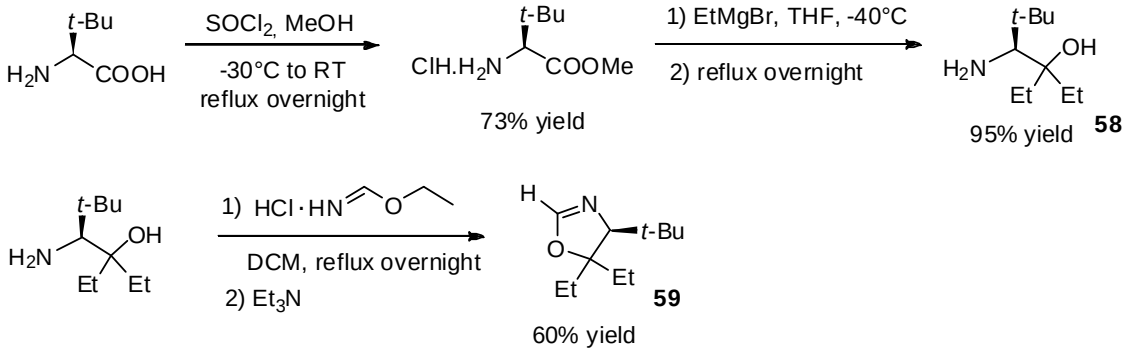
57a: R^1 = Cy, R^2 = *i*Pr, R^3 =Ph,H
57b: R^1 = Cy, R^2 = *t*Bu, R^3 = Me
57c: R^1 = Ph, R^2 = *t*Bu, R^3 = Me
57d: R^1 = Ph, R^2 = *i*Pr, R^3 = 3,5-$(CH_3)_2C_6H_3$
57e: R^1 = Ph, R^2 = *t*Bu, R^3 = 3,5-$(CH_3)_2C_6H_3$
57f: R^1 = Ph, R^2 = *i*Pr, R^3 = 3,5-(*t*Bu)$_2C_6H_3$
57g: R^1 = Cy, R^2 = *t*Bu, R^3 = Et
57h: R^1 = 3,5-$(CF_3)_2C_6H_3$, R^2 = *t*Bu, R^3 = Et

The C5-substituted ligands **57a**-**57f** were prepared by the Pfaltz group and successfully applied in the asymmetric Henry reaction.[45] Their synthesis starts from commercially available chiral amino acids, which are then converted into the corresponding amino acid esters. The ester functionality is then a suitable handle for introduction of the new substituents into the C5position of the future oxazoline. By reaction with two equivalents of a Grignard reagent, a chiral amino alcohol is obtained, and is subsequently converted into the 2*H*-oxazoline by the Meyers protocol.[48] In the synthesis of 5,5-dimethyl substituted 2H-oxazoline, the Grignard addition was a problematic reaction step (*Scheme 12*) which was then circumvented by using an N-protecting group in order to obtain higher yields.[45]



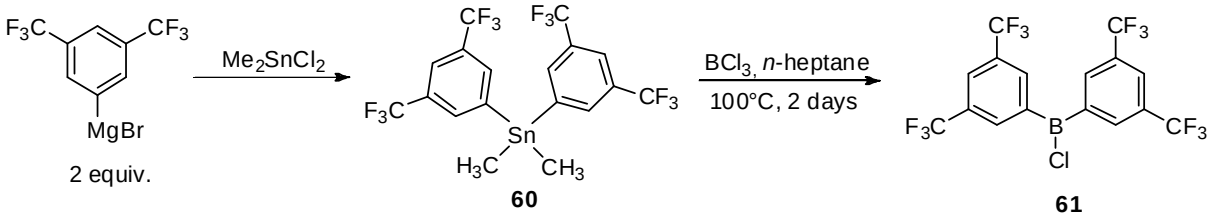
Scheme 12: 5,5-dimethyl-2*H*-oxazoline synthesis.

Therefore, in planning the synthesis of the 5,5-diethyl substituted 2H-oxazoline an amine protection step was also incorporated to avoid problems during the Grignard addition. Unfortunately, although the Grignard addition was complete and the reaction clean, deprotection of trifluoroacetyl protected aminoalcohol **58** was impossible and did not go to completion even after a day under reflux with methanolic hydroxide. Ultimately, the synthesis of **59** (*Scheme 13*) was successfully accomplished by the addition of an excess of ethylmagnesium bromide to the hydrochloride salt of the aminoalcohol, which led to a very clean reaction.



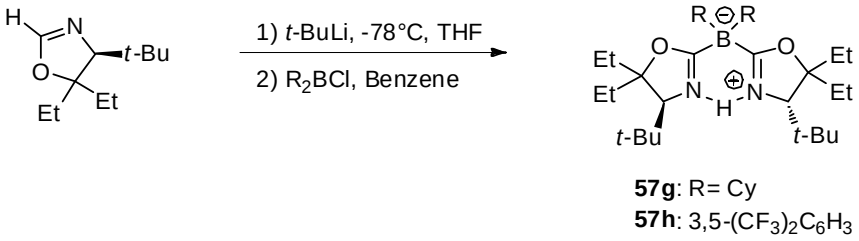
Scheme 13: Synthesis of 5,5-diethyl-2*H*-oxazoline.

The reaction of the alcohol **58** with ethyl formimidate hydrochloride delivered the 5,5-diethyl-2H-oxazoline **59** in good yield. The next step in the synthesis of the new 5,5-disubstituted borabox ligands **57g** and **57h** was preparation of the starting chloroborane **61** (*Scheme 14*), which was done by the method of Peters et al.[34]



Scheme 14: Synthesis of bis(3,5-bis(trifluoromethy)phenyl)chloroborane.

This method utilizes the moderate reactivity of dimethyltin dichloride, which, in reaction with two equivalents of a Grignard reagent, delivers the addition product **60**. In the subsequent step, the aryl substituents are transferred from the tin to boron to obtain **61**. Although the use of dicyclohexyl chloroborane in this method could be considered a drawback, owing to the difficulty of its preparation, this potential problem was obviated by the commercial availability of the compound. Then, following the general procedure for formation of the borabox ligand (*Scheme 15*), 2 equivalents of **59** were deprotonated by *tert*-butyllithum and allowed to react with the corresponding chloroboranes.[36]



57g: R= Cy
57h: 3,5-$(CF_3)_2C_6H_3$

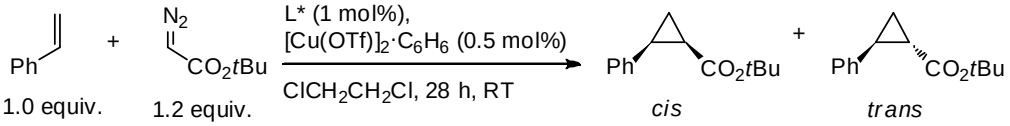
Scheme 15: Preparation of new 5,5-disubstituted borabox ligands.

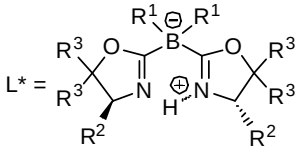
Both ligands **57g** and **57h** were purified by the column chromatography on silica gel, but neither of these complexes could be well separated, because they are unstable and decompose during chromatography. The use of triethylamine in the eluent mixture to reduce the acidity of the silica gel has been found to be beneficial, but both ligands are very nonpolar and so the use of triethylamine is not acceptable, therefore they were purified on neutral alumina. In case of the **57g**, this led to the pure compound, but this was not the case for **57h**. Therefore, purification of the crude ligand **57h** was attempted by crystallization with $CuSO_4$ or $CuCl_2$; however, in neither case were crystals produced, thus the impure ligand was used in all further investigations.

3.10.2 Cyclopropanation using 5,5-disubstituted borabox complexes

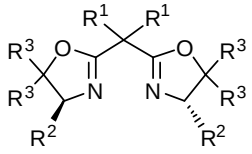
The newly prepared ligands **57g** and **57h** were then tested in the cyclopropanation reaction using styrene and *tert*-butyldiazoacetate as substrates and the results compared with those of the previously prepared 5,5-unsubstituted analogs; the results are summarized in the *Table 6*.

Table 6: Cyclopropanation of styrene using 5,5-disubstituted borabox complexes.





57g: R^1 = Cy , R^2 = *t*Bu, R^3 = Et
57h: R^1 =3,5-$(CF_3)_2C_6H_3$, R^2 = *t*Bu, R^3 = Et
55e: R^1 = Cy, R^2 = *t*Bu, R^3 = H
55f: R^1 = Ar_F, R^2 = *t*Bu, R^3 = H



56c: R^1 = Me, R^2 = *t*Bu, R^3 = H

Entry	Ligand	R^1	R^2	R^3	*cis*/*trans*[a]	*cis*[b] *ee* [%]	*trans*[b] *ee* [%]	Yield [%][c] (*cis*+*trans*)
1	**56c**	Me	*t*Bu	H	19:81	93	96	75
2	**55e**	Cy	*t*Bu	H	9:91	82	73	63
3	**55f**	Ar_F	*t*Bu	H	17:83	86	92	65
4	**57g**	Cy	*t*Bu	Et	8:92	47	74	73
5	**57h**	Ar_F	*t*Bu	Et	22:78	11	13	84

[a] Determined by 1H NMR spectroscopy. [b] Determined by GC or HPLC analysis. [c] After chromatography [d] Ligand contained impurities.

Box ligand **56c** was found to be the most selective, providing the favored *trans* product in *ee* 96 %. When comparing **55e** with **57g**, it can be seen that the 5,5-disubstituted borabox ligand **57g** is only slightly better in the *cis*/*trans* ratio of its products and in the selectivity of the *trans*-isomer, as well as providing a better yield of isolated product; however, this is counteracted by a significant loss in the enantioselectivity of the *cis* product. When compariing ligands **55f** and **57h**, only small drop in the *cis*/*trans* ratio of the products from the 5,5-disubstituted borabox ligand **57h** is observable, but again the product was isolated in a significantly higher yield. The enantiomeric excesses provided by ligand **57b** cannot be compared with those of its analog, as the impurity present in the ligand most likely significantly undermined the enantioselectivity of the reaction.

3.10.3 Conclusion for cyclopropanation using C5-disubstituted borabox ligands

The borabox ligands proved to be effective in many types of metal-catalyzed chemical reactions. They were designed for the same broad range of the potential applications as their bis(oxazoline) (box) analogs, mainly for use in enantioselective copper- and palladium-catalyzed reactions. For example, the synthesis of chiral pyridyl alcohols[41] allows direct access to synthetically valuable precursors for the synthesis of efficient cationic iridium catalysts.[42a] The palladium-catalyzed allylic oxidation of cyclopentene reached an *ee* of 76 %, which is one of the best results obtained for this substrate to date.[49] The borabox ligands also exhibited the versatility of their use in the Lewis acid catalyzed Diels-Alder reaction and also the Henry and Aza-Henry reactions.[45] However, as opposed to the box ligands, which were successfully applied in the asymmetric palladium catalyzed reaction, the borabox ligands do not catalyze allylic substitution.

Excellent results were obtained in the copper-catalyzed asymmetric cyclopropanation of various olefins, where the borabox ligands surpass the box ligands in the number of substrates. A positive influence was also observed when the steric bulk of either the substrate or the ligand side of the catalyst was increased. In general, more sterically demanding substituents, such as *tert*-butyl, in the C4 position of the oxazoline produced better enantioselectivities. The substituents on the boron atom can tune the catalyst in two ways, either by influencing the bite angle of the bis(oxazoline) bidentate ligand through their sterics, or by influencing the electronic properties through changes in the distribution of negative charge along the ligand. New ligands **57g** and **57h** were tested in the cyclopropanation reaction with *tert*-butyldiazoacetate, in which previous experiments had not provided high enantioselectivities. The 5,5-disubstituted borabox ligands **57g** and **57h** gave basically the same results in terms of reactivity and selectivity as their 5,5-nonsubstituted borabox analogs. The expected positive effect on selectivity of the asymmetric induction by increasing the steric bulk around the metal center in the C5 position of the oxazoline does not seem to occur. This may be due to the already remote position of those substituents, which then do not play an important role in the transition state, as the substrate is approaching the metal center without observable difference.

Chapter 4

Preparation of non-symmetrically substituted boron compounds

4. Preparation of non-symmetrically substituted boron compounds

4.1 Introduction

In the previous chapter a wide range of potential uses for boron-bridged bis(oxazolines) as efficient ligands in asymmetric catalysis was demonstrated. The scope of the applications ranges from the kinetic resolution of 1,2-diols, which has been applied as an useful tool in the kinetic resolution of pyridyl alcohols[41, 50], to copper-catalyzed allylic oxidations[37], Lewis acid catalyzed Diels-Alder cycloadditions, asymmetric Henry reaction,[45] and, last but not least, in the asymmetric copper-catalyzed cyclopropanation of the olefins[36]. The scope of the applications for the borabox ligands it is not just limited to the above mentioned reactions, but it can also be extended to many other reactions where the box ligands were more or less successful. As previously demonstrated, the properties of the borabox ligands can be tuned both electronically and sterically. Variation of the substituents R^1 (*Figure 9*) on the boron atom mainly influences the electronic properties at the metal center. Sterical properties can be then tuned by substitution of the oxazoline ring either in the C4 position by using different amino acid sources or by incorporation of R^3 substituents at the C5 position into the amino acid backbone prior the oxazoline ring closure.

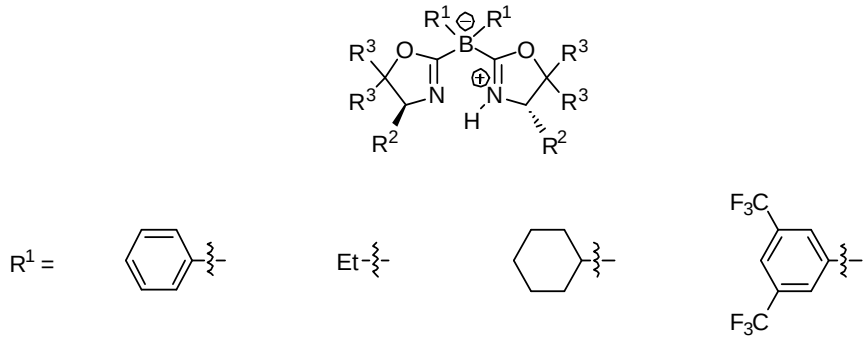


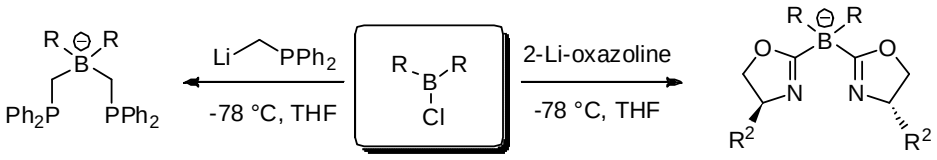
Figure 9: General borabox scaffold with a list of different boron substitunents.

While the modification of the R^3 or R^2 groups of the oxazoline ring were very well established during the period where oxazolines became a powerful and widely used tool, the modification of the boron atom remains underexplored. However, while the synthesis of the

borabox ligands seems to be straightforward and versatile, just a few examples using different boron substituents were prepared (*Figure 9*). The main problem is that almost all the needed boron precursors are not commercially available and their preparation is often tedious, requiring special techniques and safety precautions. Hence, there remains room for improvement to make the boron chemistry more accessible for wider use in organic synthesis.

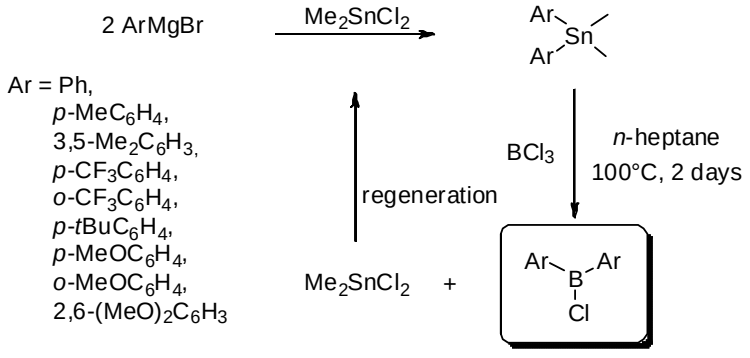
4.2 Preparation of the chloroborane precursors

As was previously shown, chloroboranes are precursors for borabox ligand syntheses as reported by Pfaltz and Mazet in 2005.[36] Their synthesis was inspired by the protocol used by Peters et al. in their 2003 publication on bis(phosphino)borates (*Scheme 16*).[34]



Scheme 16: Synthesis of the bis(phosphino)borates and the boron-bridged bis(oxazolines).

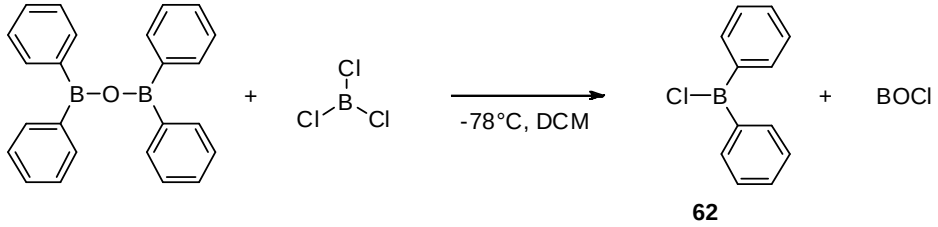
Peters demonstrated that a wide range of aromatic chloroboranes can be prepared by using a modification of the protocol of Chivers[51] and Piers,[52] which was originally described for the preparation of the perfluorinated chloroborane $(C_6F_5)_2BCl$. Until then, no efficient experimental protocol for the the preparation of diarylchloroboranes had been described.



Scheme 17: Preparation of the diarylchloroboranes using dimethyltin dichloride.

The protocol uses a reaction between dimethyltin dichloride and two equivalents of the corresponding Grignard reagent in the first step, wherein all listed aromatic group precursors

formed the desired diaryldimethystannanes. The second step, which relies on a ligand exchange between boron trichloride and Me_2SnAr_2, led to the desired diarylchloroboranes, except for the *ortho*-methyl-substituted analogs, which produced mostly methyl aryl ethers, while the *ortho*-trifluoromethtyl analogs led to a mixture of products. As shown in *Scheme 17*, after the second step the relatively expensive and highly toxic dimethyltin dichloride can be recovered from the reaction mixture either by crystallization from hydrocarbon solvents or by vacuum sublimation. This method is the most versatile, but it requires dimethyltin chloride, which is the only disadvantage. Therefore analogous methods, which could be useful for the preparation of many types of haloboranes, but which also use tin chemistry, were not considered.[53] A more environmentally friendly method is described in *Scheme 18*. The synthesis utilizes the reaction between diarylborinic acid anhydride and boron trichloride, leading to the desired diphenylchlroborane **62**.[54]



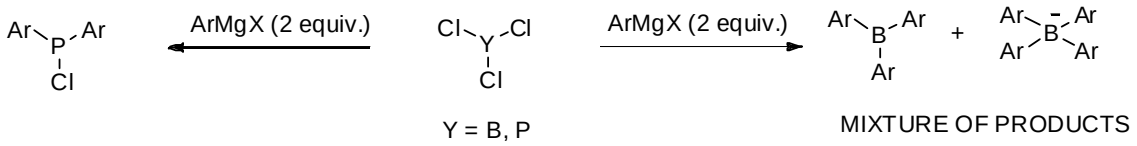
62

Scheme 18: preparation of dimethylchloroborane from diphenylboroinic acid anhydride.

In case of diphenylchoroborane, this method is easily applicable and it was used in our group for preparation of the title compound. But the procedure is limited to diphenyl borinic acid anhydride, which is the only derivative commercially available to date. The other borinic acids would have to be prepared in order to use this method as an alternative to the previous one using Me_2SnCl_2. The preparation of the borinic acid anhydride was reported by Zimmerman in 1961, but a description for a wider range of substrates is missing.[55] The published procedure describes the preparation of diphenylborinic acid, which must be stored as an ethanolamine ester and is converted back to diphenylborinic acid after hydrolysis of the ester bond by treatment with mineral acid. The borinic acid decomposes over time (within hours) and has to be used immediately in the second dehydration step which leads to the desired borinic acid anhydride.

The preparation of dialkylhaloboranes, which are in general more unstable and air and moisture sensitive than their aromatic analogs, was also not considered as a robust process for supplying the desired chloroboranes precursors.[53, 56]

From the described protocols, which are either not general or involve toxic tin compounds, it is clear that the preparation of those highly reactive and air unstable compounds is not trivial. Therefore, the incorporation of aryl substituents on the boron atom in a stepwise fashion, as is done with phosphorus compounds, could be considered. However, there is a dramatic difference in the reactivity of boron trichloride and phosphorus trichloride as shown in *Scheme 19*.



Scheme 19: Different reactivity of phosphorus trichloride and boron trichloride.

In the case of phosphorus trichloride, diphenylchlorophosphine can be easily obtained by the addition of two equivalents of the Grignard reagent,[57] whereas in the case of boron trichloride, the corresponding diphenylchloroborane is not formed. Boron trichloride is far more reactive and such a reaction will generally end up with a mixture of trisubstituted and tetrasubstituted boron compounds. The reaction of phenylmagnesium bromide was tested and triphenylborane was not even a major product.

Therefore, some less reactive boron compounds had to be examined to avoid undesired multiple substitution on the boron atom. Suitable candidates, which are far less reactive then the chloroboranes, are esters of the boric acid, so called boronates. The natural Lewis acidity of boron is suppressed in the boronates by their electron-donating substituents (*Figure 10*).

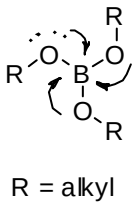
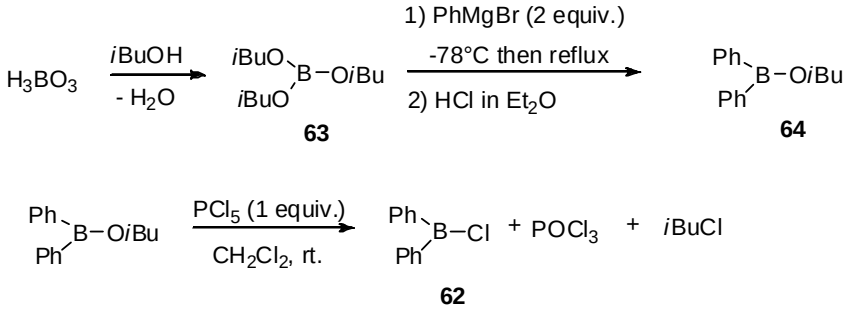


Figure 10: Decreased Lewis acidity of the boron in the alkylboronates.

The crucial electron-donating role of these compounds is played by oxygen, which is directly bound to the boron atom and the oxygen's lone pair electrons push the electron density towards the electron-deficient boron center. The electron-donating effect of the alkyl chain is negligible compared to the donation of the oxygen lone pairs. This electron-donation effect is

also reflected in the stability of such compounds. For example, trialkylboranes spontaneously combust upon exposure to air, while the corresponding boronates can be handled in air without any special precautions. The boronates approach was published by Mikhailov et al. in 1955, where he uses diphenyl(isobutyl)boronate as a starting material.[58] This method seems to be generally applicable because he was able to prepare a wide range of chloroboranes using reasonable conditions and starting from commercially available compounds. Therefore, we decided to test the synthesis by reproducing the previously published results from Mikhailov.

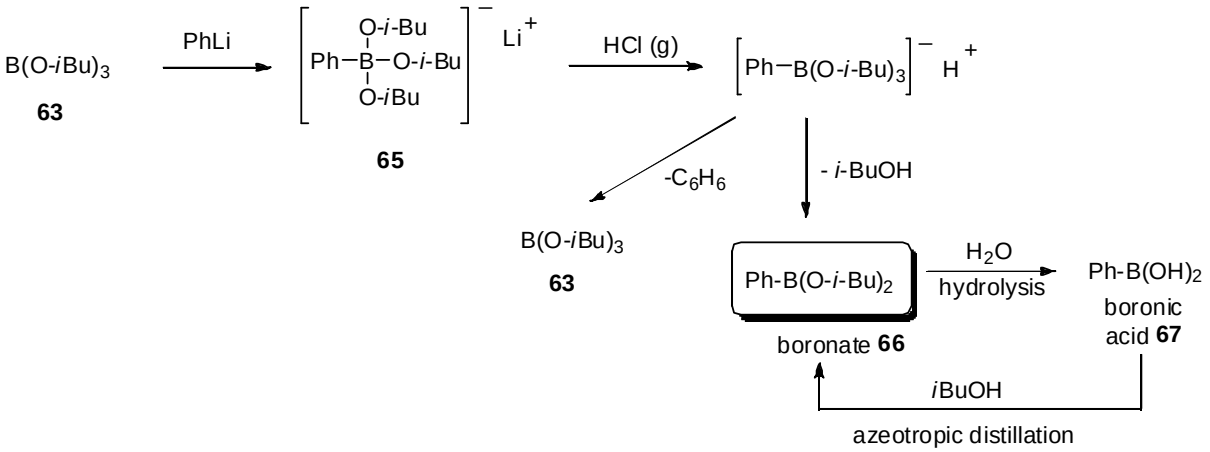


Scheme 20: Synthesis of diphenylchloroborane starting from boric acid.

The synthesis of diphenylisobutyl boronate **64** (*Scheme 20*) starts from tris(isobutyl)boronate **63**, which can be readily obtained by simple esterification of boric acid with the corresponding alcohol, in this case isobutanol, by refluxing both neat reagents while continuously removing the water generated by use of a Dean-Stark distillation apparatus. The choice of isobutylalcohol for the esterification was based on the same reasoning as the choice of boronates as reactants for the next modification, that being the higher stability of the final boronate, which is determined by the length of the alkoxy substituents. The obtained boronate **64** was purified by fractional distillation after the anhydrous workup and treated with phosphorus pentachloride in the next step. This reaction is very fast, slightly exothermic, and complete after several minutes; the product can be isolated either by distillation or by crystallization from the dry hydrocarbon solvent.

The first part of the synthesis is analogous to the well established synthesis of boronic acids, which are widely used in reactions such as the Suzuki coupling. The organolithium or Grignard reagent first attacks the electrophilic boron center of the trialkylborate to form the ate complex **65** which is then quenched by a mineral acid. When this step is done under anhydrous conditions, quenching is done either by gaseous HCl or by ethereal solution of HCl

and the product is arylboronate **66**. When an aqueous workup is used, the product obtained is the boronic acid **67** (*Scheme 21*).

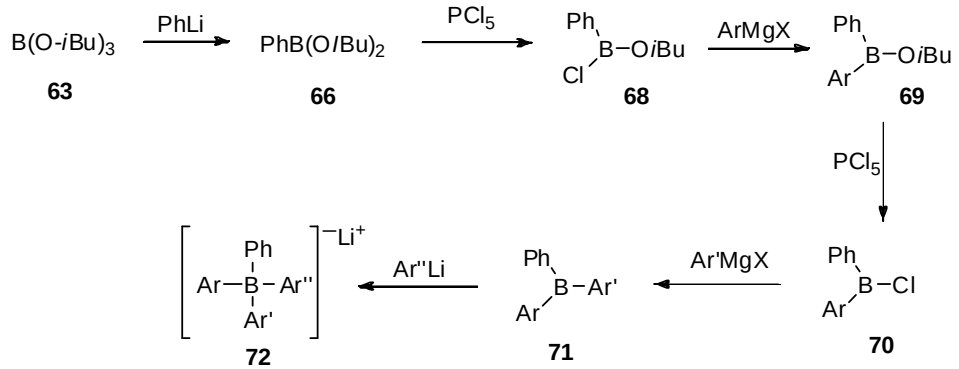


Scheme 21: Mechanism of the addition of the organolithium reagent to the boronates.

The cleavage of the phenyl-boron bond can also take place during the workup while releasing the starting trialkyl boronate **63**. This undesired reaction was never significant in the tested reactions and the products could be easily separated by fractional distillation.

The more convenient aqueous workup could be used as well and the obtained boronic acids could be subsequently converted back to the boronic esters by azeotropic distillation with the corresponding alcohol.

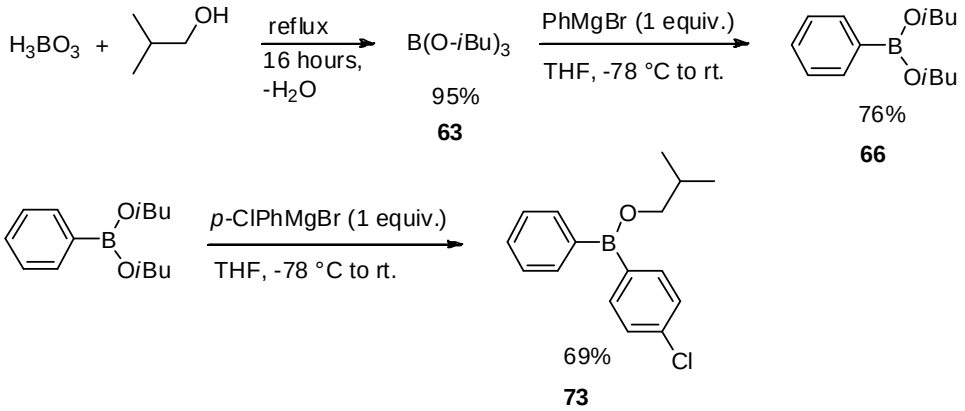
A wide range of substrates can be prepared by this boronate approach, and this was extensively studied by Mikhailov et al. Most of the transformations utilizing this method are for aromatic substrates, but there are a few examples with aliphatic substrates. The reaction sequence which was used by Mikhailov to demonstrate the versatility of the method is shown in *Scheme 22*.[59]



Scheme 22: Stepwise substitution on boron using boronates and aromatic nucleophiles.[59]

The reaction sequence starts from tri(isobutyl)boronate **63**, where in the first step the ester of phenylboronic acid **66** is formed. By treatment of the product with 1 equivalent of the phosphorus pentachloride, one of the alkoxy groups is replaced by chloride to form chloroborane **68**, which readily reacts with the next aryl-metal reagent to produce diarylborinic acid ester **69**. The next step, already described in the previous section, was used to convert diarylboronate **69** into diarylchloroborane **70**, which, upon the addition of the next Grignard reagent, forms triarylsubstituted borane **71**. By using another equivalent of the arylorganometallic reagent, tetrasubstituted boranes **72** can be formed with four different substituents.[59]

The last two steps combined into one were also used in the borabox ligand synthesis, or in the synthesis of the bis(phosphino)borates, just by using two equivalents of the nucleophile. More interesting were the initial steps where the substitution on the boron atom could be controlled in a resourceful way by starting from the readily available trialkylboronate. This boronate approach seemed to be a versatile method for the preparation of the diarylchloroboranes, because it did not use any drastic conditions, or involve the reaction of gaseous reagents, or make use of any toxic metals. Therefore we decided to test the reaction protocol and to make sure that it is reproducible under current laboratory conditions. For that purpose we chose the preparation of (*p*-chlorophenyl)phenyl(isobutyl)boronate (*Scheme 23*).



Scheme 23: Preparation of an unsymmetrical diarylboronate.

The synthesis of the non-symmetrically substituted boronate **73** starts from triisobutylboronate **63** and by consecutive addition of two different Grignard reagents produces the desired product in very good yield under rather mild reaction conditions.

An important observation in this case was that the weakly electron withdrawing chloro-susbstituent of the Grignard reagent in the *para*-position had a positive electronic effect on the second substitution. As was shown in *Scheme 20* for the preparation of the diphenylisobutyl boronate, subsequent heating after the Grignard addition was necessary to reach good conversion to the diarylboronate **64**. In this case simply warming the reaction mixture to room temperature led to **73** in good conversion and produced a very clean product. This is an illustrative example of how electronic fine tuning of the boron substituents can have an strong impact on the reactivity of the selected boron compounds with nucleophiles. The results from those experiments where the general reactivity of the boron was investigated were used for planning of further syntheses.

IF AT FIRST YOU DON'T SUCCEED, TRY, TRY AGAIN.
THEN GIVE UP;
THERE'S NO USE BEING A DAMN FOOL ABOUT IT.

-- W. C. FIELDS

4.3 Modification of existing ligands using chloroboranes

In the previous chapters the importance of bidentate ligands such as **74** or **77** in asymmetric catalysis was demonstrated. Recently new ligands bearing tetrasubstituted boron were developed. In 2003, bis(phosphino)borates **75** were invented by Peters[34] and boron-bridged bis(oxazoline) ligands **76** in 2005 by Pfaltz.[36]

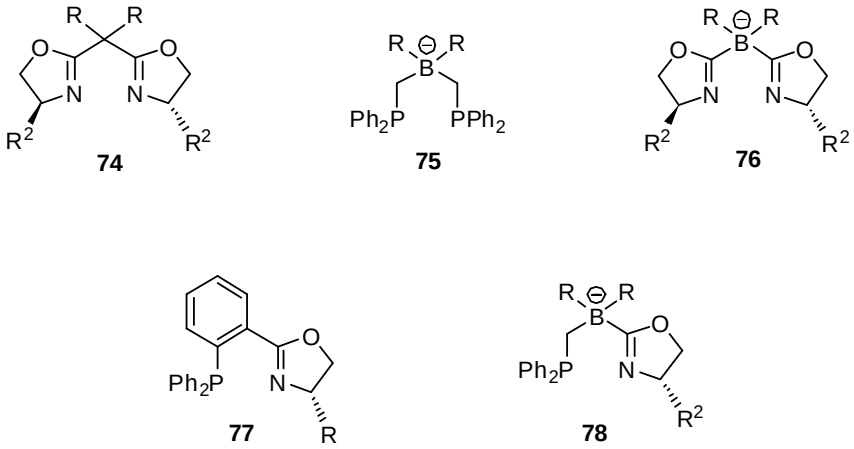


Figure 11: Structural motifs of the bidentate ligands.

A very efficient bidentate chiral ligand that was successfully applied in many metal-catalyzed asymmetric transformations is the phosphino-oxazoline **77**. From the list of known chiral ligands in *Figure 11* it is clear which modification to the current ligand scaffold could be done next. Therefore structure **78**, which would be a combination of the phosphino-oxazoline ligands **77** with a negatively charged boron, as present in ligands **75** and **76** was proposed.

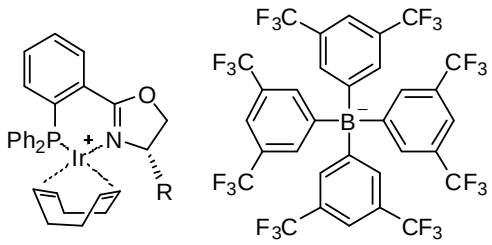


Figure 12: Cationic phosphino-oxazoline ligand with the negatively charged boron as a counterion.

The bidentate P,N-ligands in general are widely used in our group as ligands for iridium-catalyzed homogeneous hydrogenations, where they are complexed with iridium to form

cationic complexes. The counterion that has proven to be the best choice is tetrakis(3,5-bis(triflouromethyl))borate (BAr_F; *Figure 12*) which allows much higher turnover numbers than $PF_6^{(-)}$ or similar anions. An additional advantage of these borate anions is that iridium complexes bearing a chiral ligand can be easily purified by column chromatography. In view of the strong anion effect observed, it would be interesting to compare the ligands with similar backbones in one case as an ionic pair and in the second case bearing the negatively charged boron atom within the catalyst molecule to form zwitterionic metal complexes.

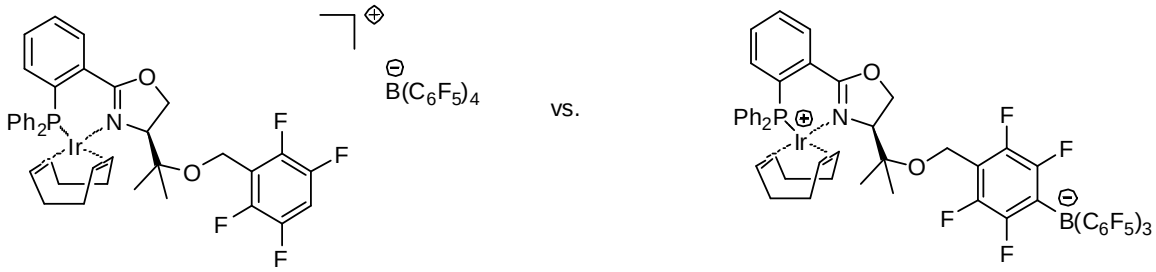
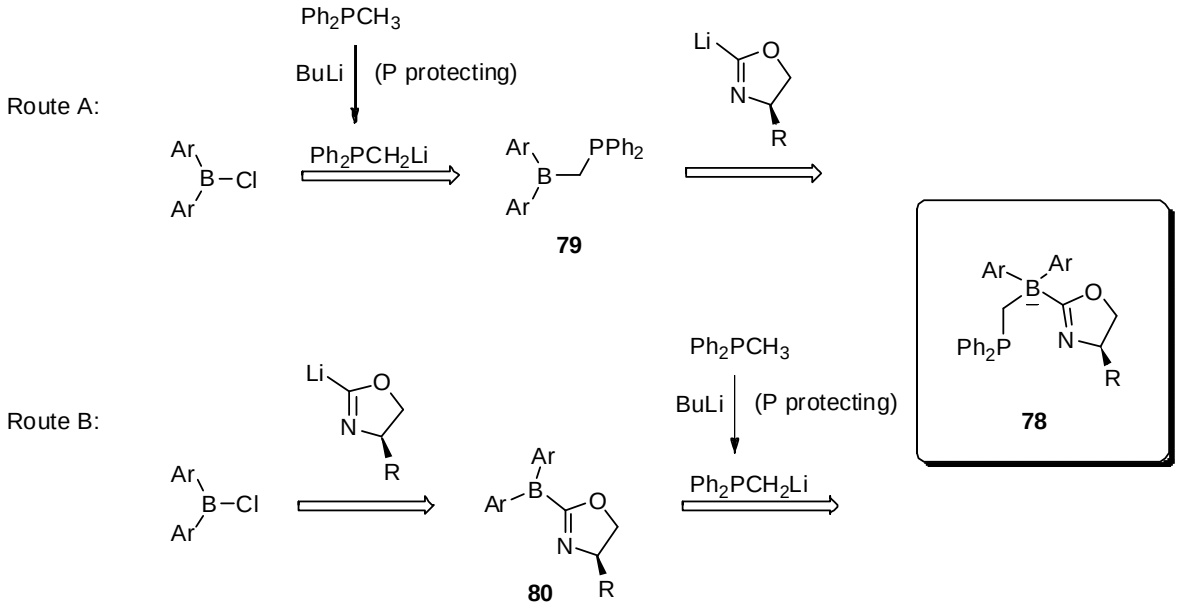


Figure 13: Comparison between zwitterionic structures of the catalyst and the cation-anion pair.

The effect of ion pairing was previously studied in our group by Axel Franzke, who prepared several zwitterionic complexes and applied them together with structurally similar compounds (*Figure 13*) in iridium-catalyzed hydrogenation reactions.[60] However no definitive conclusion could be reached from those studies.

There were already several investigations done in our group by Clement Mazet, Valentin Köhler, and Axel Franzke[61] to prepare the desired oxazoline and phosphorus-substituted tetravalent compounds with the structural motif **78**. Unfortunately, none of them was successful and so we decided to focus more in depth on this topic.

We planned the synthesis based on the knowledge from the synthesis of borabox ligands **76** and the literature examples for the synthesis of bis(phosphino)borates **75**. We chose two logical routes for the preparation of the boron-bridged phosphino-oxazoline ligands **78**, as shown in *Scheme 26*, using conditions from the preparation of ligands **75** and **76**.



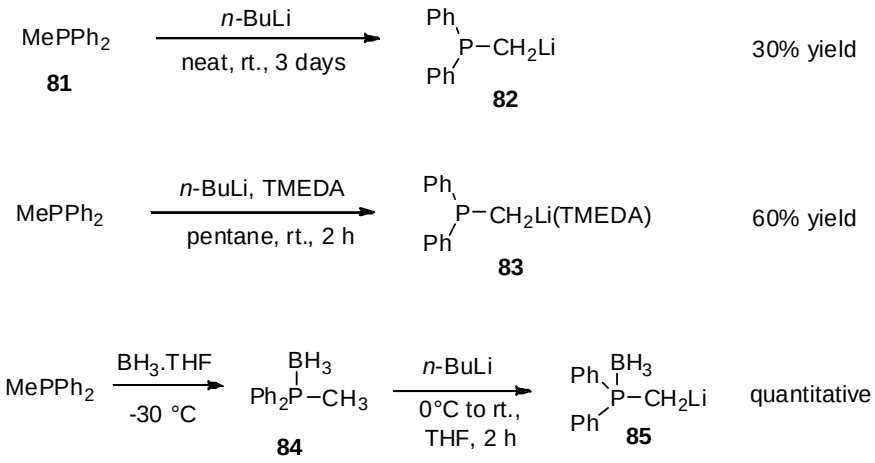
Scheme 24: Synthetic strategy for the preparation of the boron-bridged phosphino-oxazoline ligands.

The proposed synthetic route A (*Scheme 24*) starts from the diarylchloroborane and, contrary to Peter's route,[34] only one equivalent of the phosphine is added to form the desired adduct **79**. Subsequent addition of one equivalent of the oxazoline lithium salt is supposed to deliver the desired product **78**. Route B involves an analogous reaction sequence only in the opposite order with regard to the reagents added. The first step is taken from the borabox ligand synthesis,[36] but reacting just with one equivalent of lithiated oxazoline to form adduct **80** that should deliver the same product **78** as route A upon addition of the lithium phosphine salt.

4.3.1 Preparation of Li salts from the methyldiphenylphosphine

In both reaction pathways A and B (*Scheme 24*), lithiated methyldiphenylphosphine salt is considered as a synthon for the phosphorus part of the desired product **78**. Protection of the phosphine should be considered to avoid undesired interactions with the boron atom that is incorporated the ligand structure. However deprotection of the final product, which possesses a tetravalent boron atom, might be problematic. Therefore, it was planned to also investigate a sequence without protecting groups.

There are several literature examples showing how to prepare either protected or unprotected lithiated methyldiphenylphosphine **81** (*Scheme 25*).[34]

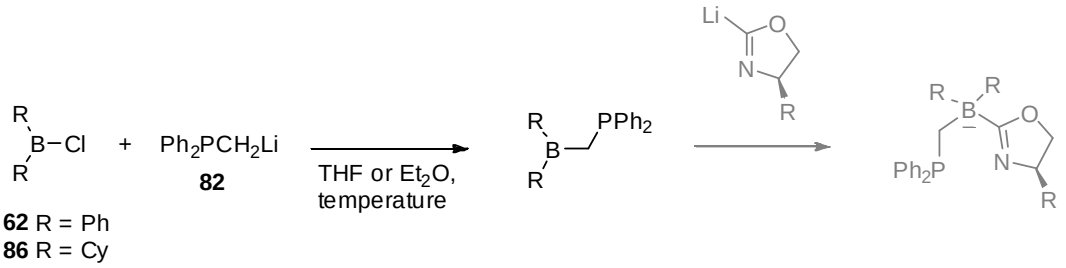


Scheme 25: Preparation of the lithium salts of methyldiphenylphosphines using different methods.

In the first example neat methyldiphenylphosphine **81** is deprotonated by the action of *n*-butyllithium to form **82** as a highly hygroscopic white powder. A reaction time of 3 days at room temperature is required to obtain at least 30 % conversion. [62] The yield can be slightly improved by using *sec* or *tert*-butyllithium. The second reaction follows the method of Peterson [63] and Schores[64] to generate Li(TMEDA) salt **83** from the unprotected phosphine **81**. Significant improvement in the yield (60 %) and the reaction time was observed in this reaction. This is mainly due to the better properties of the pregenerated *n*BuLi(TMEDA) reagent, which is more reactive than just simple *n*-butyllithium. However, we should be aware that the presence of the N-coordinating ligand can have an undesired influence on boron-containing compounds. The final Li(TMEDA) salt, **83**, can be used without purification after dissolving the reaction mixture in THF, but for better reaction control the product was isolated by filtration under inert atmosphere and weighed for the reaction as a solid. In the third reaction in *Scheme 25*, protection with BH_3·THF was used to obtain the protected phosphine **84**. The BH_3 protecting group has the desirable effect of avoiding undesired interactions between phosphorus and boron. Furthermore, the electron withdrawing properties of BH_3 are beneficial during the deprotonation step making the protons of the methyl group significantly more acidic than in unprotected phosphine **81.** Therefore only 2 hours at room temperature are required to achieve full conversion.[65]

4.3.2 ROUTE A: Addition of the Phosphinemethylenelithium salts to chloroboranes

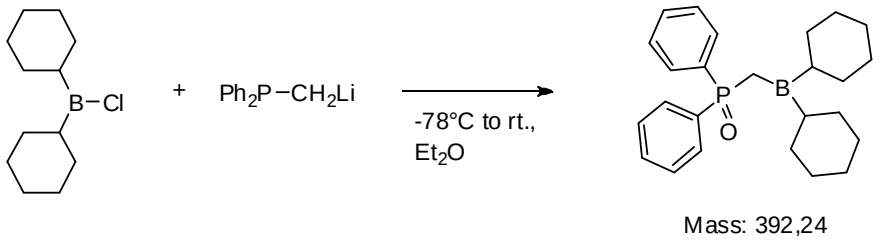
The first synthetic strategy that was tested involved reaction of the methyl diphenylphosphine lithium salt **82** and two different chloroboranes (*Scheme 26*). The reaction conditions were chosen according to Peter's procedures for the preparation of bis(phosphino)borates.[34].



Scheme 26: Reaction of the lithiated phosphine with chloroborane.

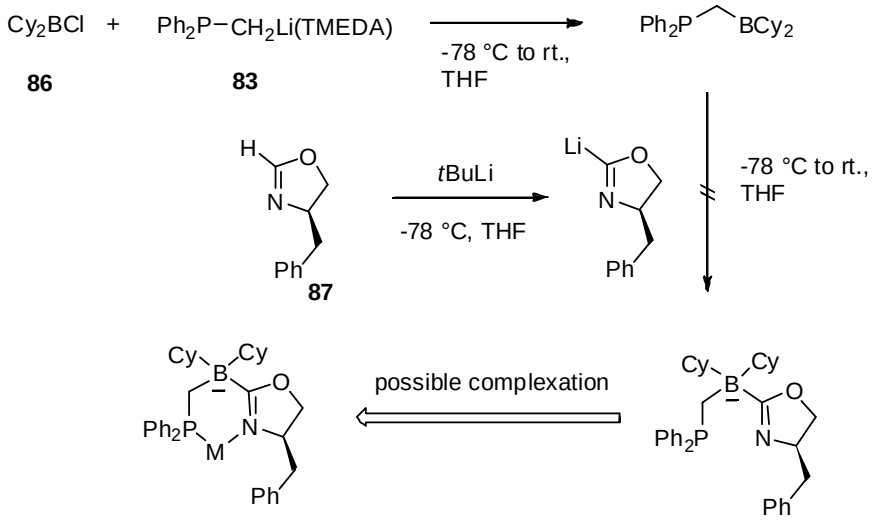
The reaction of diphenylchloroborane **62** with the phosphine **82** was performed in diethylether at -78 °C, wherein the previously prepared and isolated phosphine salt **82** was dissolved and then carefully added to the precooled chloroborane solution. This reaction sequence should avoid formation of the undesired doubly substituted boronate. Proton and phosphorus NMR analysis of the crude reaction showed it to be a complex mixture. Therefore the phosphine lithium salt source was changed to lithium(TMEDA) salt **83**. Following exactly same protocol as for the lithium phosphine salt **82**, only traces of the starting material were observed but again a very complex phosphorus spectrum was obtained. After the aqueous workup, mainly starting methyldiphenyl phosphine **81** was observed.

Another chloroborane that we decided to test was dicyclohexylchloroborane, because it is commercially available as a hexane solution and because the aliphatic chloroborane was thought to have different reactivity than the aromatic derivative **62**. Unfortunately, the reaction mixture was not much cleaner based on the phosphorus NMR spectrum of the crude reaction mixture. MALDI-TOF analysis showed the mass of an oxidized product consistent with the corresponding phosphine oxide (*Scheme 27*).



Scheme 27: Reaction of chlorodicyclohexylborane with the phosphine lihium salt.

Since we were not able to purify the (likely unstable) product, we decided to test the impure reaction mixture in the next step and if possible purify the product afterwards. This time, the reaction sequence (*Scheme 28*) involved addition of Li(TMEDA) phosphine **83** to the dicyclohexylchloroborane at -78 °C and after the crystallization workup described above, a THF solution of this impure mixture was added to the preformed lithium oxazoline salt at low temperature.

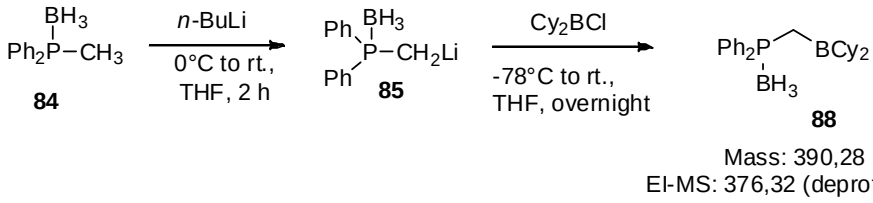


Scheme 28: Planned synthesis of the phoshinooxazoline starting from the chloroborane and including possible complexation.

This time the oxazoline lithium salt in the last reaction step was in excess and if any of the desired phosphinoborane adduct was formed it would have a chance to react with the lithiated oxazoline. Keeping in mind that the product of the reaction could be unstable, the reaction mixture was directly analyzed by spectroscopic methods without subsequent reaction workup. Since the starting material was already not clean, the NMR spectrum of that reaction mixture showed a complex mixture of compounds. Therefore the mass spectrum of the reaction mixture was recorded by MALDI-TOF and the signal corresponding to the oxidized product

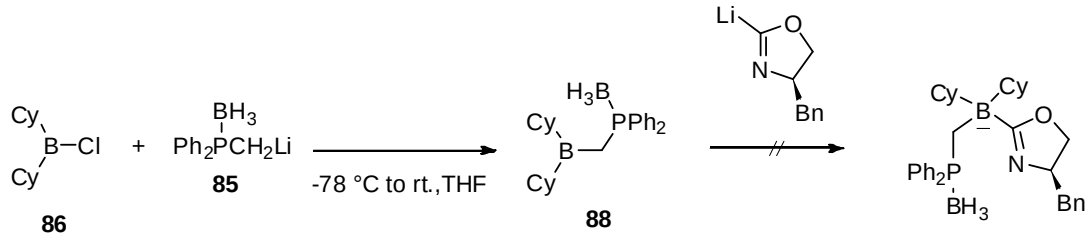
was detected. By using EI-MS, only a very weak signal from the non-oxidized product was observed. Therefore, there was a good chance that the product was formed, but since it was in a very impure reaction mixture and probably air sensitive we decided to isolate it as a metal complex which should be far more stable. For complexation, we chose copper (II) chloride, which was added to the reaction mixture together with dichloromethane. However no traces of the the desired product or a corresponding fragment was observed by mass spectroscopy.

Due to the previously unsuccessful trials using unprotected phosphine for the preparation of the desired methylene-bridged boron-phosphorus adduct, the BH_3-protected phosphine **84** was used instead (*Scheme 29*).



Scheme 29: Reaction of the chlorodicyclohexylborane with the BH_3-protected phosphine lihium salt.

The use of protected phosphine **84** has distinct advantages over the unprotected phosphines **82** and **83**. Firstly, there is no possible interaction of the boron intermediates with the nitrogen atoms of the TMEDA, as in **83**, and secondly, the preparation of the protected lithium phosphine **85** could be done in situ and quantitatively, unlike in case of **82** (*Scheme 25*). In addition the phosphineoxide formation would be prevented. The sequence started with the deprotonation of methylphosphine **84** to obtain an orange solution of **85** that was then added to a precooled solution of the chloroborane **86**, again in order to keep chloroborane in excess during the addition. The EI-MS spectrum was recorded, which showed the mass of the deprotected product **88** (*Scheme 29*). The BH_3 group from the phosphine could be lost under the ionization conditions of the EI mass spectroscopy. As in the case of the non-protected phosphine, the NMR spectrum was complex and non conclusive. Purification by sublimation led to an impure sample based on the NMR spectrum.
Chromatographic workup delivered only the starting material as phosphine **84**. Unfortunately, attempts to purify the product by crystallization also failed because of the high solubility of the product even in pure hydrocarbon solvents. Even repeatedly precipitating the byproducts from benzene/pentane solution did not lead to the pure compound **88**, therefore it was used without purification in the next reaction with Li-oxazoline (*Scheme 30*).



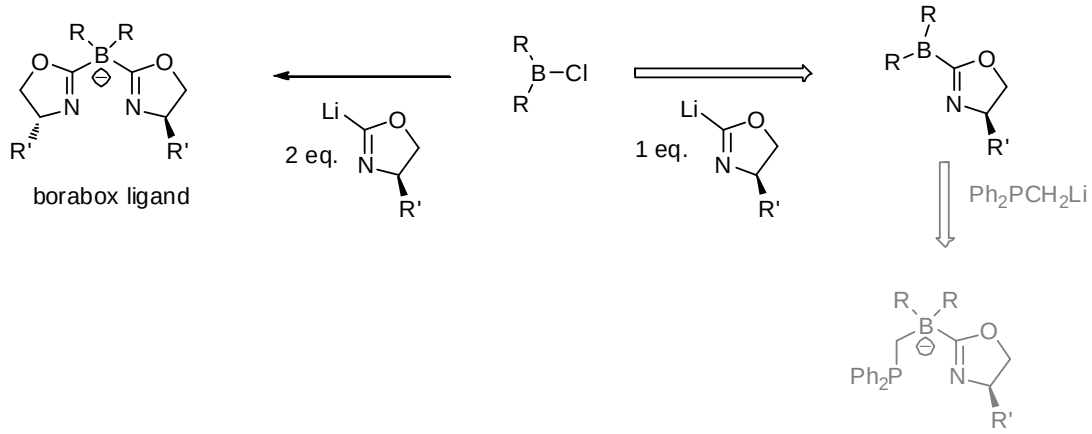
Scheme 30: Reaction of BH_3-protected methyldiphenylphosphine with dicyclohexylchloroborane.

Based on NMR analysis, before any workup, the reaction mixture contained many byproducts. MALDI-MS showed the desired masses of the product and also a fragment lacking BH_3, but both signals were very weak compared to the other signals that could not be assigned to any fragment or byproduct. This time the purification of the product by complexation, as shown in *Scheme 28*, was not performed because of the very complex reaction mixture, which would still require a deprotection step to prepare the metal complex.

After this unsuccessful attempt at preparation of clean **88** for the next reaction, a transmetallation step involving either zinc or palladium was carried out after the formation of **85** (*Scheme 30*) in order to tune the nucleophilicity of the phosphine **85**. When either zinc chloride or $Pd(PPh_3)_4$ was used, no product **88** was observed and only starting phosphine **84** was recovered.

4.3.3 ROUTE B: Addition of the lithium-oxazolines to chloroboranes

The alternative approach depicted in *Scheme 24* was based on the related reaction used for preparation of the borabox ligands, where the corresponding chloroborane (1 equiv.) was added to the lithiated oxazoline (2 equiv.) at low temperature.[36] In the borabox synthesis, the addition of the chloroborane to a solution of the lithiated oxazoline was also used, which was always in excess in order to preferentially form the doubly substituted product.

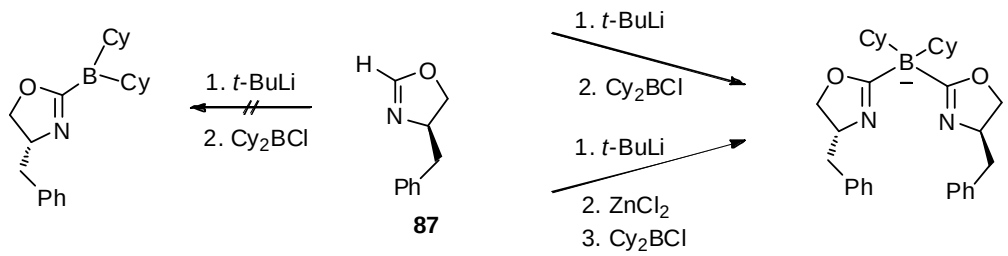


Scheme 31: Synthetic strategy for preparation of monosubstituted boranes.

The initial idea was to use lithium-oxazoline and chloroborane in equimolar ratios under the same conditions as described for the borabox ligand preparation, only the ratios of reagents was different (*Scheme 31*). After the chromatographic workup of the complex reaction mixture was only borabox ligand isolated in about 40% yield. This result implied that the addition of the oxazoline salt to the chloroborane is very fast and proceeds even at low temperatures, where it results in the doubly substituted product and leaves half of the chloroborane unreacted.

Therefore the addition was carried out in reverse order, thus always having the chloroborane in excess to avoid double substitution. One equivalent of the lithium oxazoline was added via precooled cannula to a precooled solution of the chloroborane in THF. Nevertheless, only borabox ligand was isolated from the reaction mixture after the workup, in about 20 % yield.

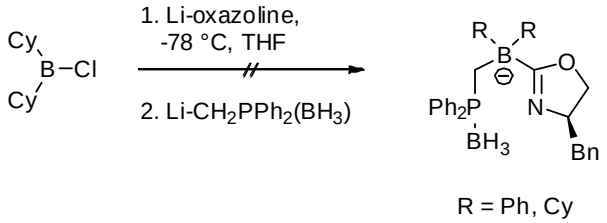
Transmetallation with $ZnCl_2$ was also tried in order to lower reactivity of the deprotonated oxazoline. Unfortunately, the same results, the exclusive formation of the borabox ligand, were obtained (*Scheme 32*).



Scheme 32: Addition of the lithium oxazoline to the chloroborane.

We thought that if the reaction proceeds so much in favor of the borabox ligand even at low temperatures, that this could be due to the relatively fast addition of the lithium oxazoline through the precooled cannula. We did not find any information in the literature about the stability of the lithium oxazoline salts, because the previous protocols used the lithium oxazoline only at low temperatures. Hence, we decided to test whether the THF solution of the deprotonated oxazoline survives handling at room temperature, to allow for slow addition to the chloroborane. For this purpose we deprotonated the oxazoline under standard condition and then warmed the solution to room temperature. After quenching with CD_3OD the deuterium incorporation was almost quantitative. This showed that the lithium oxazoline salt can be handled at room temperature. Unfortunately, however even slow dropwise addition of the lithium oxazoline at room temperature led to the borabox ligand, as in all the previous experiments.

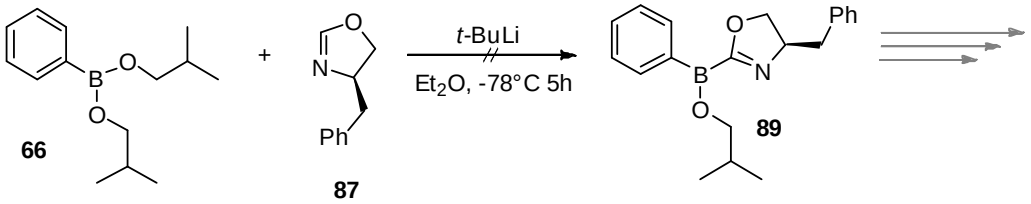
Since it was not clear whether the desired monosubstituted product was being formed during the previous reactions and is perhaps just unstable, the phosphine **85** was directly added to the reaction solution after addition of Li-oxazoline. Unfortunately this reaction did not lead us to the desired product (*Scheme 33*).



Scheme 33: Addition of lithium-oxazoline and lithium phosphine to the chloroborane.

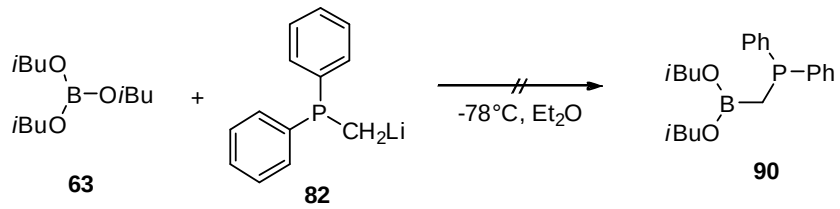
4.4 Boronates approach

Isobutyl esters of boric acid, such as **63** and **66**, which were used for preparation of the non-symmetrically substitutes borates (*Scheme 23*), were also shown to be good building blocks for the preparation of diarylchloroborates (*Scheme 20*). Based on the previous work of Mikhailov et al., where boronates were used in reactions with either aryllitium or arylmagnesiumhalides to obtain substituted borates and boronates (*Scheme 22*) the following synthesis was proposed (*Scheme 34*).



Scheme 34: Reaction of the phenylboronate with the lihium-oxazoline.

In analogy with the synthesis of the borabox ligands, phenylboronate **66** was used instead of disubstituted chloroborane, and was added to lithium-oxazoline **87** at low temperature to obtain 2-substituted oxazoline **89**. The monosubstituted boronate was chosen because of the higher reactivity of the electrophilic boron atom compared to the double substituted one. The addition of the reagents was done in both orders, but based on the NMR analysis of the crude reaction mixture none led to the desired compound **89**. As the reaction sequence using oxazoline **87** in the first step failed, addition of the lithiated phosphine **82** was also tested as shown in *Scheme 35*.

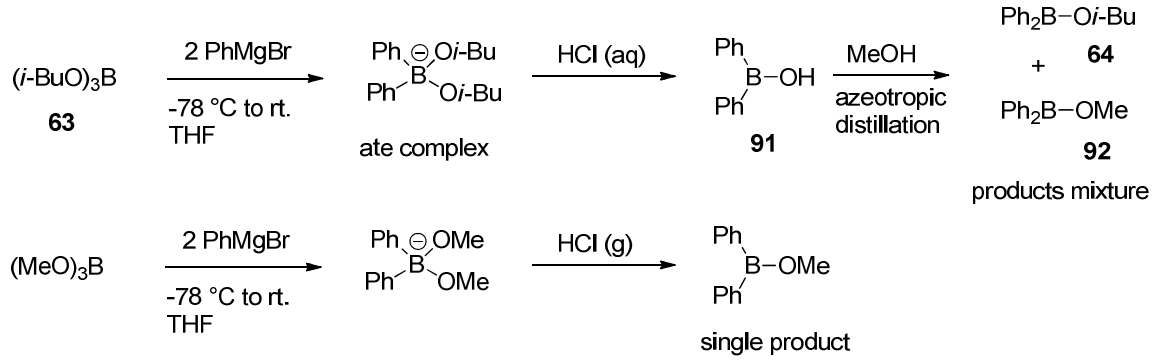


Scheme 35: Reaction of triisobutylboronate with diphenylmethylphosphine lithum salt.

For the oxazoline route (*Scheme 34*) the workup was limited to a neutral workup because the oxazoline itself is acid labile and undergoes ring opening. However, in the reaction with the

phosphine **82** an acidic workup should be possible. Therefore, several acidic workup procedures were examined but none of them resulted in product **90**.

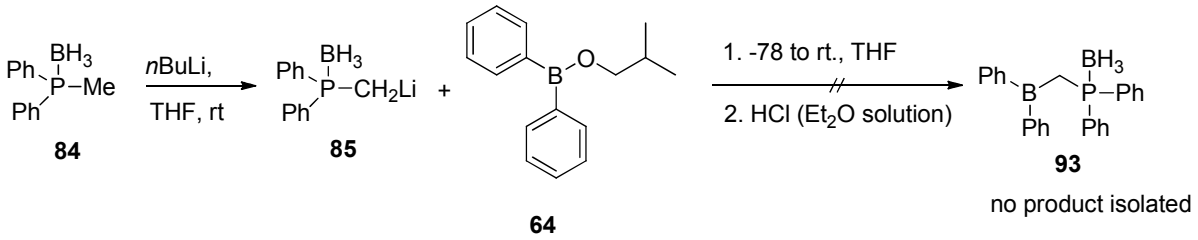
To change the reactivity of the system, the synthesis of boron-phosphorus adduct **88** was reconsidered using the boronates approach. The use of this route was selected even though doubly substituted boronates, such as diphenylisobutyl boronate **64**, are less reactive than their monosubstituted analogs. As described in *Scheme 20*, the ester of borinic acid **64** could be prepared by the addition of two equivalents of PhMgBr to triisobutlyboronate **63**, followed either by quenching with aqueous HCl to obtain diphenylborinic acid, or by quenching with gaseous HCl to deliver the borinic acid ester without breaking the ester bond (*Scheme 36*). The shorter alkyl chain esters are generally less stable and more reactive.



Scheme 36: Preparation of the diphenylborinates from boric acid esters.

Two different borinates, **64** and **92**, were prepared as previously described in *Scheme 20*. In the first reaction sequence, after quenching of the ate complex by aqueous HCl and the usual extraction workup, diphenylborinic acid **91** was esterified with methyl alcohol. A mixture of esters **64** and **92** was obtained, which is difficult to separate by fractional distillation. A possible reason why a mixture of these products was obtained is that borinate **64** is a quite stable ester and even treatment by aqueous HCl does not lead exclusively to borinic acid **91** (which is unstable and is usually not isolated). Another explanation could be that after workup *i*BuOH is still present in the mixture and then competes in the next step with methanol as a second alcohol in the esterification reaction, therefore leading to the product mixture. For preparation of borinate **92** an alternative synthesis starting from trimethylborate followed by workup with anhydrous ethereal hydrochloride acid solution was then used.

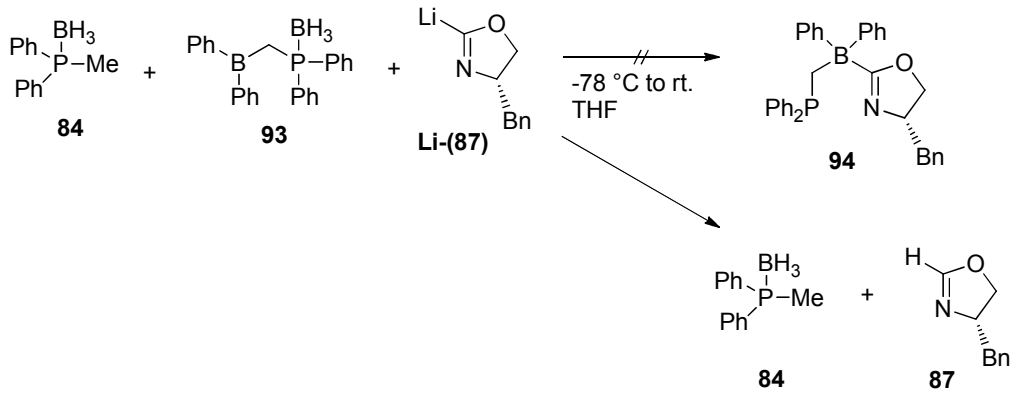
Esters **92** and **64** were both used in the reaction with phosphine lithium salt **85** in analogy to the reaction with trialkylboronate **63** shown in *Scheme 35*. For the following reaction (*Scheme 37*) the less nucleophilic protected phosphine **84** was used and also the reactivity of the borinate **64** is lower then reactivity of the monosubstituted boronate **63**.



Scheme 37: Reaction of the borane-protected phosphine with diphenylboronate.

The reaction (*Scheme 37*) provided quite a clean reaction mixture based on ^{1}H NMR analysis, which contained starting phosphine **84** and additional species which could be a desired product. An approximate ratio of a 2:3 for these two species was obtained reproducibly every time the reaction was done under the same reaction conditions. In the phosphorus decoupled ^{1}H NMR spectrum, the new doublet at 2,4 ppm was transformed into a singlet. This suggested that the proton signal must come from the phosphorus-containing compound and be placed close to the phosphine due to the coupling constant, which was 16 Hz. In the ^{11}B NMR spectrum of the crude, unquenched, reaction mixture one broad signal with a shift of 0 ppm was found, which is the typical region for tetravalent boron compounds. After quenching of the reaction mixture by ethereal HCl, this signal shifted to 46 ppm. That change indicates the transformation of the tetravalent boron species into a trivalent one. In the phosphorus NMR spectrum of the crude reaction mixture two species in a 1:1 ratio were observed. After quenching the reaction with HCl, the phosphorus NMR signal ratio remained basically the same, but these signals became more separated. One of the signals corresponds to **84** and the second broader signal with a chemical shift 3 ppm higher and a more complex splitting pattern was assigned to the expected product **93**. This observation strongly supported the presence of a second boron atom in the expected product **93**, which also shows coupling with the phosphorus nucleus. However, when separation by column chromatography was attempted, only starting phosphine **84** was isolated. This observation could be explained by the instability of the product on the column, which is unlikely due to the fact that it had already survived the HCl workup. From the quenched reaction mixture a ^{1}H NMR spectrum was recorded and, after quick filtration over a plug of silica gel, was recorded again. The

integral of the potential product doublet with a chemical shift of 2.4 ppm in the ^{1}H NMR spectrum was smaller compared to the starting phosphine **84**, but it was still present. This proved that the column chromatography has some negative impact on the tracked compound, even though the product does not immediately decompose after contact with the silica gel. Another method to prove the presence of product **93** was mass spectroscopy but GC-MS analysis showed only the signal of phosphine **84**.



Scheme 38: Previous reaction mixture with lithium oxazoline.

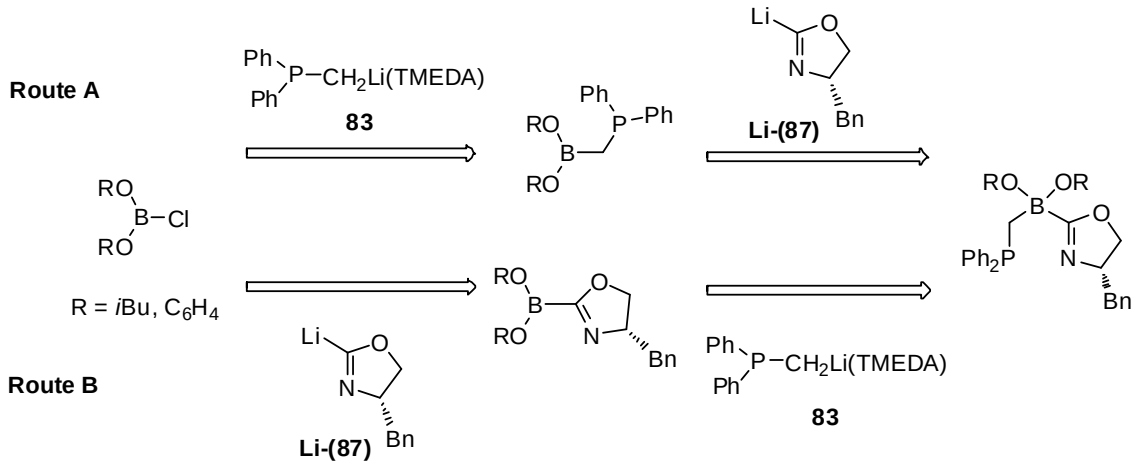
Although attempts at characterization of product **93** were unsuccessful, we decided to test the subsequent reaction step (*Scheme 38*) with the previously described reaction mixture from *Scheme 37*. The reactant ratios were based on the expected composition of the products from the previous reaction and were in a 1:1 ratio with the oxazoline nucleophile. Therefore the mixture of two phosphine species, including starting phosphine **84** and expected product **93**, were added to the pregenerated lithium oxazoline salt at -78 °C and after warming up the reaction to room temperature, an NMR spectrum of the crude mixture was recorded. The spectrum showed a 1:1 mixture of **84** and the H-oxazoline **87**.

This result was surprising because a more complex reaction mixture would be expected from the mixture of these three reaction components.

The results obtained during the examination of the boronate approach developed by Mikhailov suggested that this method cannot be applied to a wider spectrum of substrates. However, although this approach cannot be applied for desired *P,N*-ligands, it was at least successfully applied in the synthesis of chloroboranes, which are valuable boron building blocks.

4.5 Chloroboronate approach

An alternative synthetic strategy using chloroboronates as boron building blocks was proposed. This strategy is still related to the Mikhailov method using boronates, because he also transformed certain boronates into chloroboronates (by action of PCl_5) in order to reach higher reactivity of the boron building blocks as it was shown earlier in *Scheme 22*.

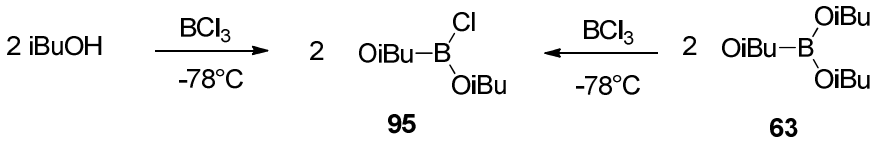


Reactivity of the boron compounds:

B-F > B-Cl > B-O > B-C

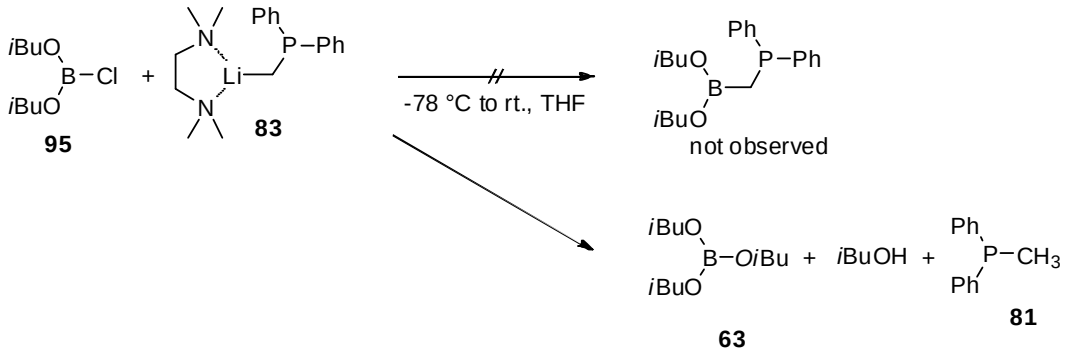
Scheme 39: Synthetic strategy using chloroboranes as boron building blocks.

The use of the chloroboronates would change the electronic properties of the boron intermediates in the planned synthesis (*Scheme 39*) compared to the previous approaches.
The reactions are analogous to the previous reactions examined using the chloroboranes as synthons, but in contrast to those they have two oxygen atoms directly bound to the boron instead of carbon substituents and this is reflected in their reactivity (*Scheme 39*).
For preparation of the chloroboronates, more convenient methods than those of Mikhailov could be chosen for our purpose, such as the reaction of trichloroborane with the corresponding alcohol. This method could be applied for the preparation of somewhat simpler chloroboronates, although it is more limited in scope than the Mikhailov method. Or an alternative chloroboronate synthesis could be used that starts from boric acid ester **63**, which is transformed into the chloroboronate **95** upon treating with trichloroborane in the proper stochiometric ratio (*Scheme 40*).



Scheme 40: Two different pathways for the preparation of chloroboronates.

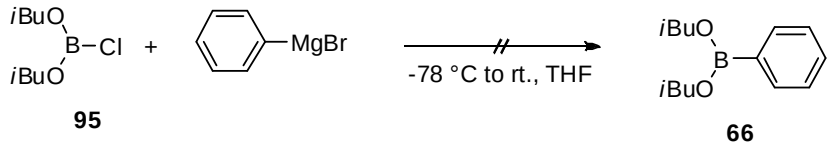
Both synthetic approaches were examined and the second method using boronate **63** seemed to give a cleaner reaction mixture. In the synthesis of **95** starting from isobutyl alcohol two molecules of hydrochloric acid are released during the reaction and have to be removed, which makes the preparation less convenient.



Scheme 41: Reaction of the diisobutylchloroboronate with the Li(TMEDA) salt of the methyl-diphenylphosphine.

The chloroboronate **95** was then used in the reaction with the phosphine synthon as was depicted in *Scheme 39* using **Route A**. For this reaction lithium(TMEDA) salt **83** was used and was added as a THF solution to a solution of chloroborane **95** at -78 °C. Unfortunately, no expected product was observed and three compounds were identified from the unusually clean crude reaction mixture. The first compound was the starting phosphine **81** and was the only phosphorus-containing compound, the other two compounds were isobutanol and triisobutyl boronate **63** (*Scheme 41*). The proton NMR spectrum intensities correspond to the equimolar amount of the starting chloroboronate **95** and the phosphine **83**. The formation of these species cannot be explained by any simple mechanism, but one possible explanation could be that during the reaction a boronate complex is formed and further undergoes some redistribution reactions between the reaction intermediates, thus transferring some isobutanolate groups to the other boron atom. That would explain the formation of compound **63** and the presence of the isobutyl alcohol in the reaction mixture as a quenched migrating group.

To test this hypothesis a control experiment was performed. The reaction of phenylmagnesium bromide was chosen because the expected product had already been prepared via a different reaction sequence (*Scheme 23*).

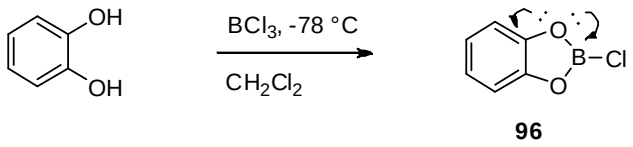


Scheme 42: Reaction of the chloroboronate with the Grignard reagent as a control experiment.

The reaction of chloroboronate **95** with phenylmagnesium bromide also did not lead to the desired product **66** and, as in the previous reaction, isobutyl alcohol was also detected in the reaction mixture (*Scheme 42*). This observation, which was analogous to the previous observation from the reaction of the phosphine **83**, inidicated that the undesired behavior is not due to the presence of the heteroatoms interacting with boron, but rather the result of a redistribution reaction, including the transfer of alcoholates between different boron species.

4.5.1 Aromatic chloroboronate approach

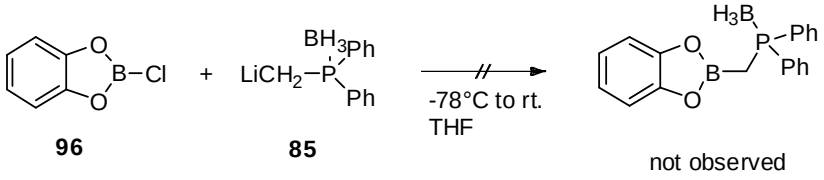
Based on the previous observations further investigations to change the chloroboronante species seemed more promising than examining **Route B** (*Scheme 39*) with the same chloroboronate **95**. As migration of the ester function of the phosphine was a problem in previous reactions, chloroboronates with an ester function derived from diols were chosen. Two diols were considered as potential candidates, pinacol and catechol. The preparation of the pinacolchloroborane was described by Bettinger in 2008.[66] The synthesis employs the same synthetic strategy as was described in *Scheme 40*, but the reaction is accompanied by formation of the undesired dimeric pinacolboronate, which lowers the yield of the desired pinacolchloroborane to 30%. The synthesis of the chlorocatecholboronate **96** from catechol was described by Gerrard et al. in 1959, as depicted in *Scheme 43*.[67]



96

Scheme 43: Preparation of catecholchloroborane from catechol and BCl_3.

As opposed to diisobutylchloroboronate **95**, which is a low boiling liquid, the catechol derivative **96** is a solid and could be isolated by sublimation in pure form. Also, the electronic properties of the aromatic and aliphatic chloroboranes differ as shown in *Scheme 43*. The difference is in the ability of the aromatic ring to accept the electron density of the oxygen lone pairs and thus weaken the electron donating effect towards the boron. Therefore the boron atom in the related chloroboranes is more Lewis acidic in case of the aromatic esters then in the aliphatic ones. BH_3-protected methylphosphine **85** was chosen as the nucleophile in the reaction of **96** (*Scheme 44*).



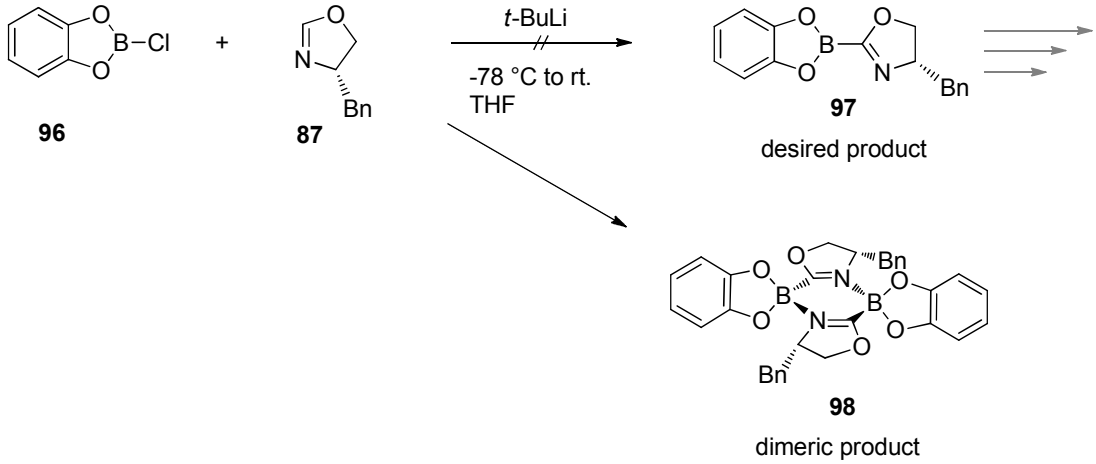
96 **85** not observed

Scheme 44: Reaction of catecholchloroborane with the Li salt of methyl diphenylphosphine.

The reaction was carried out by adding **96** to **85** or in reverse order so that either phosphine **85** or the chloroboronate **96** were in excess, but both protocols basically resulted in the same product mixture. When the ^{11}B NMR spectrum of the crude reaction mixture was recorded there were at least four different species with chemical shifts ranging from 33 to 7 ppm. These numbers represent both trivalent and tetravalent compounds, which were present in similar amounts.

After unsuccessful attempts using **Route A**, we decided to investigate **Route B** by employing the chemistry of chlorocatecholboronate **96**. The reaction of chloroboronate **96** with oxazoline **Li-(87)** under standard reaction conditions was performed to obtain the desired addition product **97**. The reaction proceeded very cleanly and only one major product was observed. In the proton NMR spectrum all signals matched expected changes in the chemical shifts and all integrals fitted with structure **97**. After purification of the reaction mixture by column

chromatography a ^{11}B NMR spectrum was recorded wherein there was only one major boron signal, as expected, but surprisingly the chemical shift of that signal was 5 ppm, which is in the typical region for tetravalent boron compounds. The integral in the aromatic region of the proton NMR spectrum was higher than anticipated for **97**. This could possibly come from the phenyl groups of the oxazoline, indicating that the product of double addition of **Li-(87)** might have formed, since chloroboronate **96** was added to the pre-generated lithium oxazoline **Li-(87)** and so the latter species was in excess during the course of the addition. The data obtained from the MALDI-MS showed a signal corresponding to the double value of the molecular mass of product **97** (*Scheme 45*).



Scheme 45: Reaction of the catecholchloroborane with the 2-lithium oxazoline leading to the undesired dimeric product.

Based on all analytical data obtained, structure **98** was proposed. Since the product was a crystalline compound it was attempted to grow crystals in order to confirm the structure by X-ray analysis. Even though it was not possible to remove contaminating catechol from the sample, crystals suitable for X-ray analysis could be prepared. Selected bond lengths from the crystallographic measurement are shown in *Table 7*.

Table 7: Selected bond lengths from the X-ray structure of **98-catechol** (*Figure 14*)

Bond	B-N[a]	B-N[b]	B-C(oxaz)[a]	B-C(oxaz)[b]	cat**O**H-O**B**[a]	cat**O**H-O**B**[b]
Length [Â]	1,545	1,547	1,626	1,635	3,260	4,002

Bond	cat**O**H-**O**B[a]	cat**O**H-**O**B[b]	catO**H**-**O**B[a]	catO**H**-**O**B[b]
Length [Â]	2,717	2,796	2,005	1,943

[a] closer monomeric fragment, [b] remote monomeric fragment

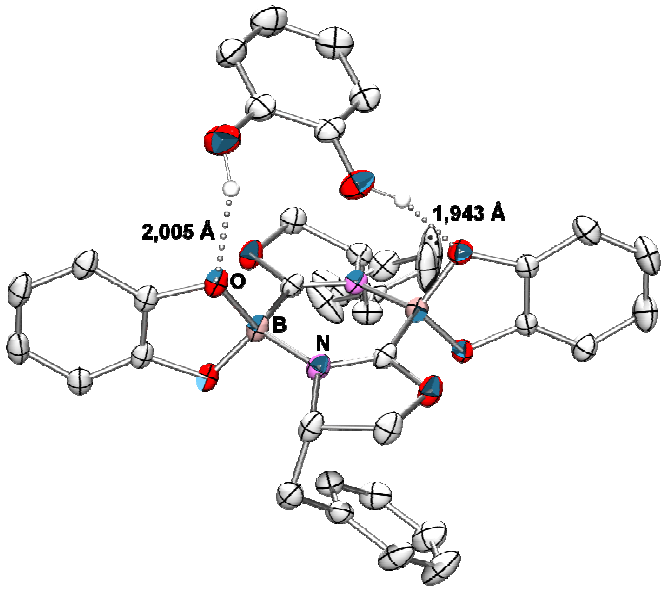


Figure 14: Crystal structure of the dimeric oxazoline-catecholboronates cocrystallized with catechol as an impurity **98-catechol** (hydrogen atoms are omitted for clarity).

The resulting crystallographic structure was in agreement with the proposed product structure **98**, but was cocrystallized with one molecule of catechol (**98-catechol**) within the crystal cell (*Figure 14)*. There are clear hydrogen bonding contacts between catecholboronate oxygen atoms and the hydroxy protons of the cocrystallized catechol. The other interesting observation was that the boron-nitrogen interaction has the character of a covalent bond with a length of 1.5 Å, which is even shorter than the boron-carbon bond of the oxazoline part (*Table 7*).

After the crystal structure of **98-catechol** was refined there were also separation conditions found for removing the catechol molecule from the **98-catechol** which had persisted even after column chromatography or crystallization. Column chromatography which uses either

neutral alumina as the stationary phase or dichloromethane as an eluent even for chromatography on silica gel can be used for isolation of pure **98**.

Using crystallization conditions that were used for the preparation of **98-catechol** crystals for X-ray analysis provided in case of pure **98** just thin fiber crystals which were not suitable for crystallographic measurement. However, when a temperature driven crystallization was performed instead of the solvent diffusion method, a different crystalline form was obtained and these crystals were suitable for the crystal structure elucidation. The resulting X-ray structure is depicted in *Figure 15* and several selected crystallographic bond lengths of compound **98** are listed in the *Table 8*.

Table 8: Selected bond lengths from the X-ray structure of **98** (*Figure 15*)

Bond	B-N[a]	B-N[b]	B-C(oxaz)[a]	B-C(oxaz)[b]	catO-B[a]	catO-B[b]
Length [Å]	1,548	1,546	1,627	1,638	1,487(1,472)	1,480(1,469)

[a] closer monomeric fragment, [b] remote monomeric fragment

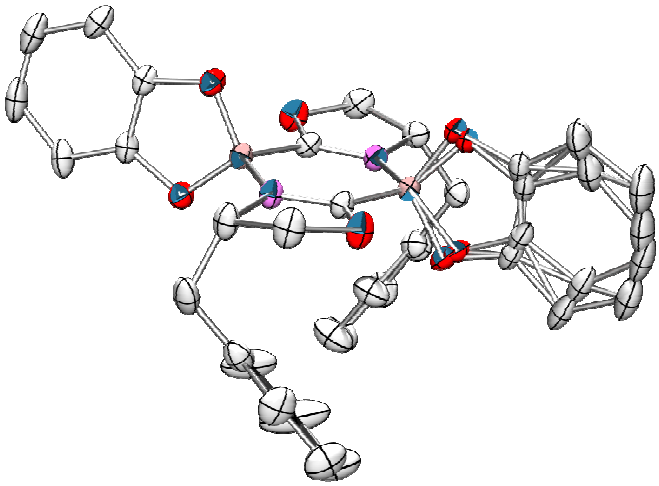
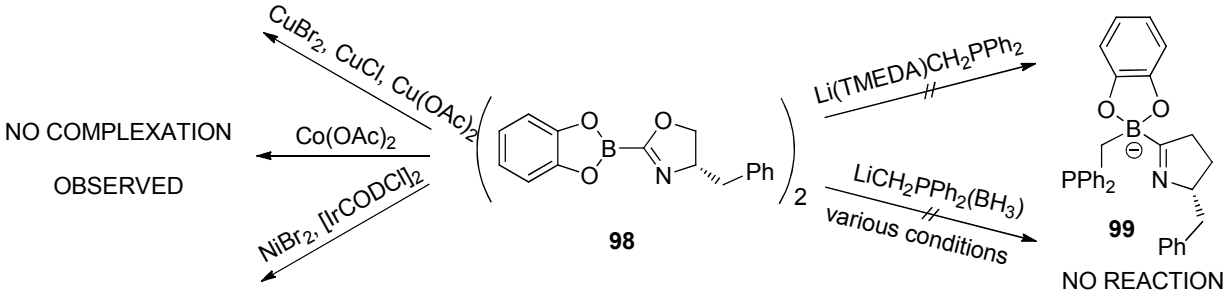


Figure 15: Crystal structure of the dimeric oxazoline-catecholboronates without cocrystallized catechol **98** (hydrogen atoms are omitted for clarity).

Comparison of the lengths of the boron-nitrogen bonds in *Table 7* and *Table 8* showed that the distances between those nuclei in both compounds (**98** and **98-catechol**) are identical. The additional coordination of the catechol molecule does not have any influence on the structure of the compound **98**. The only significant change in the crystal structure is that one of the catecholboronate units has a disordered phenyl ring. To supress this dynamic behavior, the

crystallographic data were recorded at 100 K instead of 123 K but the lower temperature did not show a positive effect on the disorder of the phenyl group.

Even though the product of the lithium oxazoline **Li-(87)** addition to chlorocatecholboronate **96** produced undesired dimeric product **98** instead of **97**, the reactivity of the dimer was examined in order to incorporate the phosphine function and to obtain target molecule **99** (*Scheme 46*).



Scheme 46: Reactivity of the dimer **98** with nucleophiles or with various metal salts.

In this reaction two lithium phosphines, Li(TMEDA) salt **83** and BH_3-protected lithium phosphine **85**, were tested (*Scheme 46*). The addition of **83** to dimer **98** as well as the addition of **98** to **83** left the phosphine unchanged based on the ^{31}P NMR spectrum, but at the same time led to oxazoline ring decomposition. When the addition of the reagent was performed in the reverse order there was no conversion observed, even at low temperature or after 16 hours at room temperature. Even when salt **85** was added to a boiling solution of the dimer **98** in THF and refluxed overnight, no reaction was observed.

That no reactivity at the boron center was observed in those reactions was in agreement with the strong covalent B-N bond observed in the crystal structure. Another option to recover the trivalent boron species would be acidic cleavage of the B-N bond. Unfortunately, this approach could not be applied to substrate **98**, because it contains acid-labile oxazoline moieties, which would open up under those acidic conditions.

Therefore the use of a Lewis acids was considered instead and Cu(I), Cu(II), Co(II), Ni(II) and Ir(I) salts were tested (*Scheme 46*). Solutions of the selected salts were prepared in various solvents, dimer **98** was added, and after 5 hours the MALDI-MS was recorded to prove the eventual existence of metal complexes. However, although all the metal salts changed color, the desired mass (*m*/*z*) was not observed. Attempts to identify the metal

complexes by X-ray analysis also failed. Unfortunately none of the crystals obtained were of the desired metal complex.

The two crystal structures as well as the complexation studies with several metal salts and the experiments with the phosphine nucleophiles clearly demonstrate the low reactivity of dimer **98**. For better understanding of the reactivity of **98** the charge distribution was modeled by quantum chemistry simulations. The method used for this investigation was mapping the electron density on the structure obtained from X-ray analysis, which should offer a good image of the charge distribution within the molecule.The electrostatic charge distribution was calculated using the ChelpG method[68] and it is represented as molecular electrostatic potential (MEP) density surface (*Figure 16*).

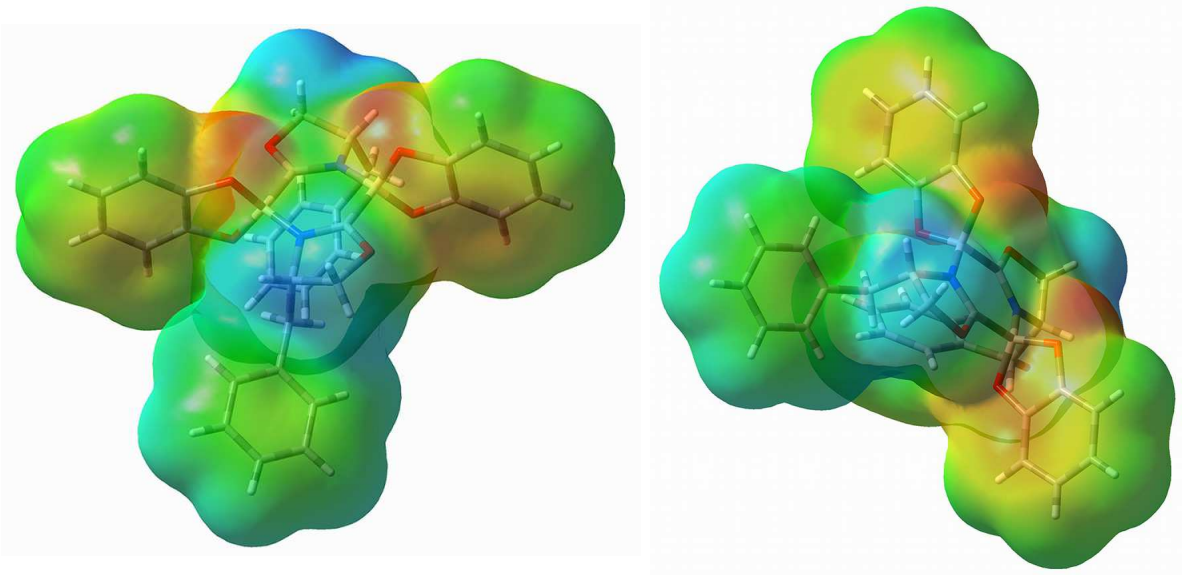


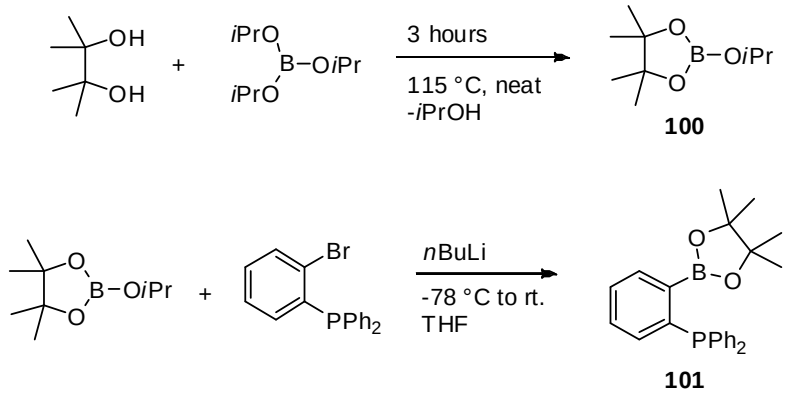
Figure 16: Molecular electrostatic potential (MEP) for the X-ray structure of **98** (two different views) calculated in Gaussian 09, B3LYP/6-311g(d,p) by the ChelpG method.

The shell surrounding the molecule represents the electron density space and the color range describes the distribution of the electron density along the density surface. The red surface color stands for the highest electron density and the blue regions are the ones with the lowest electron density within the molecule. This is a useful tool for predicting the reactivity of organic molecules by locating their nucleophilic and electrophilic centers. In the case of dimer **98** this analysis should tell whether the boron atom still should have a tendency to react with nucleophiles, or if the Lewis acidity of the boron center was entirely suppressed by the interaction with the oxazoline N atom. The answer is displayed in *Figure 16* (left structure), where it is clearly visible that the more electropositive part in this case is the oxazoline ring

rather than the boron atom. The other attribute which is nicely represented in both views is that the places with the highest electron density are on the oxygen atoms of the catecholboronate, namely on the side where the benzyl groups of the oxazoline are not present. This is in agreement with the observation of the structure of **98-catechol** where the hydrogen bonding is pointing towards those atoms. A further important observation is that the electron density of the catecholboronate phenyl ring is clearly delocalized from the neighboring oxygen atoms along the entire aromatic ring (*Figure 16*, right structure) as was previously described in *Scheme 45*. This observation explains why the aromatic boronates are more Lewis acidic than their aliphatic analogs.

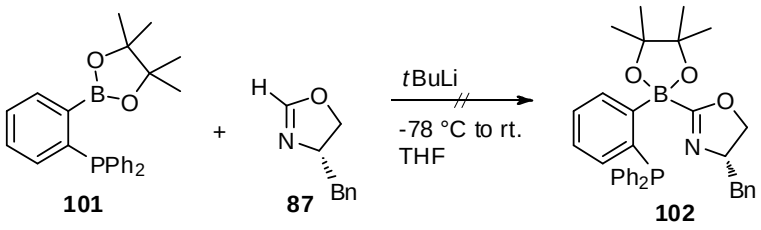
4.5.2 Phosphine aliphatic boronate approach

In a further investigation of the boronate approach aliphatic boronate **101** derived from pinacol were used. The synthesis of the boronate analog **101** was described by Bourissou in 2010 (*Scheme 47*).[69] Compound **101** is basically an analog of the previously used boronate building blocks, but its advantage is that it already has the phosphine function incorporated.



Scheme 47: Synthesis of the phosphinopinacol boronate adduct for further investigations.

The pinacolboronate precursor **100** could be prepared from pinacol and triisopropyl boronate by a condensation reaction.[70] In the next step, the monobrominated triphenyl phosphine was first transformed into the lithium salt, which then acted as a nucleophile in the addition to the Lewis acidic boronate **100**. After workup product **101** was obtained (*Scheme 47*).[69]
The pinacolboronate **101** was used in the next reaction with lithium oxazoline **Li-(87)** where it was added at low temperature (*Scheme 48*).



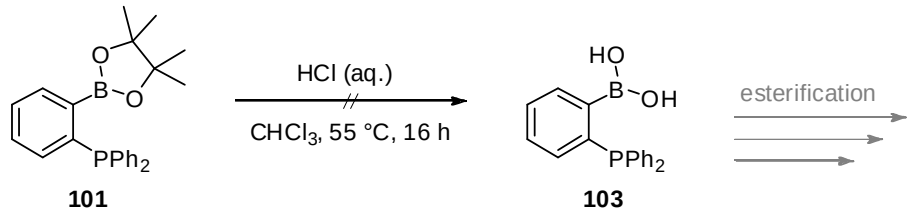
Scheme 48: Reaction of the lithium oxazoline with the aromatic pinacolboronate.

The crude reaction mixture was analyzed by ^{1}H ^{31}P and ^{11}B NMR spectroscopy. Mostly signals of the starting material, unreacted H-oxazoline **87**, and also partially decomposed phosphine **101** were visible. Part of the reaction mixture was also used for direct complexation with $[Ir(cod)Cl]_2$ in order to avoid possible decomposition of product **102**, as there is no literature data on the stability of such compounds. The metal complex with iridium should be more stable than just the ligand itself. However no changes were observed in the NMR spectra in particular, the oxazoline proton shifts were unchanged, implying that there was no desired complexation product present.

The reactivity of the boron compounds is driven mainly by two factors, electronegativity of the substituents and the steric environment of the boron atom. This might be the reason for the lack of reactivity of compound **101** with the nucleophile **Li-(87)** (*Scheme 48*), because the pinacol ester is a very sterically demanding group.

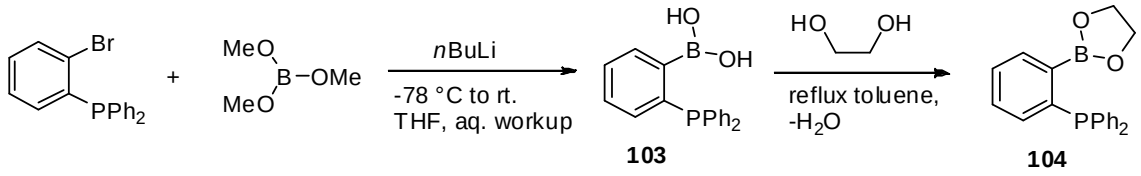
Based on those facts the next investigation was directed towards the preparation of different boronates that would be less sterically demanding than the pinacol esters, as well as less electron rich, if possible. From the general synthesis of boronic acids (*Scheme 21*) it is known that after nucleophile addition the boronate is formed first and then after acidic workup the corresponding boronic acid is obtained.

This approach was applied to the boronate **101** in order to prepare boronic acid **103**, which could be further transformed into different esters. Pinacol boronate **101** was then treated with aqueous hydrochloric acid, but only starting material was obtained, even after heating the mixture with aqueous HCl to 55 °C for 16 hours (*Scheme 49*).



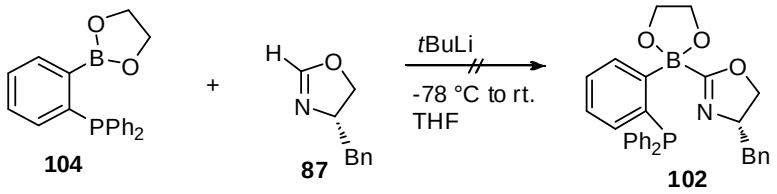
Scheme 49: Stability of pinacolboronate **101** under acidic conditions.

Since hydrolysis of product **101** was not possible, another synthesis was considered which did not start from pinacol boronate **101**, but from trimethylboronate to produce the dimethylester of **103**, which could be easily hydrolyzed to obtain the desired boronic acid **103**. This species can be further transformed into the corresponding esters by condensation with alcohols. Ethylene glycol was chosen as the diol for the condensation because it has less steric demand than pinacol (*Scheme 50*).[71]



Scheme 50: Preparation of boronic acid **103** followed by ethylene glycol ester formation.

The reaction of glycolboronate **104** was performed under standard conditions for the analogous reaction of pinacolboronate **101** in order to obtain the expected addition product **102** (*Scheme 51*).

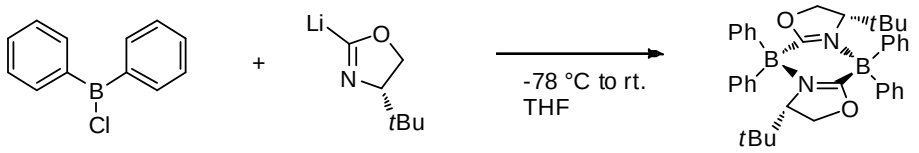


Scheme 51: Reaction of the gylcolboronate **104** with the oxazoline **87**.

Unfortunately also the ethylenegycol derivative **104** showed to be unreactive as well as the pinacol derivative **101** and did not produce any desired addition product **102**.

4.6 Aminoborane complexes

In the previous chapters the reactions either were not specific and mixtures of uncharacterized products were obtained or the reaction produced the undesired dimeric product **98**. The B-N bond in this dimer was found to be very strong and the breaking of that bond was not possible (*Scheme 46*). The analogous dimeric product was also later observed in the reaction of dipehenylchloroborane with lithium oxazoline (*Scheme 52*).



Scheme 52: Reaction of the dipehnylchlorobornate **61** with the oxazoline producing undesired dimeric product.

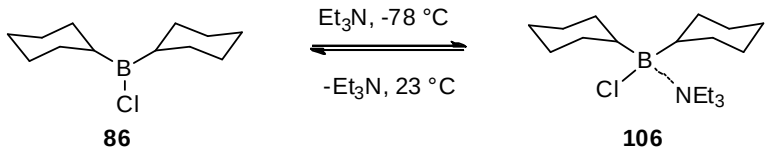
Li-(28)-*t*Bu was added into the precooled solution of chloroboronate **62** to ensure that the chloroboronate is in excess during the addition to avoid formation of the undesired borabox ligand. Based on the ^{11}B NMR spectrum a tetravalent boron species was obtained, but the chemical shifts did not match with the known borabox ligand.[36] Therefore the mass spectrum was recorded, which showed the mass of dimeric structure **105**.

Keeping in mind the inert nature of **98**, no nucleophile addition trials were then performed. Instead, we thought of how to avoid the undesired dimer formation. An option would be to reversibly block the fourth substitution position of the boron atom, which would prevent the undesired dimer formation.

As was shown in *Scheme 43*, the Lewis acidity of the aromatic boronates differs due to the increased back donation of the oxygen lone pairs as opposed to the aliphatic boronates, where electron delocalization is not possible. This different electronic behavior can be experimentally demonstrated by complexation of the selected boronates with pyridine. The aromatic boronates form pyridine complexes, whereas the aliphatic ones do not.[67] Pyridine usually forms very stable complexes with boranes,[72] which is used for example for the deprotection of BH_3-protected phosphines, where the newly formed B-N bond is much stronger than the B-P bond. Therefore, using pyridine to temporarily block the boron coordination sphere would not be feasible. The interaction of the boranes with various amines

was studied by Mikhailov, where amines like diethylamine, piperidine, pyridine, or gaseous ammonia were tested.[72-73] He found that the ammonia-boron complexes could be treated by gaseous hydrochloric acid to recover the trivalent boron compounds. This approach unfortunately cannot be applied to our previously prepared unreactive compounds **89** or **105**, because treatment of those compounds with the acid would lead to oxazoline decomposition.

Since the B-N bonding was dependent on the nature of the amine and also temperature, we decided to test weakly coordinating triethylamine at various temperatures with dicyclohexylchloroborane **86** in order to obtain reversibly protected borane (*Scheme 53*).



86 **106**

Scheme 53: Complexation of dicyclohexylchloroborane with triethylamine at low temperature to form an insoluble complex **106** in hydrocarbon solvent.

Initially triethylamine was added to the clear precooled solution of the chloroborane **86** in *n*-hexane. The white precipitate **106** already began forming during the triethylamine addition. This precipitate was completely dissolved upon warming the reaction mixture up to room temperature and a solution without precipitate was again obtained. The *n*-hexane was evaporated from the reaction mixture and there was no triethylamine present based on the ^{1}H NMR spectrum.

This weak coordination could be useful, for example, for the purification of selected trivalent boron compounds, because the reversible complexation can be driven just by temperature. Another application of the ammonium complexes is that they could be used even in reactions with nucleophiles.[74]

We were particularly interested in the reaction of amino-borane complexes with nucleophiles and therefore the same complexation as in *Scheme 53* was investigated, but in the intended reaction solvent, which was tetrahydrofuran. This reaction was performed in deutero-tetrahydrofuran to allow the changes of the amine complexation in the variable temperature ^{1}H and ^{11}B NMR studies to be tracked. For this purpose, the addition of equimolar amounts of triethylamine to chloroborane **86** was done at room temperature and subsequently a set of ^{1}H and ^{11}B NMR spectra were recorded at lower temperatures (*Figure 17 and 18*).

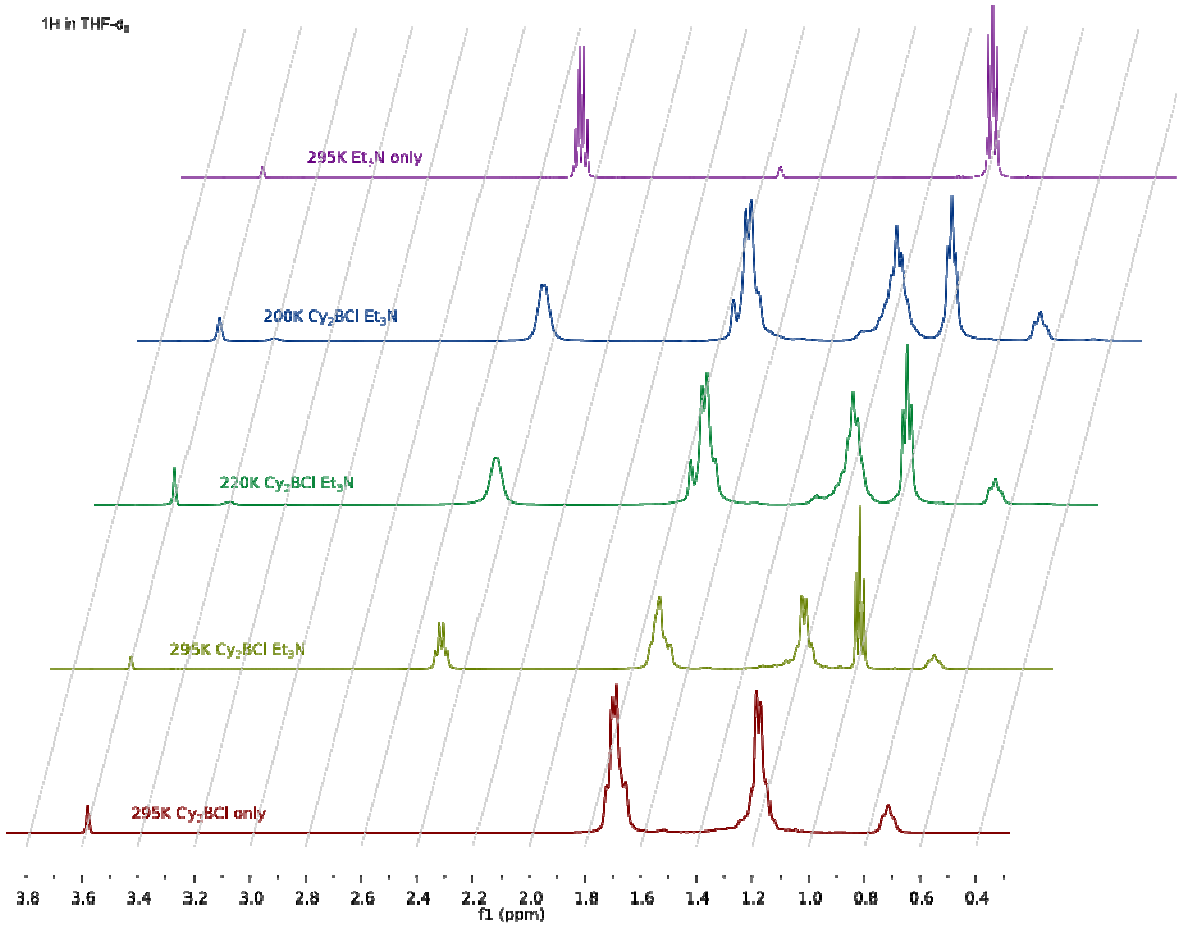


Figure 17: Variable temperature ^{1}H NMR experiment displaying complexation of the chloroboronate **86** with triethylamine in THF.

The NMR spectra of chloroborane **86** were first recorded only in THF-d_8 to see possible changes after triethylamine addition, such as whether it would already coordinate to the borane at room temperature. But this change did not occur, as is visible from the first 2 stacked spectra where neither the ^{1}H nor ^{11}B NMR spectra has changed. The major change in the ^{11}B NMR spectrum from 76 ppm to 28 ppm was observed when the NMR solvent was changed from $CDCl_3$ to THF-d_8, but no further change after triethylamine addition at room temperature was observed (*Figure 18*). After cooling the sample down to 200 K changes in the ^{1}H NMR were already visible, where the CH signal of the cyclohexyl group at 0.75 ppm moved slightly upfield as well as the signal at 1.73 ppm. The positions of the triethylamine signals were practically unchanged, but the quartet of the CH_2 group got broader and lost multiplicity, while the triplet of the methyl group remained. In the ^{11}B NMR the boron signal became broader and moved several ppm upfield. Further cooling to 200 K further enhanced that effect (*Figure 18*).

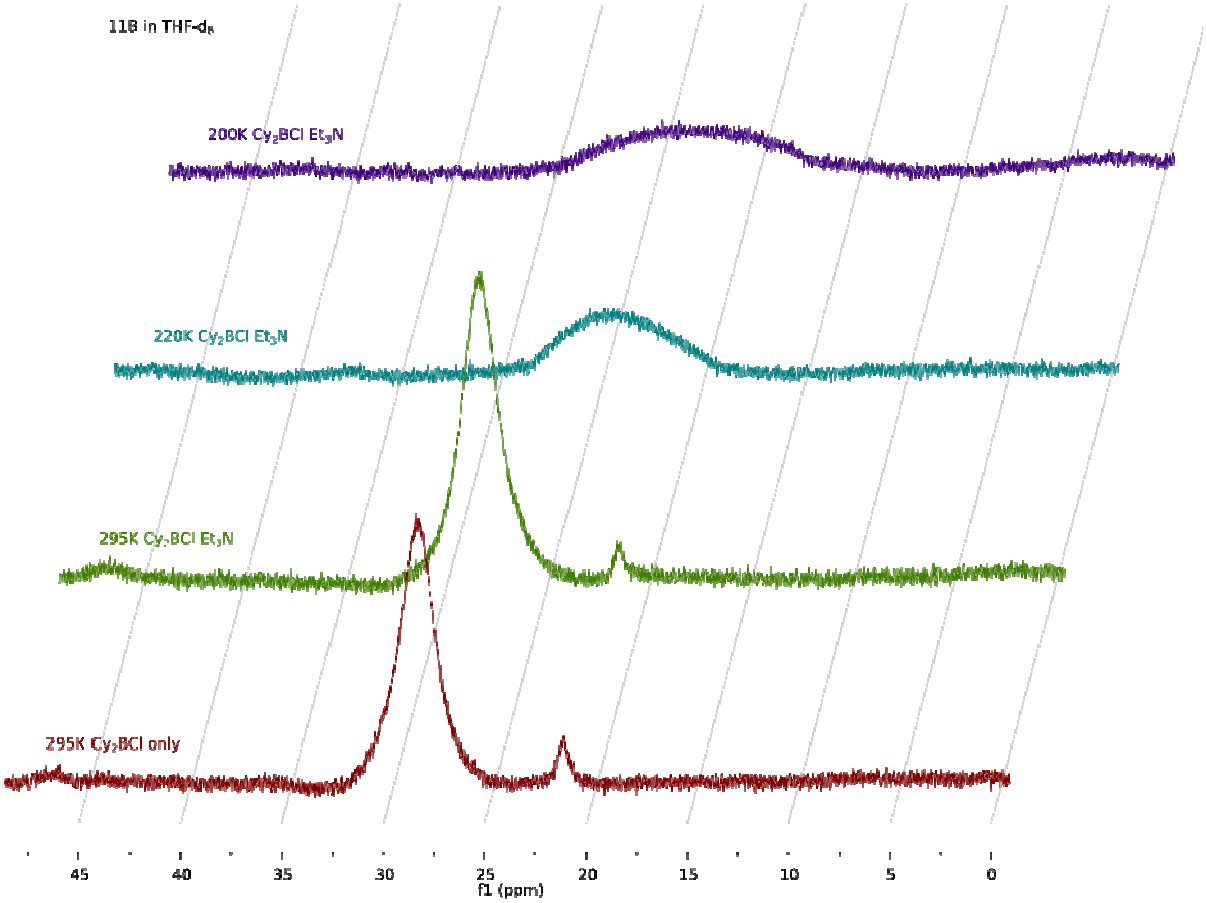


Figure 18: Variable temperature ^{11}B NMR experiment displaying complexation of the chloroboronate **86** with triethylamine in THF.

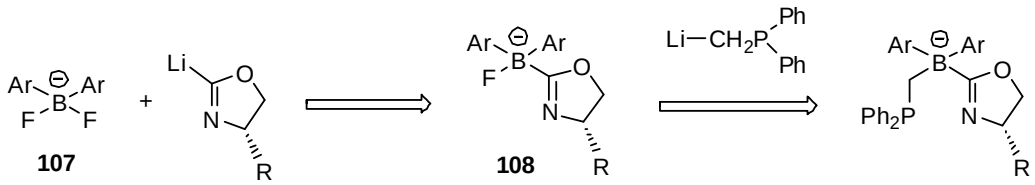
This behavior could be interpreted as an interaction of the chloroborane **86** with the nitrogen atom of the amine, which is dynamic and the amine is competing with the surrounding molecules of tetrahydrofuran. The broadening of the CH_2 proton signals of the triethylamine would support this theory, because the CH_2 group would be the one most affected by complexation and therefore broadened by dynamic process and at the same time also by possible remote coupling with the boron atom. The broadening of the boron signals in the ^{11}B NMR probably results from a complex equilibrium, where at the lower temperature the more stable ammonium complex is favored, but the concentration effect of the solvent still allows competition between the amine and THF.

The initial idea of using weakly coordinated amines as a temporary protecting group was to avoid the undesired reactions that were observed in THF (*Schemes 32, 46, and 52*). From these complexation experiments we concluded that complexation of the boranes with amines could be possibly used in general for purification of the trivalent boron compounds by

crystallizing them from hydrocarbon solvents at low temperatures. But using them to avoid the undesired reactions with other nucleophiles at low temperatures was considered unreasonable because of the similar complexation abilities of triethylamine and tetrahydrofuran (*Figure 18*).

4.7 Difluoroborates as electrophiles in the nucleophilic substitution reaction

As it was not possible to block the fourth substituent position at the boron atom by weakly coordinating nitrogen bases, another strategy was proposed, which would keep the boron atom tetravalent during the entire reaction sequence (*Scheme 54*).



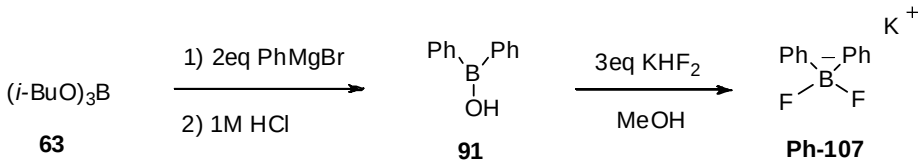
Scheme 54: Synthetic strategy utilizing difluoroborates in reaction with oxazolines and phosphines.

Diaryldifluoroborates **107** served as starting materials in the reactions with nucleophiles in order to control the stepwise substitution without the danger of either multiple substitution or undesired boron-heteroatom interactions. The diaryldifluoroborates are not widely used reagents,[75] they were almost exclusively used in the Suzuki-Miyaura coupling reaction for transferring aryl groups to substrates via palladium-catalyzed reactions.[76] The more widely used analogs in Suzuki-Miyaura reactions are potassium trifluoroaryl-boranes.
Herein we present the first use of diaryldiflouroboranes as electrophiles in a nucleophilic substitution reaction.

4.7.1 Preparation of difluoroborates

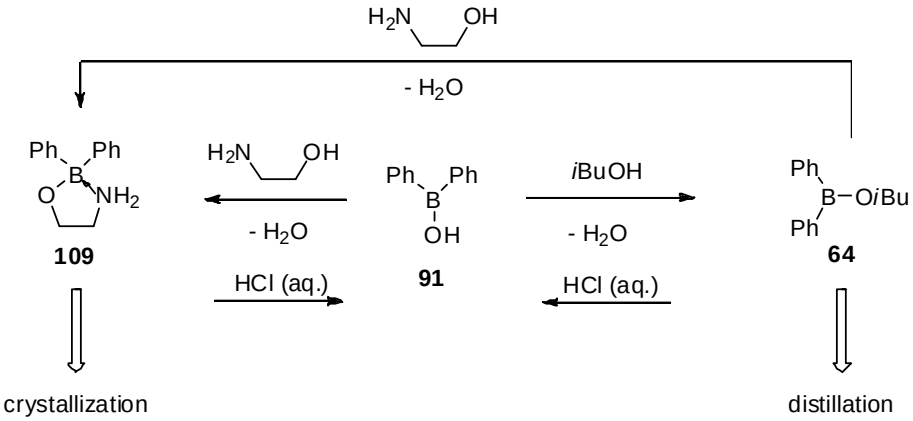
Several diaryldiflouroboranes were easily prepared from the corresponding borinic acids by reaction with potassium hydrogen difluoride. Only a few examples of potassium diaryldifluoroborates have been reported before (*Scheme 55*).[76] The resulting compounds **107** are moisture and air stable, unlike most of the boron compounds, and their final

purification could generally be done by crystallization from a methanol/diethylether mixture. Preparation of the diarylborinic acids as precursors starts from trialkylboronates and was previously described in *Scheme 36*.



Scheme 55: Preparation of potassium diphenyldifluoroborate from diphenylborinic acid.

To have a robust synthesis of borinic acids and their difluoroborates **107**, their preparation and purification were investigated. Diphenlylborinic acid **91** was chosen as a model starting substrate. This borinic acid is not stable and it hydrolyzes over time to give mainly phenylboronic acid, therefore it has to be either used immediately after preparation or it can be converted back to the isobuthylester, which can be purified by fractional distillation. Column chromatography of **91** is possible, but owing to its instability under acidic conditions, it is not the method of choice. A better method for purification is formation of the ethanolamine ester of the corresponding borinic acid. Such esters are air and moisture stable and they can be easily purified by crystallization. The high stability of these esters is due to coordination of the amino group of ethanolamine resulting in the tetravalent compound **109** (*Scheme 56*).

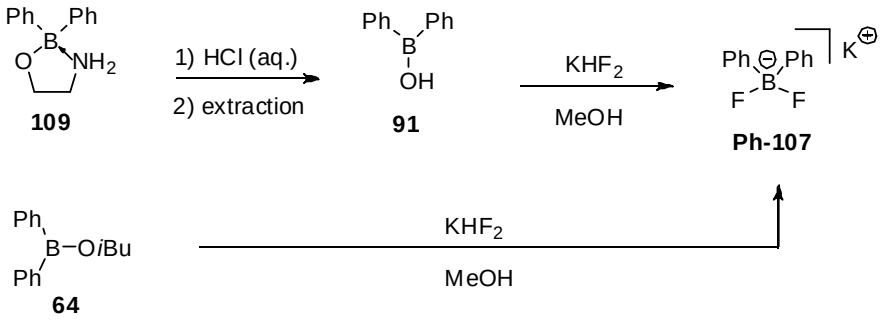


Scheme 56: Preparation of stable derivatives of the diphenylborinic acid suitable for purification.

The previously prepared isobutylborate **64** can also be directly converted into the ethanolamine ester. The driving force for the transesterification reaction is the formation of the more stable tetravalent boron species **109** (*Scheme 56*).

As described in *Scheme 55*, diphenylborinic acid **91** can be converted into **Ph-107** by using an excess of KHF_2. The starting borinic acid **91** can be also released from the ethanolamine ester **109** by treatment with aqueous hydrochloric acid followed by extraction (*Scheme 56*).

Both esters **64** and **109** can be used for direct transformation to **Ph-107** using the same conditions as for the reaction from borinic acid **91**, but in case of ethanolamine ester **109**, the reaction is significantly slower. Therefore, it is better to first transform the ethanolamine ester to **91** because the reaction with the borinic acid proceeds much faster and is complete in about 15 min (*Scheme 57*).

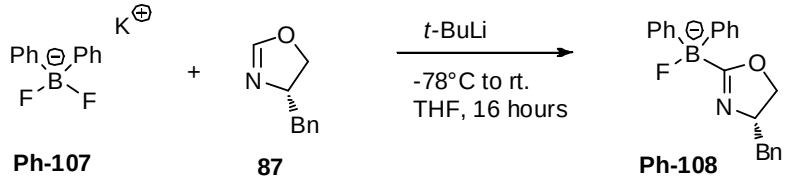


Scheme 57: Preparation of the potassium diphenyldiflouroborane **Ph-107** form the ethanolamine ester **109** and isobutylboronate **64**.

While ethanolamine ester **109** is less reactive than the borinic acid **91** in the reaction with the nucleophilic fluorine of KHF_2, the isobutyl ester reacts even faster than acid **91**, accompanied by an observable evolution of heat. The reason for these different reactivities is obvious. Amino function of the ethanolamine ester has to first dissociate from the boron center and, as was described earlier, the B-N bonds are very strong; therefore, this transformation requires more time than the reaction of trivalent precursors **64** and **91**. This reaction is nevertheless possible, probably owing to the driving force of the newly formed, and also very strong, B-F bond.

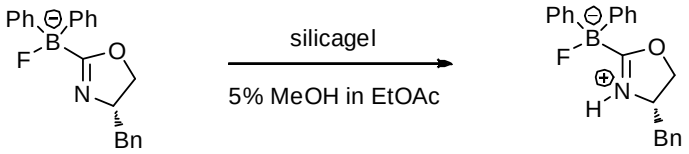
4.7.2 Reaction of difluoroborates with lithium-oxazolines

The previously prepared difluoroborate **Ph-107** was used for the reaction with lithium-oxazoline to obtain the substitution product **108**. Oxazoline **87** was selected as the first nucleophile in the reaction sequence (*Scheme 54*) because it was considered to be a weaker nucleophile than the lithiated methylphosphine **85** and therefore the addition should be done in the first substitution step. The reaction using **Ph-107** as a reactant was done at low temperature in order to decrease the reactivity of **Li-87**, which could possibly form the double substitution product (borabox ligand) because it is present in excess during the addition (*Scheme 58*).



Scheme 58: Reaction of difluoroborate **Ph-107** with lithium-oxazoline **Li-87**.

The reaction mixture was warmed to room temperature after addition and after approx 30 minutes the reaction was discolored. After another 2 hours a sample was taken from the reaction mixture and an NMR analysis was done in $CDCl_3$ because the product was expected to be soluble in chloroform. However, starting material was almost exclusively observed. The reaction mixture was allowed to react additionally overnight at room temperature and then was analyzed again. There was a signal in the ^{19}F NMR spectrum with a very low chemical shift at around -192 ppm, which did not correspond to starting material. The ^{11}B NMR mainly showed the presence of tetravalent boron, which could not be starting material because **Ph-107** was not soluble in the selected NMR solvent. The MALDI-MS was also recorded to determine the molecular mass of the product, which showed the expected mass for **Ph-108** in the negative mode. The crude product was then purified by column chromatography on silica gel where the product was eluted with methanolic ethyl acetate. The ^{1}H NMR spectrum after chromatography looked slightly different than the NMR spectrum of the crude reaction mixture, especially the signals of the oxazoline ring were all shifted. Overall the spectrum was consistent with the protonated form of **Ph-108-H** (*Scheme 59*).



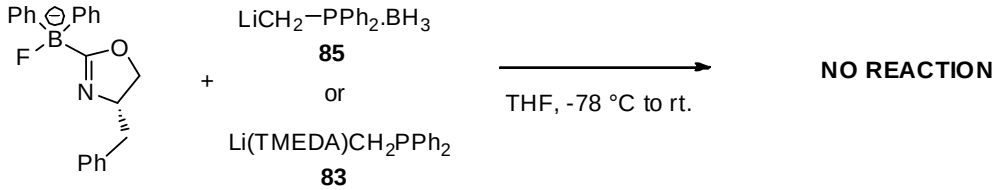
Ph-108 **Ph-108-H**

Scheme 59: Protonation of the Ph-108 on the silica gel column.

This behavior is in analogy with the previously prepared borabox ligands, which can also be converted from the negatively charged lithium salts into the zwitterionic structures.[36] The confirmation of this proposed behavior prompted FAB-MS analysis where the mass of the neutral product **Ph-108-H** was detected as an adduct with the potassium cation, which came from the KCl salt intentionally added for the measurement. FAB was selected as a soft ionization method, as ESI and MALDI had failed to detect the product **Ph-108-H** mass.

4.7.3 Reaction of oxazolinefluoroborane with the lithium phosphine

Product **Ph-108-H** was used in the next step of the planned synthesis (*Scheme 54*) with lithium phosphine salts. **Ph-108-H** was deprotonated with *n*-butyllithium under the same conditions as described for the borabox ligands.[36] The deprotonated oxazoline **Ph-108** was then used in the reaction with phosphine nucleophiles **83** and **85** (*Scheme 60*).



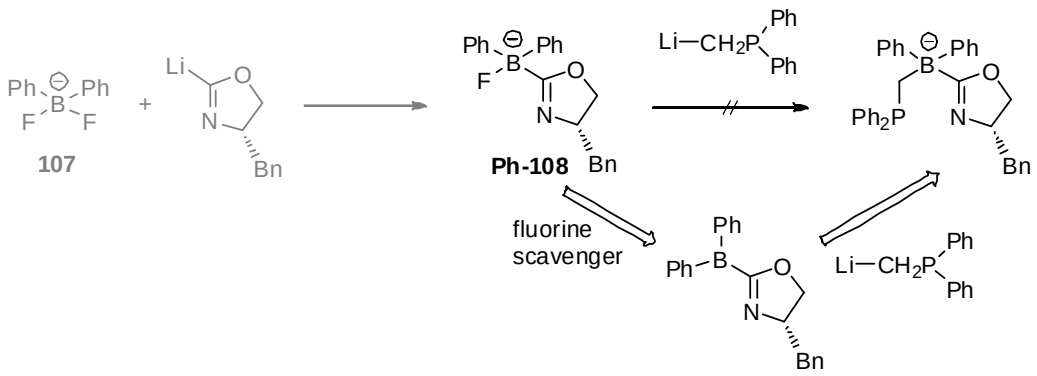
Ph-108

Scheme 60: Reaction of **Ph-108** with the lithum salt of diphenylmethylphosphine.

However lithium phosphines **83** or **85** did not undergo the proposed nucleophilic substitution with **Ph-108**, and in both cases only starting material was recovered. More forcing conditions, such as refluxing the reaction mixture in THF for an extended time period were also examined, but no reaction was observed.

4.7.4 Removing fluorine from diphenyloxazolinefluoroborane

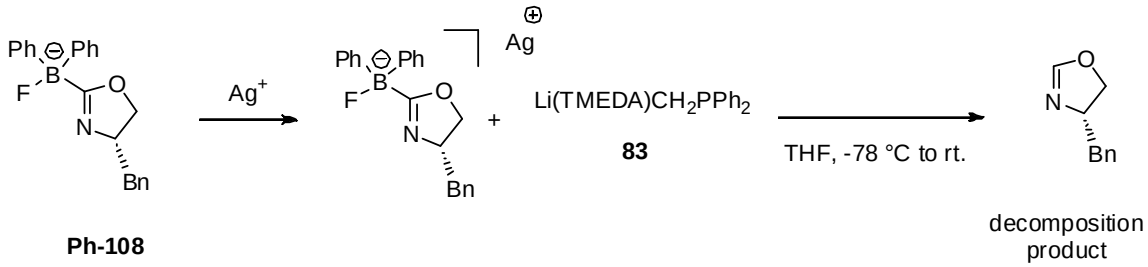
Because of the inert nature of the fluoroborate **Ph-108** it was attempted to cleave the B-F bond and possibly let the released trivalent boron species react in situ with the nucleophile in order to avoid possible dimer formation (*Scheme 61*).



Scheme 61: Adjusted synthetic strategy using **Ph-108** in the reaction with phosphine nucleophiles.

For the cleavage of the fluoride-borane adduct **Ph-108** several reagents were considered which could possibly form stronger bonds with fluoride and at the same time not interfere with the lithium reagents present in the reaction mixture.

The first method selected for the B-F bond cleavage in **Ph-108** was the use of the silver salts, which can remove the fluoride by forming silver fluoride, which is basically insoluble in tetrahydrofurane which is used as a reaction solvent. Two silver salts, $AgNO_3$ and $AgPF_6$, were tested in the reaction with either **Ph-108** or **Ph-108-H**. Silver(I) nitrate is not well soluble in THF, but if the desired silver fluoride formation were to take place then it would gradually dissolve as the reaction progresses. The silver hexafluorophosphate was selected because of its better solubility in organic solvents. In both reactions unidentified mixtures of products were obtained, which were mostly insoluble in THF. The soluble part did not contain any oxazoline signals, which suggested that the starting **Ph-108** was transformed into its silver salt, which was not soluble in THF. Despite the fact that it was not possible to identify the reaction intermediates, the reaction mixture containing the silver salts was used in the reaction with lithium(TMEDA) phosphine **83**. Instead of the expected substitution product this reaction produced only starting phosphine and the corresponding 2H-oxazoline (*Scheme 62*).

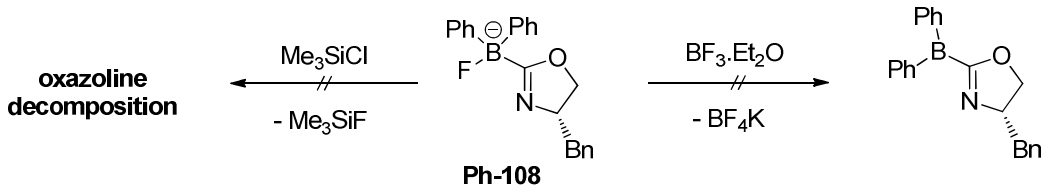


Ph-108

Scheme 62: Reaction of **Ph-108** with silver salts.

The silver salts of **Ph-108** after the first reaction step still contained the fluorine bound to the tetravalent boron based on the fluorine NMR even though silver was used in excess. An extra equivalent of silver salt should guarantee that there will still be some free Ag^+ for reaction with the fluoride. The problem in this case is probably the low solubility of the silver salts. When the protonated form **Ph-108-H** was used, decomposition of the oxazoline was observed.

As the initial attempts at removing the fluoride from **Ph-108** were unsuccessful, we proposed boron-based fluoride scavengers, such as BH_3.THF or $BF_3.Et_2O$. Those boron compounds should form adducts with the fluoride anion and liberate the trivalent boron species (*Scheme 63*).



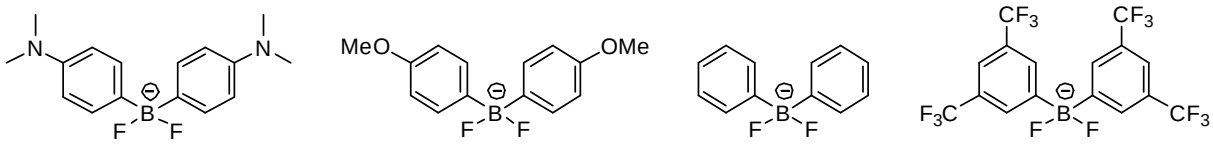
Ph-108

Scheme 63: Reaction of Ph-108 with $BF_3.Et_2O$ or with Me_3SiCl.

The driving force for the reaction should be formation of the tetrafluroborate salt, but even when $BF_3.Et_2O$ was used in excess the characteristic signal of **Ph-108** was still observed in the fluorine NMR spectrum. When a silicon-based fluorine scavenger was used, either in the form of Me_3SiCl or $SiCl_4$, only the decomposition of the oxazoline was observed, as was also the case when BH_3.THF was used.

4.7.5 Electronic tuning of the aromatic tetravalent fluoroborates

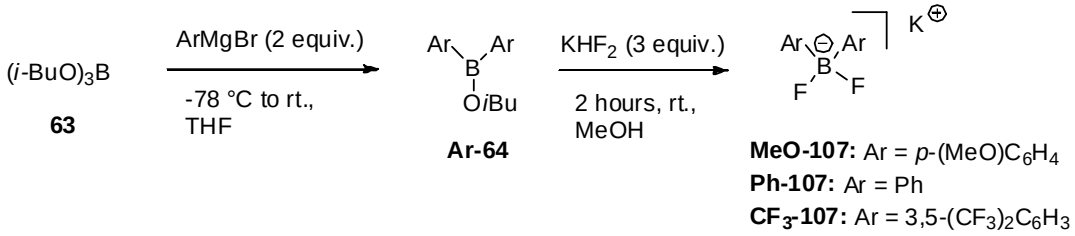
As the reaction of **Ph-108** with either **83** or **85** was not taking place and the removal of fluoride from **Ph-108** was not possible, we decided to tune the electronic properties of the starting difluoroborates. The phenyl substituents of those compounds could bear either electron-withdrawing or electron-donating substituents. The substituents were selected based on their σ Hammett constants in an effort to vary the electronic properties over a wide range. Thus the following structures were proposed (*Figure 19*).



Me_2N-107 **MeO-107** **Ph-107** **CF_3-107**

Figure 19: Proposed substituted aromatic difluoroborates for the electronic effect studies.

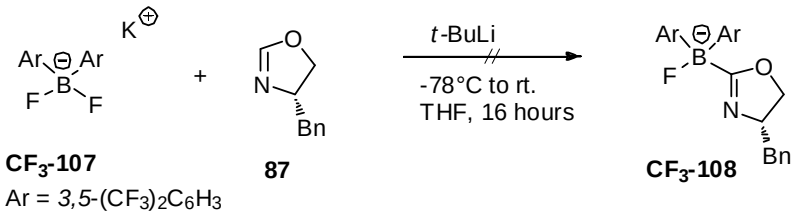
The synthesis of these new **Ph-108** analogs was done using the corresponding Grignard reagents in a reaction with boronate **63**, producing borinic acid esters which were converted into the difluoroborates by reaction with KHF_2 without isolation (*Scheme 64*).



Scheme 64: Preparation of the potassium difluorodiarylboranes.

The purification of the final difluoroborates is straightforward and should be applicable to a wider range of substrates because of their relatively similar physical properties. They can be all crystallized out of the methanolic solution by precipitation with either diethyl ether or chloroform. The only compound which was not possible to prepare was **Me_2N-107**. The reason for this different behavior could be that the dimethylamino groups can interact with the boron and form some B-N intermediates, which will not allow formation of the desired difluoroborate, but these intermediates were not detected.

The other two new products **MeO-107** and **CF_3-107** were successfully prepared and tested in the reaction with **Li-87**. The electron-poor difluoroborate **CF_3-107** was the first tested in the reaction with **Li-87** under the same reaction conditions used for the preparation of **Ph-108**. To our surprise, only starting difluoroborate **CF_3-107** and oxazoline **87** were observed and no other products were detected in the reaction mixture (*Scheme 65*).



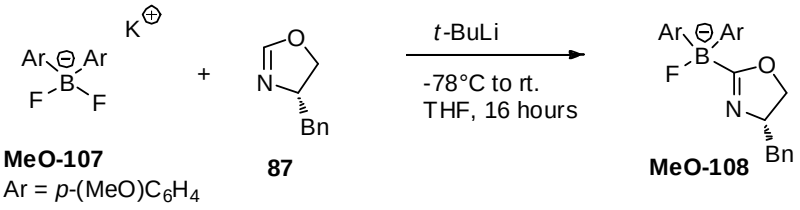
CF_3-107
Ar = *3,5*-$(CF_3)_2C_6H_3$

87

CF_3-108

Scheme 65: Attempted reaction of **CF_3-107** with **Li-87**.

In contrast to **CF_3-107**, the reaction of the electron-rich difluoroborate **MeO-107** produced the anticipated product **Me-108**. This compound had analogous properties to the previously prepared **Ph-108** and could also be purified by column chromatography, where it was converted into the protonated form, **MeO-108**, which is a white crystalline solid (*Scheme 66*).



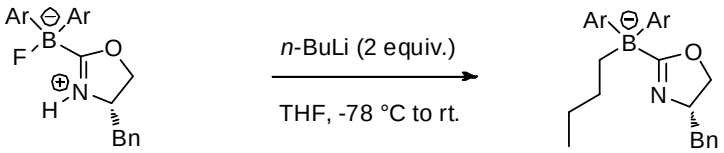
MeO-107
Ar = *p*-$(MeO)C_6H_4$

87

MeO-108

Scheme 66: Reaction of difluoroborate **MeO-107** with **Li-87** and subsequent protonation.

Although the protonated **MeO-108** was crystalline, no suitable crystals for X-ray analysis could be obtained. Fluoroborate **MeO-108** was also subjected to the reaction with lithium phosphines **83** and **85**. The reaction mixture showed a new ^{11}B signal at -13 ppm and phosphorus signals at 10 and 15 ppm. Those signals disappeared after purification attempts using column chromatography, and mostly starting material was observed in both cases. The NMR chemical shifts of the crude reaction mixture support the existence of the desired substitution product. Unfortunately successful purification conditions were not found. In one case, when the reaction sequence was started from the protonated **MeO-108** and *n*-butyllithium was used to deprotonate the starting material prior to the reaction, a compound with the proposed structure of **MeO-108-Bu** was observed (*Scheme 67*).



MeO-108-H
Ar = *p*-MeOC$_6$H$_4$

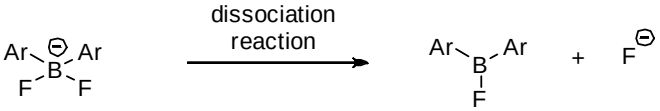
MeO-108-Bu

Scheme 67: Proposed reaction of *n*-butyllithium with **MeO-108**.

This reaction, where the tetravalent boron species was observed by ^{11}B NMR, did not show starting material in the ^{19}F NMR spectrum and in the ^{1}H NMR spectrum showed the signals of the *n*-butyl group. Since the result of this reaction was not reproducible and the initial reaction was performed only on a small scale, the compound **MeO-108-Bu** was not fully characterized. The proposed compound **MeO-108-Bu** could have also been the *n*-butoxyl derivative, which may come from *n*-*Bu*OLi traces in *n*-butyllithium. Because the reaction with *n*-butyllithium was not reproducible, a reaction with sodium ethoxide was examined to better examine the reactivity of **MeO-108-Bu** in reactions with O-nucleophiles; unfortunately, there was no product observed in this reaction.

4.7.6 Computational studies of the electronic properties in selected fluoroborates

The general reactivities of the tetravalent fluoroborates in the nucleophilic substitution reactions are not known, as similar reactions have not been previously reported. To get a better understanding of the electronic properties and reactivity of fluoroborates **Ph-108** and **MeO-108**, and difluoroborate **CF$_3$-107**, we carried out quantum chemistry studies.



reactants *products*

Ar = Ph, *p*-Me$_2$N(C$_6$H$_4$), *p*-MeO(C$_6$H$_4$),
3,5-(CF$_3$)$_2$(C$_6$H$_2$)

$$\Delta G_{reaction} = \sum \Delta G_{products} - \sum \Delta G_{reactants}$$

$$\Delta\Delta G^{Ph_2BF\ std.}_{reaction} = \Delta G^{Ph}_{reaction} - \Delta G^{Ar}_{reaction}$$

Figure 20: Gibbs free energies for the difluoroborate dissociation reaction, and definition of $\Delta\Delta G^{std.}$.

The first task of the theoretical investigation was to calculate the thermochemical data for the important, and probably rate determining step of the S_N1 reaction, which is dissociation of the fluoride from the difluoroborate molecule (*Figure 20*).

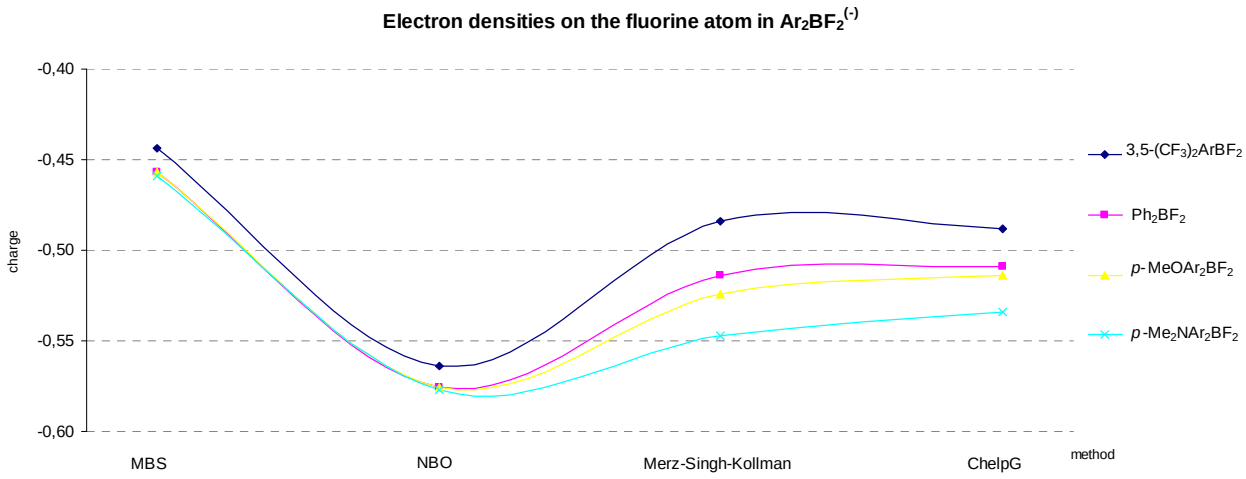
From the optimized geometries of the reactants and products the ΔG values were calculated for all fluoride dissociation reactions, with substituents ranging from electron-donating to electron-withdrawing. All of the ΔG^{Ar} values obtained were then referenced to the ΔG^{Ph} value for the **Ph-107** reaction to obtain the variable $\Delta\Delta G^{std.}$ (*Figure 20*, 2nd equation), which should express the overall difference in the Gibbs free energies between the individual reactions. These $\Delta\Delta G^{std.}$ values are then presented on the last line of *Table 9*.

Density functional theory (DFT) calculations were carried out to obtain the ground state energies of the selected fluoroborates.[77] The corresponding Gibbs free energy corrections were obtained from a vibrational analysis, which had no negative frequencies.

Table 9: Electron charge distributions in difluoroborates, B-F bond lengths, and $\Delta\Delta G^{std.}$ values.

Method	*p*-$Me_2NAr_2BF_2$	*p*-$MeOAr_2BF_2$	Ph_2BF_2	3,5-$(CF_3)_2Ar_2BF_2$
MBS	-0,459	-0,457	-0,457	-0,444
NBO	-0,577	-0,576	-0,576	-0,564
Merz-Kollman	-0,547	-0,524	-0,514	-0,484
ChelpG	-0,534	-0,514	-0,509	-0,488
$\Delta\Delta G^{std.}$ [kcal/mol]	10,1	4,6	0	-27,6
B-F [Â]	1,4464	1,4450	1,4447	1,4336

*values calculated using B3LYP/6-311+G(d,p), the charge numbers represent charges on the boron atom



Another electronic property which was calculated by quantum chemistry modeling is the charge distribution within the molecule. In this computational study four different methods for the charge distribution were examined and applied to the diaryldifluoroborates.

The first method used was Mulliken population analysis, using a minimal basis set (MBS)[78]. This method is based on the coulombic charges of the individual atoms and the assumption that the overlap between orbitals is equally shared and therefore bond polarization is neglected.

The second method used was Natural Bond Order analysis (NBO)[79] based on the localized orbitals centered on the atoms. Since those two methods are based on orbital occupancies, where the charges are localized on the atoms and the polarization of the bonds is neglected, they may not always produce an accurate representation of the charge distribution, especially in polarized systems. This was the case in our systems, where the remote electron delocalization was not well represented by these methods, because the differences in the atomic charges that would describe the desired electronic trends were too small.

Two methods, Merz-Singh-Kollman[80] and ChelpG,[68] use electrostatic potential projection. Both methods calculate the distribution of electron densities along the atomic radii, which creates the molecular Van der Waals surface. The calculated densities describe the electronic behavior of a molecule very well, because they represent charge distribution as a continuous function of the electron densities around the atoms. Those densities are then fitted onto the atoms in order to determine the atomic charges.

The data for the charge distribution obtained from all these methods are shown in *Table 9*, they are also displayed on the associated graph for better comparison of the numerical results. When we compare the electronic charges obtained from both electrostatic potential methods, the electronic trends correlate very well with the expected influence of the electron-donating or electron-withdrawing groups of the substituted aromatic rings bound to the tetravalent boron. The calculated charge values also provide us with a quantitative representation of those differences. The results from the ESP methods used clearly show that **MeO-107** and **Ph-107** closely resemble each other in terms of the charge on the fluorine atom. The fluorine charge in the **CF_3-107** is far more electropositive owing to the electron-withdrawing effect of the two CF_3 groups, which makes the B-F bond in this compound the strongest among the calculated compounds. This effect is also supported by the calculated bond length of 1.4336 Å, which is again the shortest.

The effect of the electron-donating group on **Me_2N-107** is exactly the opposite. In this case, the calculated electronic properties cannot be compared with the experimental data since the *para*-dimethylamino derivative **Me_2N-107** could not be prepared.

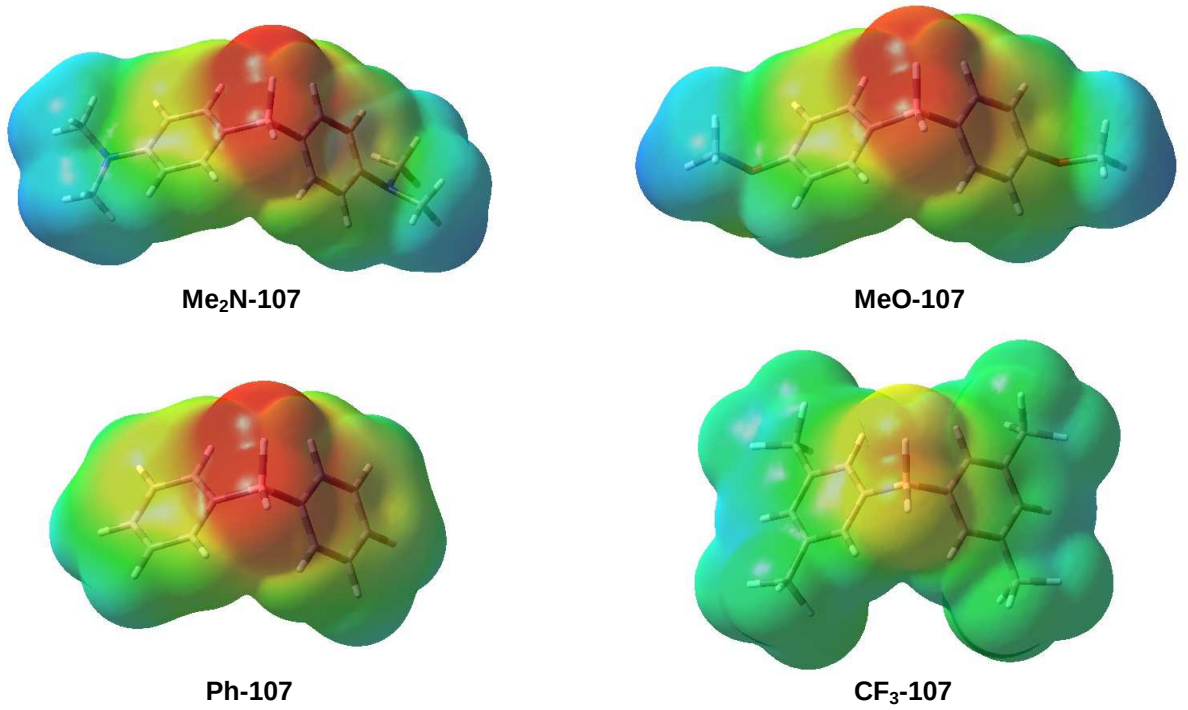


Figure 21: Molecular electrostatic potential (MEP) for selected difluoroborates **107** calculated in Gaussian 09, at the B3LYP/6-311g(d,p) level of theory by the ChelpG method.

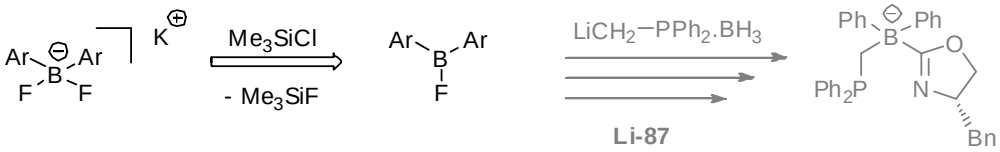
The electronic distribution in difluoroborates **107** is not obvious from the molecular structures because of the electronic effects of the phenyl substituents and the presence of highly electronegative fluorine in the molecule. Another parameter that also influences the electron density distribution is the overall negative charge of the tetravalent boron, which is delocalized both on the aromatic ring and between the fluorine atoms. A graphical representation of the charge distribution in the selected difluoroborates is shown in the electrostatic potential maps in *Figure 21*. The color levels for all molecules are set to the same range to allow for quantitative comparison between them. In the first two structures, **Me_2N-107** and **MeO-107**, the electrons from the electron-donating groups are delocalized on the phenyl rings and most of the electron density is located on the electronegative fluorine atoms. Completely different behavior was observed for the **CF_3-107**, where two CF_3 groups on the phenyl ring compete against two fluorine atoms on the boron atom and the resulting electron density is more equally distributed within the molecule.

The electrostatic charges fitted to the fluorine atom as well as the length of the B-F bonds should produce a measure for the boron-fluorine bond strength, which is an important parameter in the proposed S_N1 mechanism, where the fluoride has to dissociate. However, the bond strengths do not necessarily correlate with the thermodynamics of the process. Therefore the $\Delta G_{reaction}$ values for all of the fluorine dissociation reactions have also been calculated (*Figure 20*). All of these values had a positive sign, implying that the dissociation reactions are endothermic, which is expected as the corresponding difluoroborates are much more stable than the trivalent diarylfluoroborates. Since we had the experimental results from the reaction of **Ph-108** with the **Li-87**, the rest of the $\Delta G_{reaction}$ values were then referenced to this value to see the relative differences between various difluoroborates (*Table 9*).

From the values of $\Delta\Delta G^{std.}$ obtained, it can be seen that the dissociation of the B-F bond in **MeO-107** requires only 4,6 kcal/mol less energy than the analogous reaction with **Ph-107**. In contrast, the dissociation energy required for same bond dissociation in **CF_3-107** requires 27,6 kcal/mol more energy. This calculated value explains the experimentally observed lack of reactivity of **CF_3-107** in the reaction with **Li-87**.

4.7.7 An elimination-addition approach with fluoroborates

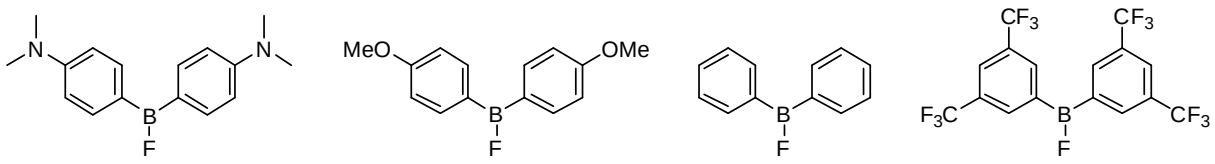
In the difluoroborate chemistry previously studied, a unimolecular nucleophilic substitution approach was used with elimination of the fluoride ion being the first, rate determining step. This step could be problematic, as the boron substituents do not have the right electronic properties. Therefore, we proposed a synthetic route that would eliminate the fluoride first in order to prepare the diarylfluoroborates in situ, which can then react further with nucleophiles in the nucleophilic substitution reaction (*Scheme 68*).



Scheme 68: Synthetic strategy using the difluoroborates in the elimination-addition approach

The reason for this strategy was not only utilization of the first elimination step by the irreversible cleavage of the fluorine, but also to test the reactivity of the fluoroborates in analogy with the chloroboranes used in previous studies. Trimethylsilyl chloride was used as a fluoride scavenger by Schrimpf et al. to eliminate fluorine from the phenyltrifluoroborate potassium salt in situ during the preparation of chiral oxazaborolidinones.[81]

It would be interesting to see whether fluoroborates would produce substitution products in reactions with nucleophiles, as chloroboranes do, [34, 36] or if they would instead form addition products, as **Ph-108** does. In this context, it would be good to know the actual B-F bond strengths in the fluoroborates. The properties which provide a measure of the bond strengths in those compounds are the bond lengths and the vibrational frequencies of the B-F bonds, which were obtained by DFT calculations (*Figure 22*).

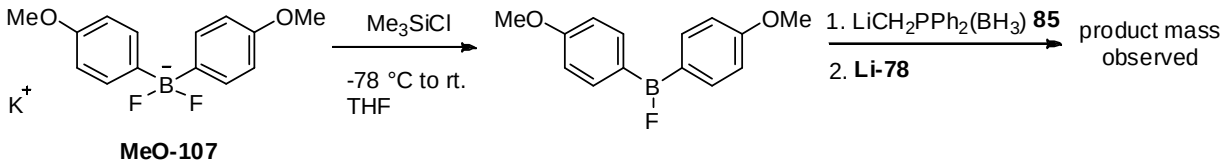


ν = 1247 cm^{-1} | ν = 1242 cm^{-1} | ν = 1250 cm^{-1} | ν = 1258 cm^{-1}

1, 367 Å | 1,362 Å | 1,356 Å | 1,346 Å

Figure 22: Calculated B-F bond stretching and bond lengths at the B3LYP/6-311+g(d,p) level of theory for selected fluoroborates.

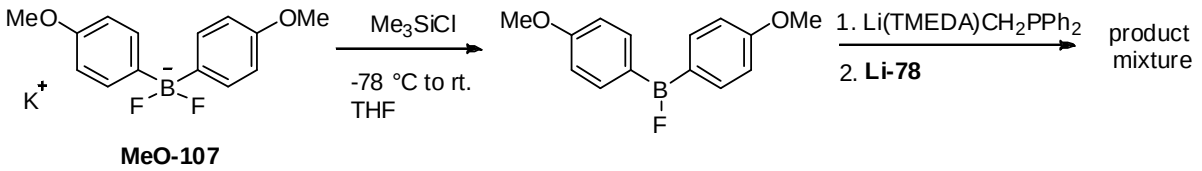
The B-F bonds in diarylfluoroborates (*Figure 22*) are generally shorter than bonds in the corresponding difluoroborates (*Table 9*). This result suggests that the fluoroborates will preferentially react with nucleophiles in an addition reaction, as the fluorine bond will probably not dissociate to produce the substitution product. Therefore, the reaction of **MeO-107** was tested first, as it has the best chance to react with the second nucleophile in the substitution reaction (*Scheme 69*).



MeO-107

Scheme 69: Elimination of fluoride from **MeO-107** followed by reaction with protected phosphine and **Li-78**.

The addition of trimethylsilyl chloride was done at low temperature and then the reaction was continued for another hour at room temperature. After cooling to -78°C **85** and **Li-78** were subsequently added, followed by stirring overnight at room temperature. The crude reaction mixture was then analyzed by NMR, where a ^{11}B signal was observed at -14 ppm and three signals in the ^{31}P NMR at 15 and 12 ppm. Those chemical shifts for ^{11}B and ^{31}P were also observed in the previous reaction of **MeO-108** with **85** (*Scheme 67*), which was postulated to give the same product. In the MALDI-MS of the crude reaction mixture the mass peak of the desired product was detected, but it was very weak; a fragment that could come from fragmentation of the product was also detected. Therefore, the reaction mixture was purified by column chromatography using silica gel or alumina, but only decomposition products were observed. Deprotection of the BH_3-protected phosphine was attempted in order to purify the product by complexation with a metal, such as Ir, Cu, Zn but these trials were unsuccessful.



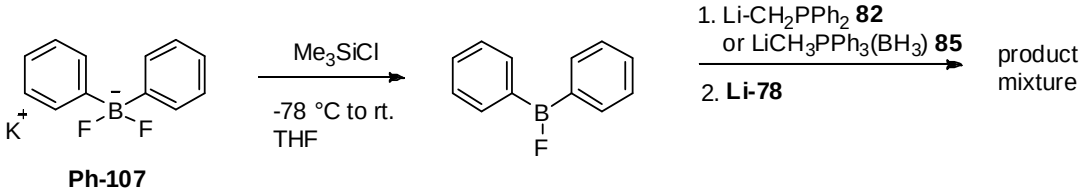
MeO-107

Scheme 70: Elimination of the fluoride from the **MeO-107** followed by reaction with non-protected phosphine and **Li-78**.

Since deprotection of the BH_3-protected phosphine product was problematic, an alternative synthesis using unprotected phosphine was attempted (*Scheme 70*). In this case the reaction

mixture showed signals at -14 ppm in the ^{11}B and -22 ppm (starting phosphine -27 ppm) in the ^{31}P NMR spectra. This crude reaction mixture was then subjected to complexation with $ZnCl_2$ in chlorobenzene, but the desired mass was not observed by MALDI-MS.

Another reactive difluoroborate used in reaction with a Li nucleophile in our previous studies was **Ph-107**. Hence, we decided to use it in the reaction sequence depicted in *Scheme 68*.



Ph-107

Scheme 71: Elimination of fluoride from **MeO-107** followed by reaction with protected or unprotected phosphine **85** and then reaction with **Li-78**.

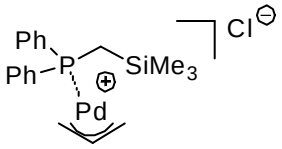
When the entire reaction sequence was done as depicted in *Scheme 71* several species were observed in the ^{11}B and ^{31}P NMR spectra, including starting materials. For the reaction with the BH_3-protected phosphine **85** signals were detected that were almost identical to the previously observed signals using **MeO-107**.

Because phosphine deprotection was problematic in the previous reaction with **MeO-107**, the reaction sequence was carried out again, this time using lithium methylenediphenylphosphine **82**. Again a tetravalent boron species was detected by ^{11}B NMR analysis and a new species also appeared in the ^{31}P NMR spectrum. Because of these promising results, several metals were employed to prepare a complex of the expected product, which could possibly be purified by crystallization.

Three different metal sources were selected, $[Ir(cod)Cl]_2$, $ZnCl_2$, and $[Pd(allyl)Cl]_2$. The complexations were done in refluxing THF and monitored by NMR spectroscopy. For the iridium and palladium complexes, all changes in the phosphorus NMR spectrum occurred within the first 30min of complexation. In the case of zinc chloride, 50% of the starting material was still observed after 20 hours. MALDI-MS spectra were recorded of all complexation mixtures, but desired masses (*m/z*) were not observed.

All crystallization attempts were unsuccessful with the exception of an iridium complex. These crystals were suitable for crystallographic measurement, but the structure could not be solved due to disorder in the crystal lattice.

Therefore, purification of the obtained metal complexes by column chromatography was attempted, as the ligand-metal complexes are more stable than the ligands alone. Only when $[Pd(allyl)Cl]_2$ was used a defined compound could be isolated. Unfortunately, after chromatography all oxazoline ^1H NMR signals were lost, as well as the tetravalent boron signal. In contrast, the phosphorus signal was unchanged and so other analyses were done in order to determine the structure of the unknown phosphine species. In analyzing the ^{31}P NMR spectrum using a pulse sequence without proton decoupling, a triplet was found, which suggests the presence of two protons neighboring the phosphorus atom. As the signals of one trimethylsilyl group were still present in the purified sample, structure **109** was proposed (*Figure 23*).

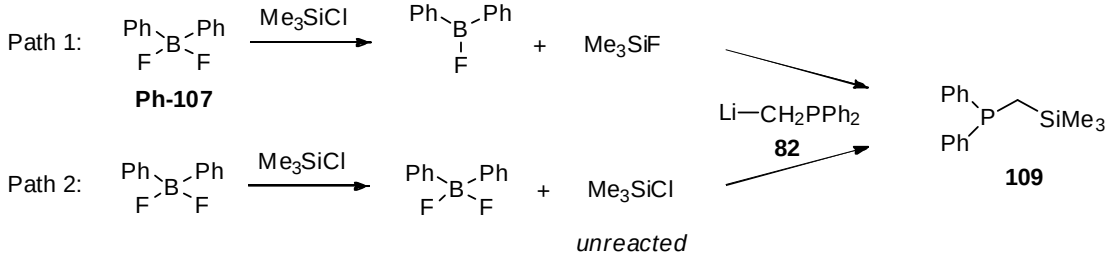


109-Pd

Figure 23: Undesired product observed in the reaction sequence shown in *Scheme 71*.

Based on this observation the spectra of all previous reactions were revisited to find out whether the precursor of the silylated metal complex **109** was already present in the reaction mixture before the oxazoline addition. After finding literature precedents and the corresponding spectroscopic data for these silylated phosphines [82] it was confirmed that the silylated product was already present after the second reaction step after in situ scavenging of the fluorine from the difluoroborates and addition of the lithium phosphines **83** and **85** (*Scheme 71*).

There could actually be two possible ways for the trimethylsilyl group to be incorporated into the phosphine backbone (*Scheme 72*).



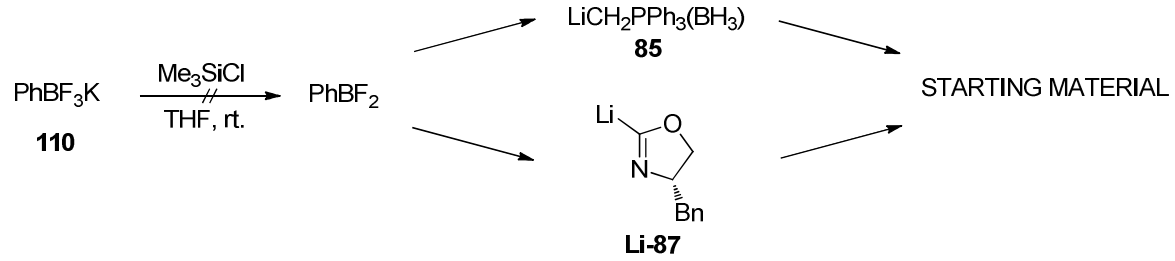
Scheme 72: Postulated mechanism for the formation of undesired silylated phosphine **109**.

Product **109** could be formed is if trimethylsilyl fluoride is still present in the reaction mixture after the elimination of fluoride from **Ph-107** and reacts with lithium phosphine **82** before the latter can add to diphenylfluoroborane (*Scheme 72*, *Path 1*). Alternatively, trimethylsilyl chloride, which is still present in the reaction mixture, could react with **82** and deliver the undesired product (*Scheme 72*, *Path 2*).

To find out which reaction pathway is actually taking place, the reaction mixture was carefully analyzed after elimination of the fluoride. The reaction solvent was carefully evaporated from the reaction mixture, but not to dryness, because diphenylfluroborane has a boiling point of 42°C / 100 Torr.[83] The ^{11}B NMR spectrum was then recorded in chloroform and the trivalent boron species was exclusively detected. The insoluble starting **Ph-107** cannot be seen because it is insoluble in the NMR solvent. This indicates that one of the fluorides from **Ph-107** must have been eliminated. No ^{1}H NMR signals from the trimethylsilyl group were observed, which was expected as the boiling point of trimethylsilyl fluoride is only 16°C / 760 Torr.[84]

Because the starting material **Ph-107** was not present in the reaction mixture after the first reaction step, the second proposed pathway can be ruled out, because it requires unreacted trimethylsilyl chloride. All of these results suggest that the preferred reaction pathway was *Path 1*, where substrate **82** reacts with the low-boiling trimethylsilyl fluoride. A possible way to avoid formation of the undesired product **109**, which most likely comes from the reaction of trimethylsilyl fluoride with **82**, was to apply low vacuum to the reaction mixture in order to evaporate the undesired low-boiling Me_3SiF while preserving the diphenylfluoroborane. Unfortunately, after applying those conditions to the reaction sequence depicted in *Scheme 71*, no products were observed and mostly starting material was recovered.

The reaction of potassium phenyltrifluoroborate **110** was also investigated (*Scheme 73*) in order to compare its reactivity with that of diaryldifluoroborates **107**. The protocol used in this case was inspired by analogous reaction used for preparation of oxazaborolidinones.[81]



Scheme 73: Reaction of potassium phenyltrifuoroborate with Me_3SiCl in THF does not produce the elimination product.

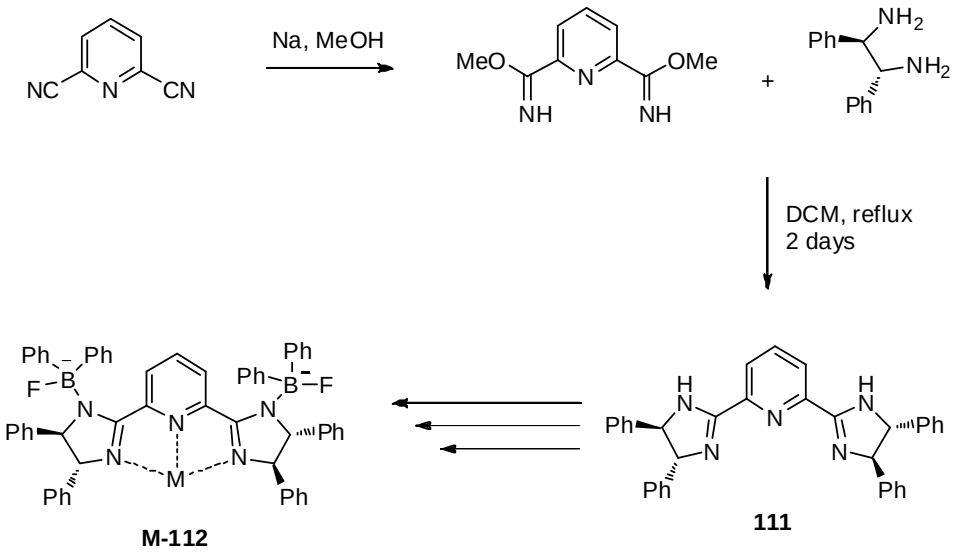
An elimination reaction of fluoride from **110** was also used in the preparation of the chiral oxazaborolidinones, but the reaction solvent in that case was acetonitrile. The reason for using **110** in polar solvents, even in Suzuki coupling reactions, is its low solubility, but in our reactions we were quite limited in the solvent selection because of the lithium reagents used. These reactions were tested anyway, because even though the solubility of **110** in THF is low, the anticipated elimination product should be soluble. However, only starting material was observed in both cases using **85** and **Li-87**.

4.7.8 Potential applications of the fluoroborates

During the experimental and theoretical investigations of fluoroborane chemistry novel reactions of these compounds were discovered, which were also supported by quantum chemistry calculations. Unfortunately, none of the approaches led to our target molecules, which bear both a phosphine and a chiral oxazoline unit and could serve as a chiral ligands for metal-catalyzed asymmetric transformations.
Nevertheless, we decided to investigate possible applications of difluoroborates as reagents in nucleophilic substitution reactions and also to explore possible applications of the chiral products **Ph-108** and **MeO-108**.

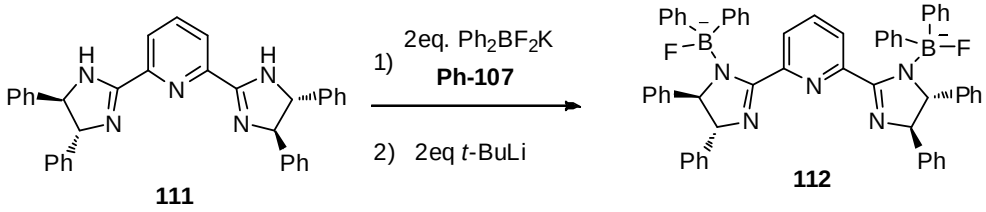
4.7.8.1 Application as synthons for zwitterionic metal complexes

Inspired by the facts that boron can form strong B-N bonds and that difluoroborates are able to react in nucleophilic substitution reactions, we decided to investigate these compounds as easily accessible precursors for the synthesis of zwitterionic compounds. *N*,*N*,*N*-Tridentate pyridinebisimidazoline (pybim) ligands looked to be good candidates for this investigation, as they had the desired imidazoline unit incorporated. These ligands were developed by M. Beller et al. in 2005 and used for the Ru-catalyzed asymmetric epoxidations of olefins.[85] The authors had prepared ligand **111**, because they could gain an additional position (on the secondary amine) for tuning their properties compared to the established chiral pyridinebisoxazoline (pybox) ligands.[86] They demonstrated this modification in several examples, substituting the secondary amine position by reaction with acid chlorides in the presence of bases such as NaH or dimethylaminopyridine. We decided to prepare this ligand and test it in the reaction with our boron reagent **Ph-107** (*Scheme 74*).



Scheme 74: Synthetic strategy for the application of **Ph-108** as a reagent in the synthesis of zwitterionic compounds.

The synthesis of **111** started from pyridine-2,6-carbodinitrile, which was converted into the corresponding bisimidate in the first step. In the next step, the bisimidate reacted with (*R,R*)-1,2-dipehenylethylene diamine and formed the final pyridinebisimidazoline ligand **111**. This ligand was then subjected to the reaction with **Ph-107**. We decided to use *tert*-butyllithium as a sterically hindered base for the deprotonation of the imidazolines (*Scheme 75*).



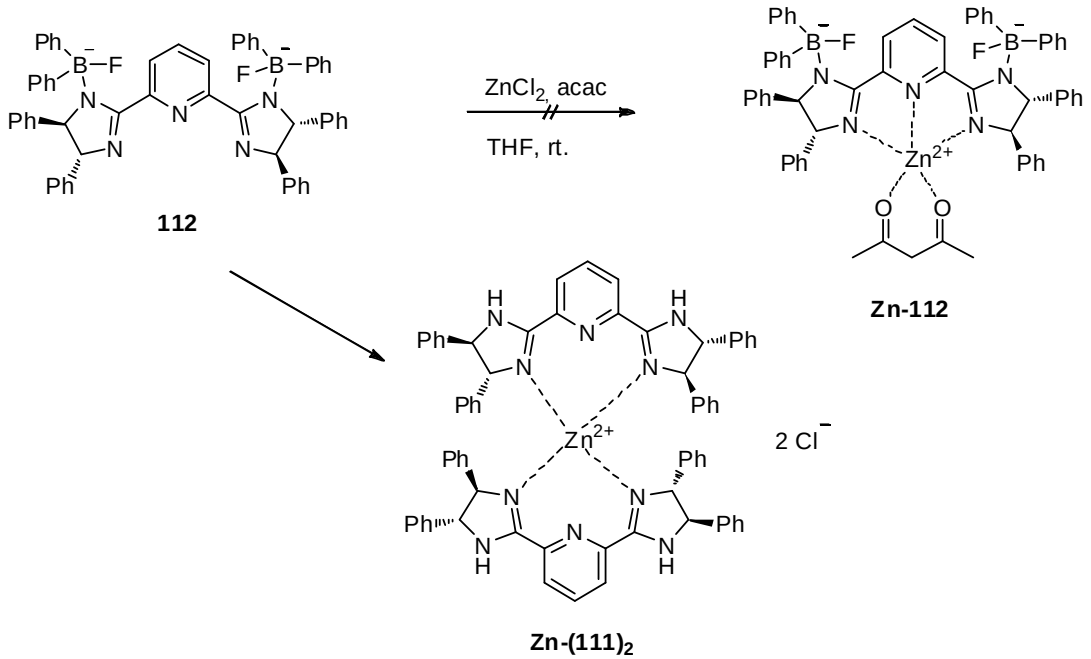
Scheme 75: Substitution reaction of potassium diphenyldifluoroborate with the pybim ligand.

THF-d_8 was used as solvent to allow for tracking of reaction progress by NMR analysis without any workup. The substitution reaction was done at -78 °C, after dissolving 1 equivalent of **111** and two equivalents of **Ph-107** at room temperature, followed by the addition of 2 equivalents of the base. At that low temperature a white precipitate was formed and completely dissolved upon warming up to room temperature. The reaction was then cooled back to -78 °C to see whether it was the product or some reaction intermediate that is insoluble at low temperature. However, when the reaction mixture was cooled down again, no

precipitation was observed. It may be that the **Ph-107** potassium salt exchanges cations with the *tert*-butyllithium present and this product may not be soluble in THF.

When the crude reaction mixture was analyzed by ^{11}B and ^{19}F NMR spectroscopy immediately after warming up, mostly starting material was observed. Therefore, the reaction was allowed to react for another 4 hours and then the NMR analysis was repeated. This time changes in the boron and phosphorus NMR spectra were already observable: the ^{11}B signal of the starting material had moved from 7,9 ppm to 2,5 ppm and the ^{11}F signal from 159,2 ppm to 171,3 ppm. Those changes in the NMR chemical shifts clearly support the formation of **112**. The ^{11}B NMR showed exclusively one tetravalent species with a different shift than the starting material, which was no longer visible in the spectrum. The full conversion of the starting material was further supported by ^{19}F NMR analysis.

As we had obtained a new compound bearing a double negative charge, it was necessary to prepare some zwitterionic complexes to separate the ligand salt **112** as a metal complex, because separation of the dianion would be significantly more difficult. Therefore Zn^{2+} was chosen as a cation to form the **Zn-112** metal complex. Since after complexation additional coordination sites on the zinc ion would remain free, an additional equivalent of acetonylacetone (acac) was added (*Scheme 76*).

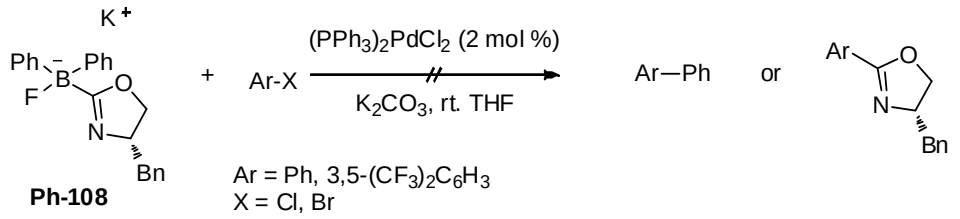


Scheme 76: Preparation of the metal complex of **112** by complexation with zinc chloride.

The resulting reaction mixture was analyzed by MALDI-MS where one signal of 1102 *Da* was exclusively observed in the positive mode with the typical zinc complex isotopic pattern. By ^{11}B and ^{19}F NMR analyses traces of **Ph-107** were observed but starting material **112** was not present at all. Based on these results, product structure **Zn-(111)$_2$** was proposed (*Scheme 76*), which is in agreement with all of the analytical observations obtained. The observed *m/z* ratio for **Zn-(111)$_2$** in the MALDI-MS corresponds to a monocationic Zn-bisligand complex. Most likely one of the imidazoline units is deprotonated. Therefore, product **112** must have decomposed during the complexation process with zinc chloride. The instability of **112** could be due to steric strain induced by the bulky $BFPh_2$ groups.
Despite this negative result, further investigations of this approach to synthesize zwitterionic metal complexes might be worth while.

4.7.8.2 Application in the Suzuki-Miyaura reaction

Potassium trifluoroborates are widely used in organometallic chemistry because they can serve as reagents in the Suzuki coupling reaction.[87] Suzuki reaction an important synthetic transformation which can be applied to a wide range of substrates. In 2010 Prof. Akira Suzuki was awarded the Nobel Prize in Chemistry for his contributions to the field of the organometallic chemistry, in which the reaction bearing his name played a significant role.
The difluoroborates discussed in this chapter were also used by Ishino et al. as reactants in palladium-catalyzed coupling reactions.[76] Because of the structural similarity of our substrate **Ph-108** to the tri- and difluroborates, where the boron atom is tetravalent and bears aromatic substituents, we decided to investigate its reactivity in the Suzuki reaction (*Scheme 77*).



Scheme 77: Possible application of the difluoroborate **Ph-108** in the Suzuki coupling reaction

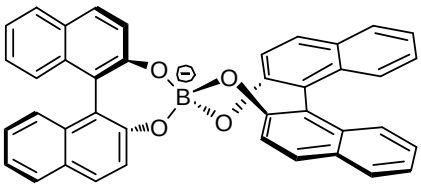
In the proposed reaction, one of the phenyl groups could be transferred to either the aryl halide or the oxazoline moiety. Which of the groups of **Ph-108** will be transferred is difficult

to predict, as there is no literature data for similar reactions available. We tested the coupling reaction under the usual conditions using $(PPh_3)_2PdCl_2$ as catalyst, potassium carbonate as the base, and THF as the reaction solvent at room temperature with simple aryl halides. However, no coupling product was observed and only starting material was recovered. We tested two different substrates, a simple chlorobenzene and a second derivative bearing electron-withdrawing CF_3 groups in order to vary the electronic properties of the aryl halide. In both cases the reaction produced none of the possible coupling products (Scheme 77).

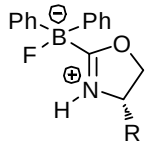
Although there was no coupling reaction observed in our investigation, there is still room for improvement of the reaction conditions, especially including polar solvents, such as dimethylformamide,[88] or alcoholic solvents,[89] or employing various palladium catalysts.

4.7.8.3 Possible application of the oxazoline-fluoroborates as chiral anions

Since we obtained compounds **Ph-108** and **MeO-108**, which have a tetravalent boron unit bearing a fluorine atom and also a chiral oxazoline backbone, in our previous investigations, we examined possible applications for these compounds. One application would be to use them as chiral anions for metal complexes to improve the selectivity of asymmetric transformations. An analogous chiral boron anion based on BINOL was used by Arndtsen et al. in a Cu-catalyzed aziridination and cyclopropanation reaction (*Figure 24*).[90]



BINOL-boronate



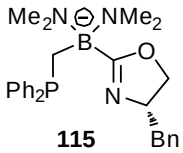
Ph-108-H

Figure 24: Comparison of structurally similar boron compounds used for asymmetric transformations

4.8 Aminoboranes as building blocks

In this work reactions of boron compounds with nitrogen-based reagents were already described. The first compound of this class was obtained when an undesired boron-nitrogen bond was formed during the synthesis of **98**. The final dimeric structure, including the tetravalent boron atom bound to the nitrogen of the oxazoline, was very stable and a B-N bond could not be broken by any of the various methods tried. Another example was the complexation of amines with chloroborane. In that case the interaction was reversible and temperature dependent. In general this type of interaction of tetravalent boron compounds with amines can be reversible or irreversible depending on the nature of the borane and the amine.[72-73]

In further investigations we decided to focus on the synthesis of trivalent boron compounds bearing nitrogen substituents. The aminoboranes obtained could be applicable to the synthesis of tetracoordinated boron compounds substituted with chiral oxazoline and phosphine to prepare *P*,*N*-ligands, which can be of potential use in asymmetric catalysis (*Figure 25*).

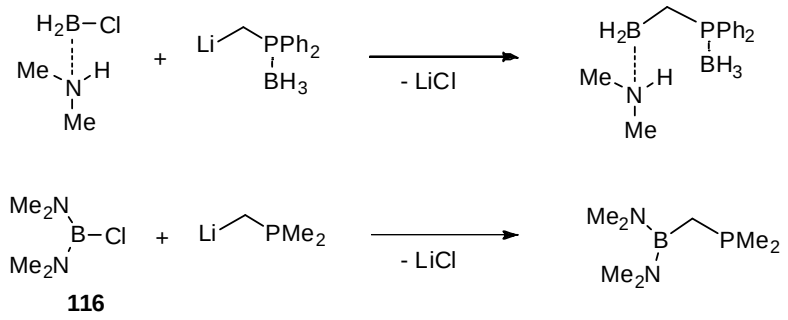


115

Figure 25: Proposed ligand structure based on the aminoborane building block

As described by Peters et al., *P*,*P* bidentate ligands are obtained by reaction of **83** with chloroboranes .[34] Analogous *N*,*N*-ligands were also developed by Peters and coworkers. [91] From our previous investigations we knew that the chloroboranes are very reactive and it is not possible to avoid double addition of two nucleophiles. Therefore, using aminoboranes as precursors, which are less reactive, might be a solution to this problem.

There are some literature examples describing the formation of boron containing phosphines as shown in *Scheme 81* with the aminoborane motif that could possibly serve us as a precursor for our intended transformations. Manners et al. described the synthesis of a borane, methylene-bridged to a BH_3-protected phosphine.[65] The synthesis uses chloroborane complexed with dimethylamine (*Scheme 78*).



116

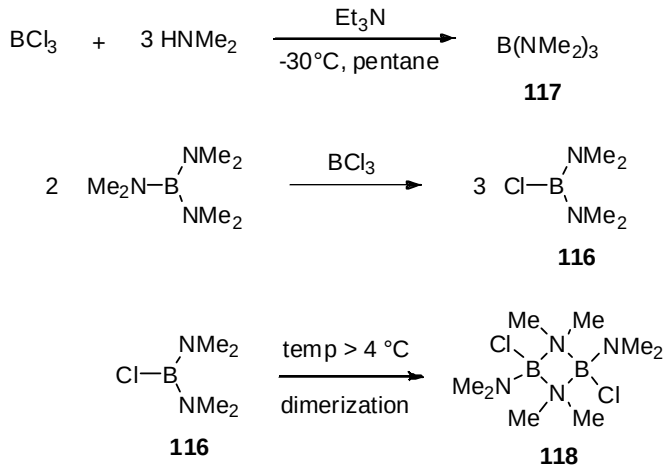
Scheme 78: Synthesis of the aminoboranes bearing phosphine function.

Another synthetic route reported by Garner et al., describing the preparation of a B-CH_2-P backbone lithium methylenedimethylphosphine and bis(dimethylamino)chloroborane **116**.[92] This product had the scaffold that we wanted use in our attempt to prepare the chiral ligand **115**.

4.8.1 Preparation of the aminochloroboranes

The preparation of the phosphine aminoborane, described by Garner et al. starts from aminochloroborane **116**. The method for preparation of this compound described by Zeiss et al. requires neat gaseous reagents, such as boron trichloride and dimethylamine.[93] Since we were not planning to use the aminochloroboranes in large quantities, we decided to optimize the synthesis of **116** for a smaller laboratory scale.

For our preparation of **116** we used a commercial solution of boron trichloride in hexanes and an ethereal solution of dimethylamine freshly prepared from dimethylamine hydrochloride. The solution of diethylamine was used in excess to completely convert the boron trichloride into tris(dimethylamino)borane **117** (*Scheme 79*).

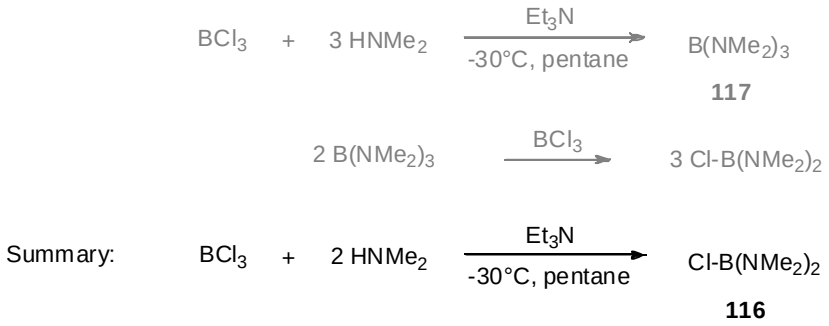


Scheme 79: Preparation of bis(dimethylamino)chloroborane from BCl_3 and Me_2NH in solution.

The triaminoborane **117** obtained could be isolated by distillation and stored. When boron trichloride was added in the proper molar ratio, another ligand exchange reaction between boron and amine took place and delivered **116**. This aminochloroborane is a colorless low boiling liquid that is highly air and moisture sensitive and hydrolyzes very rapidly. The first samples of this low boiling compound were purified by fractional distillation and turned overnight into transparent crystals. Thus, **116** must be prepared fresh from **117** for each reaction using this compound. Analysis of the sample obtained by the transformation of **116** into transparent crystals by ^{11}B NMR showed only one signal in the region expected for tetravalent boron compounds. This signal was very sharp which is not typical for boron compounds. This sharp signal was very informative, because it suggested the presence of a highly symmetric boron compound. Based on this information structure **118** was proposed; this compound is highly symmetrical and the boron is tetravalent. Dimeric compound **118** as a complex with $TiCl_4$ was previously described by Schram et al.[94]

Having identified the undesired product **118**, we wanted to avoid this dimerization process by cooling the monomeric **116** in order to avoid the dimer **118** formation. Indeed the liquid **116**, which is completely transformed into **118** overnight at room temperature, can be kept at 4 °C for months without any signs of dimerization.

With those results in hand we could update the synthesis of the **116** into a one step synthesis without the need for the two distillations of **117** and **116** (*Scheme 80*).

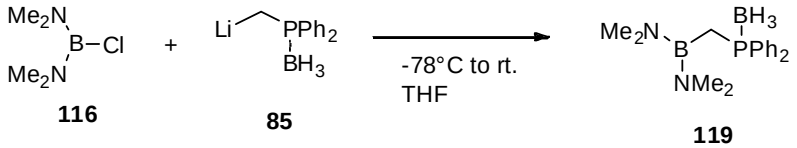


Scheme 80: Optimized bis(dimethylamino)chloroborane synthesis.

In this optimized synthesis, **116** can be prepared directly from BCl_3 and dimethylamine by mixing those reagents in the desired molar ratios and after isolation the product can be stored at low temperature for further reactions.

4.8.2 Preparation of the phosphine-aminoborane adduct

For the preparation of the desired adduct containing the B-CH_2-P backbone with **116** we combined both the synthesis of Manners[65] and Garner.[92] We then allowed the BH_3-protected phosphine **85** to react with aminochloroborane **116** at low temperature; after gradually warming up the reaction, the desired product **119** was obtained (*Scheme 81*).



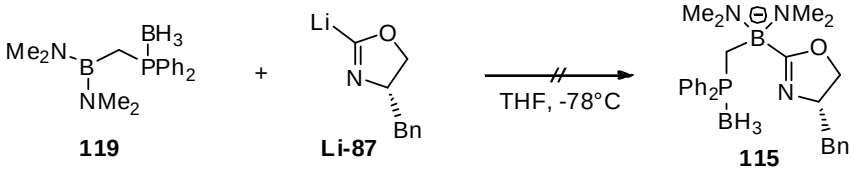
Scheme 81: Reaction of bis(dimethylamino)chloroborane with the protected phosphine **85**.

Only one boron species was observed in the ^{11}B NMR of crude reaction mixture after the reaction was complete. The crude product, after optimization of the reaction conditions, was clean and contained only the substitution product **119**. As **119** decomposes over time, we tried to develop a method for purifying samples that were not freshly prepared. Unfortunately, all

attempts to purify the sample resulted in further decomposition, so **119** was prepared fresh for all subsequent reactions.

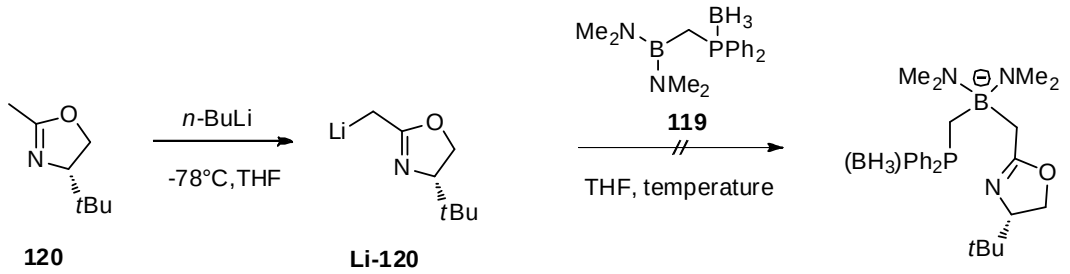
4.8.3 Reaction of the phosphine-aminoborane adduct with oxazolines

After the successful preparation of intermediate **119**, it was then subjected to reaction with oxazoline **87** to prepare the desired target molecule **115**. Therefore, the freshly prepared **116** was added at low temperature to the lithium salt of oxazoline **Li-87**, however, after stirring overnight at room temperature no reaction was observed and both reactants were detected completely unchanged (*Scheme 82*).



Scheme 82: Reaction of the aminoborane-phosphine **119** with the oxazoline **Li-87**.

Since the addition reaction didn't take place at room temperature, we decided to increase the temperature and the mixture was refluxed in THF for several hours, but only decomposition products, along with unreacted starting material, were observed. 2-methyloxazoline **120** was also used as a nucleophile. This oxazoline was readily obtained from the condensation of acetimidate hydrochloride with the corresponding aminoalcohol.[95] The acidic proton of the methyl group was easily removed by *n*-butyllithium to form **Li-120**. We added our adduct **119** at low temperature and allowed it to react overnight at room temperature (*Scheme 83*).

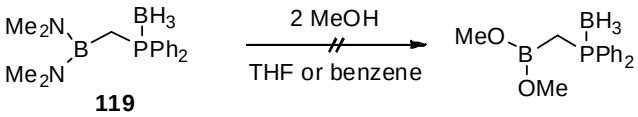


Scheme 83: Reaction of the aminoborane-phosphine **119** with the oxazoline **Li-120**.

However, no product was observed under these conditions. After reflux in THF for 48 hours, NMR spectroscopy showed only adduct **119** along with some methylphosphine **84** and BH_3-deprotected phosphine **119**. The low reactivity of the boron atom of **119** can be explained by conjugation of the nitrogen lone pairs with the boron π^* orbital, which strongly reduces the electrophilicity of the boron center.

4.8.4 Transformation of the aminoborane into the more reactive intermediates

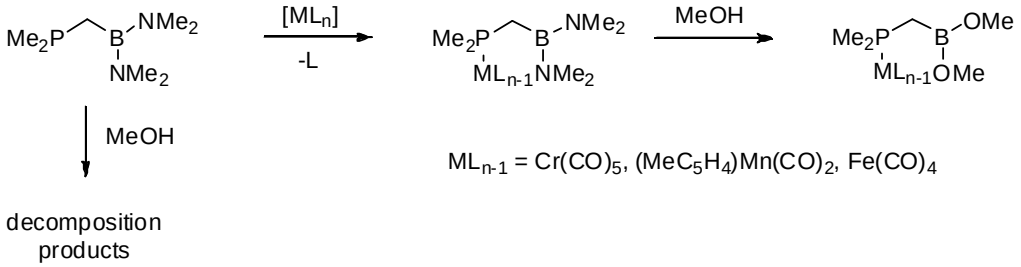
As we knew from previous results that esters of the boronic acids could be used in reactions with nucleophiles (*Scheme 23*), exchange of the dimethylamino group with alkoxy groups was attempted.[96] The alcohol of choice for this type of transformation was methanol (*Scheme 84*).



Scheme 84: Reaction of the dimethylaminoborane **119** with the methanol

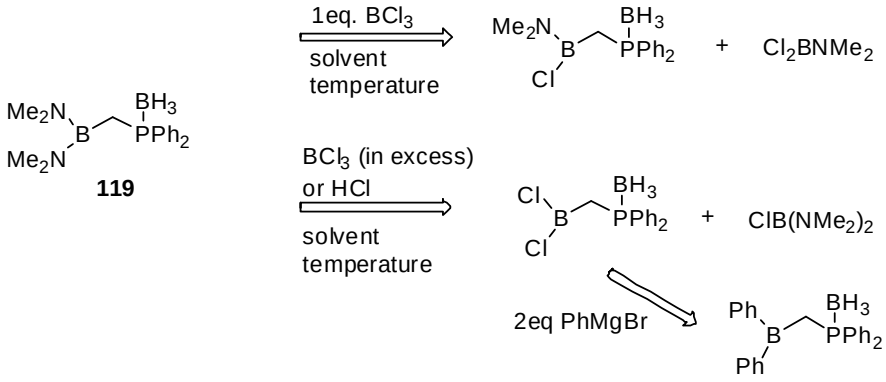
The reason for this choice was that the methylesters of boronic acids are known to be more reactive than other alky esters. When aminoborane **119** was treated with methanol in THF, a mixture of products including methylphosphine **84** was formed. This means that methanolysis of aminoborane **119** does not exclusively remove the dimethylamino groups, but also cleaves the boron carbon bond. The result obtained was practically the same when the reaction was performed in benzene instead. A mixture of decomposition products was also observed when other alcohols, such as *iso*-butanol, pinacol, or catechol, were used.

Although, the transformation of aminoboranes to boronates by reaction with alcohols seems to be a generally applicable reaction, it is probably very substrate dependent. A similar problem also experienced by the authors of the previously mentioned work using $(Me_2N)_2BCH_2PMe_2$ (*Scheme 85*).[92]



Scheme 85: Indirect conversion of aminoboranes into boronates.[92]

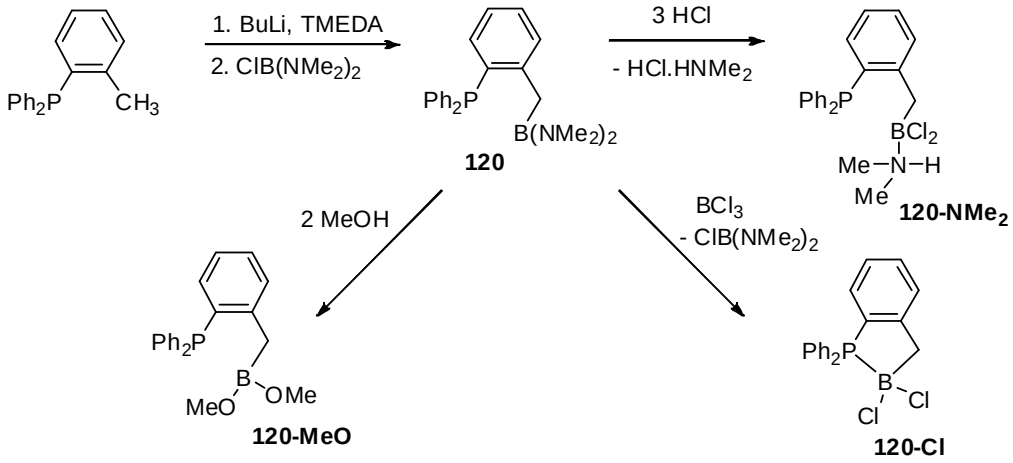
When they carried out the methanolysis directly with $(Me_2N)_2BCH_2PMe_2$ they observed only mixtures of undesired products. However, transformation to the dimethylboronate was possible when the phosphine was coordinated to a metal (*Scheme 85*). In our investigations we had thought that the electron-withdrawing phosphine BH_3 protecting group would have a similar beneficial effect as the metal. Attempts to use chloroboranes prepared from **119** as electrophiles also failed (*Scheme 86*).



Scheme 86: Postulated reactivity of the aminoborane **119** with the boron trichloride.

4.8.5 Aromatic aminoborane approach

In the previous example of a methanolysis reaction of $(Me_2N)_2BCH_2PMe_2$ from Braunschweig et al., the conversion of the aminoborane to the alkoxy derivative was only possible under certain conditions when the phosphine was coordinated to a transition metal (*Scheme 85*). In another example, also from Braunschweig, it was possible to obtain both alkoxy and chloro derivatives. These conditions differ in the reagents used for the particular transformation (*Scheme 87*).[96e]



Scheme 87: Transformation of a bis(dimethylamino)boryl group by Braunschweig et al. [96e]

The success with these transformations was likely due to the higher stability of triarylphosphines compoundes to trialkyl phosphine.[96e] Therefore, we decided to test aminoborane **120** by converting it to the boron dichloride derivative **120-Cl** with BCl_3 and then perform the intended transformation, including introduction of the phenyl substituents to the boron.

The transformation of **120-Cl** into the corresponding diphenylderivative with a Grignard reagent was possible, but the reaction mixture contained many byproducts. However, the ^{11}B and ^{31}P NMR spectra taken after the reaction still showed a coupling between boron and phosphorus, which means that B-P bond is still present. This would be a problem for our proposed introduction of another chiral substituent, because the boron is already tetracoordinated and the B-P bond is usually strong.

The other derivatives prepared by Braunschweig et al. were also considered for further transformations, but their rather difficult preparation led us to abandon this approach in our investigations.

4.8.6 Reactions of the dimetylaminoboryldichloride

The aminoboranes in our previous investigations showed that the bis(dimethylamino)boryl group is stable to the action of nucleophiles and introduction of the fourth substituent into this system is not possible. Hence we wanted to attach only one dimethylamino group to the boron

atom which would not require its removal and which would form stable trivalent boron compound **124** structurally related to the C_2-symmetrical oxazoline box ligands. There are examples in the literature which describe a tetravalent boron atom with three oxazoline substituents **123** (*Figure 26*).[97]

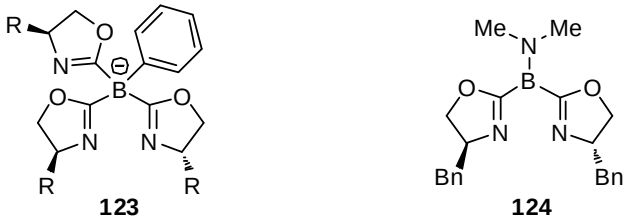
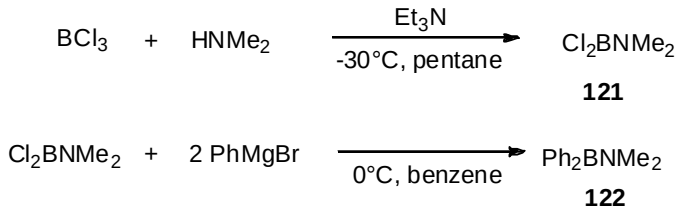


Figure 26: Structures of the tridentate oxazoline ligand **123** and the proposed structure **124**.

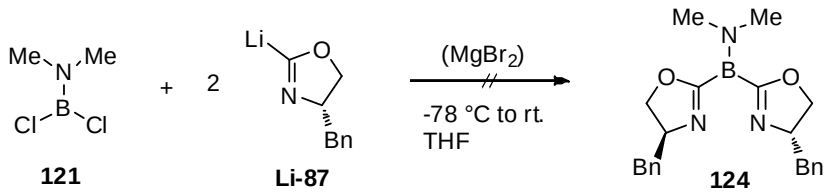
Preparation of the aminoborane **123** was proposed in analogy to the reaction used for preparation of diphenyldimethylaminoborane **122**. The first step in its synthesis is the ligand redistribution driven by the ratio of the mixture of BCl_3 and $HNMe_2$. The resulting dimethylaminoboryldichloride **121** is then converted into **122** by reaction with two equivalents of phenylmagnesium bromide (*Scheme 88*).[98].



Scheme 88: Preparation of aminodiarylboranes from corresponding chloroderivative **121**.

Aminoborane **122** can serve also as a precursor for the diphenylchloroborane[99] in a reaction with BCl_3 or for diphenylfluoroborate[53] treating it with $BF_3.Et_2O$. This route avoids the uncontrolled substitution of the organometallic reagent to the trihaloboranes by decreasing the reactivity of the boron center by electron-donating dimethylamino groups. This might be useful synthetic route for preparation of fluoroborates since direct synthesis from BF_3 is possible just for dimesitylboronfluoride.[100]

Ligands **123** were prepared from three equivalents of the lithium oxazoline and one equivalent of $PhBCl_2$, with all there substituents introduced in one reaction step.[97] In our proposed structure **124** the fourth substitution step could not take place because of the electronic effect of the dimethylamino group (*Scheme 89*).

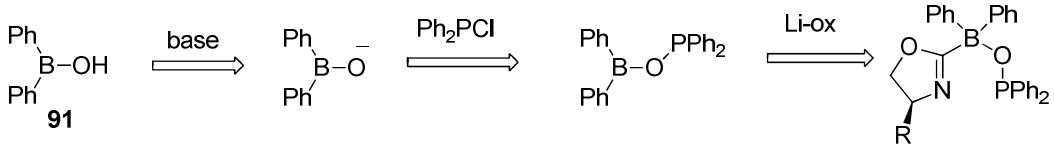


Scheme 89: Reaction of the dimetylaminoboryldichloride with the lihium oxazoline

Compound **121** was added to **Li-87** at low temperature and then stirred for several hours at room temperature, following the conditions for the preparation of **122**. The crude reaction mixture contained tetravalent boron species with an ^{11}B NMR chemical shift of 2,2 ppm. This species could not be separated and the possible structure could not be assigned in the mixture. Because of this formation of an unexpected tetravalent species, we decided to change the reaction conditions. The reaction of **121** with the phenyl Grignard reagent proceeded very cleanly and produced **122** in good yield. Therefore we thought that changing **Li-87** to the corresponding Grignard reagent via transmetallation with $MgBr_2$ might be beneficial. Unfortunately, the reaction involving the transmetallation step did not lead to the desired product either.

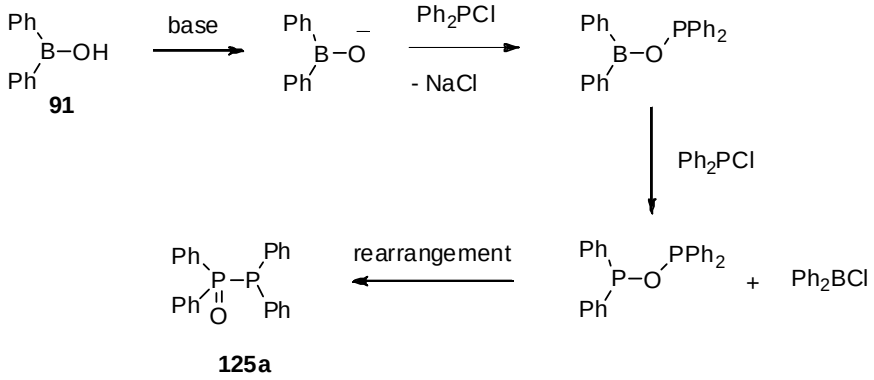
4.9 Attempts to prepare B-O-P scaffolds

In the attempts to modify the boron-phosphorus building block, the formation of a B-O-P backbone was also considered. The first step would involve the deprotonation of diphenylborinic acid, which would then react in the next step with the diphenylchlorophosphine to form the desired B-O-P backbone. This adduct can possibly react with the lithium oxazoline to form the target molecule (*Scheme 90*).



Scheme 90: Synthetic strategy using the borinic acids as building blocks for B-O-P bond formation

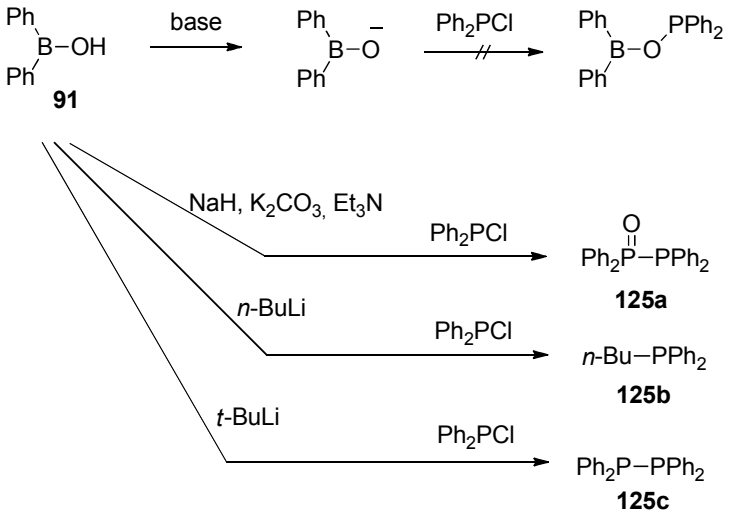
For the deprotonation of borinic acid **91**, KH was the first base examined after treatment with the diphenylchlorophosphine, the reaction mixture was analyzed by ^{31}P NMR spectroscopy. The spectrum showed two doublets with shifts of 33 ppm and -25,5 ppm and a very large coupling constant of 228 Hz. This pattern was also obtained when other bases, such as K_2CO_3 in THF or triethylamine were used. Therese signals are consistent with the diphosphine species **125a**. This product was reported to be formed in the in the reaction of Me_3SiONa with diphenylphosphine chloride.[101] In analogy with this reaction, we propose the following mechanism for the formation of **125a** in our boron-based reaction (*Scheme 91*).



Scheme 91: Proposed mechanism for the reaction of the borinic acid **91** with the diphenyl-chlorophosphine in the presence of the base.

This mechanism involves a B-O-P intermediate that undergoes an exchange reaction with the borinate in the presence of chlorophosphine, whereupon the product of this reaction rearranges into the final diphosphine **125a**.

To avoid the formation of Ph_2P-O-PPh_2 in the third step, the chlorophosphine should not be in excess and therefore should be added to the deprotonated diphenylborinic acid. For the deprotonation of the borinic acid we instead used *n*-butyllithium at low temperature. In this case there was no desired B-O-P adduct observed either, only *n*-butyldiphenylphosphine **125b** was detected. We decided to use *tert*-butyllithium as a sterically hindered base for our further investigations. In the reaction of **91** with diphenylchlorophosphine diphosphine **125c** was formed in contrast to the reaction with NaH, which led to **125a**, which had one phosphorus atom oxidized (*Scheme 92*).



Scheme 92: Teaction of the borinic acid **91** with the various bases.

Another possibility for the formation of the desired backbone could be the use of phosphine oxides, which after deprotonation can act as *O*-nucleophiles. But the conclusion from our observations is that even when the desired B-O-P intermediate is possibly formed, it either undergoes undesired rearrangements or other undesired products are being formed during the reaction.

Chapter 5

NeoPHOX ligands in asymmetric catalysis

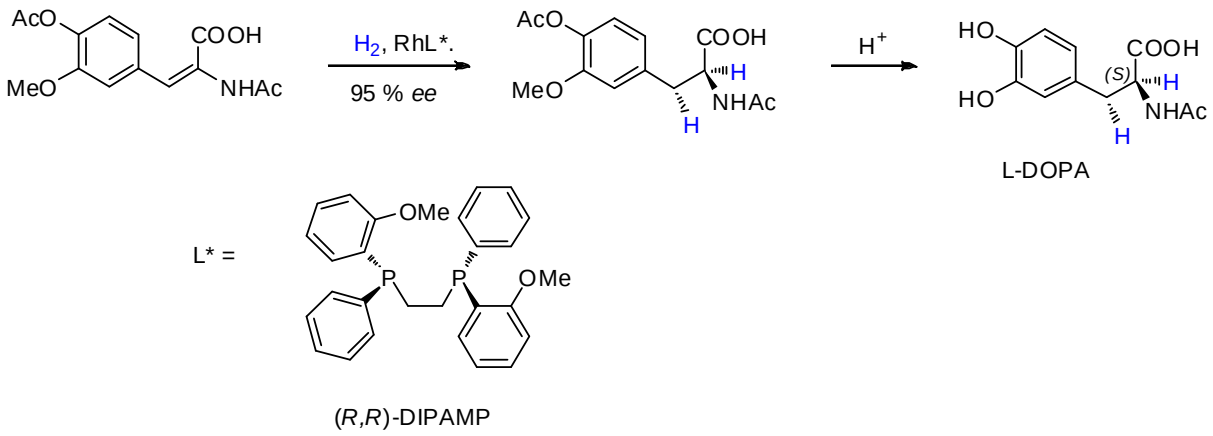
5. NeoPHOX ligands in asymmetric catalysis

5.1 Asymmetric hydrogenation – Introduction

Asymmetric hydrogenation became an important part of the field of enantioselective transformations in the early 1970s.[102] The popularity of the method arose with the first industrial application of asymmetric hydrogenation by Monsanto for the preparation of L-DOPA, which is a chemical substance widely used in medicinal applications as a prodrug of the neurotransmitters dopamine, noradrenaline, and adrenaline. This precursor is used because dopamine itself cannot pass the hematoencephalic barrier and therefore it is delivered as L-DOPA, which then undergoes certain biological transformations that deliver the desired dopamine molecule.[103] The effects of increased dopamine levels can be used in various applications, for example, for treatment of the Parkinson's disease.

The process developed by Monsanto was initially inspired by the Wilkinson rhodium catalyst, which was the first of its kind that could effectively catalyze the hydrogenation of olefins in a homogenous process.[104] Then new monodentate chiral phosphine ligands which replaced triphenylphosphine in the Wilkinson catalyst were developed by Knowles in Monsanto. Bidentate ligands, which were much more effective than their monodentate analogs, were also developed. By using the DIPAMP ligand in the asymmetric hydrogenation reaction, the process was improved to 95 % *ee* and was immediately turned into a commercial industrial process with high efficiency (*Scheme 93*).

This catalytic synthetic approach opened a new area for the discovery of new chiral ligands for asymmetric transformations. Until that time, various methods for the separation of racemic mixtures, mainly based on the co-crystallization of enantiomers with some chiral agent, were used to obtain enantiopure compounds. These methods were far less effective than the catalytic process, because a theoretical maximum of 50% yield can be obtained during the separation of the enantiomers from the racemic mixture, which makes the whole process uneconomical.



Scheme 93: Industrial process by Monsanto using a chiral phosphine ligand in a homogenous hydrogenation reaction for the preparation of L-DOPA.

Asymmetric hydrogenation is still a widely used industrial process for the preparation of optically active compounds, mainly due to the atom economy, very high enantioselectivities low catalyst loadings, and high turnover numbers with usually quantitative yields that this method provides.[105] The chiral Rh and Ru complexes that are used in the hydrogenation reactions still have some limits, because, in order to achieve high enantioselectivities, the presence of a coordinating group in the substrate is necessary. Later on in the group of Professor Pfaltz, new chiral catalyst based on iridium that can reach high enantioselectivities in the hydrogenation of unfunctionalized trisubstituted or even tetrasubstituted olefins, were developed.[106]

The development of new chiral catalysts for homogenous asymmetric hydrogenation is still in progress in our group, in an effort to also allow for the hydrogenation of various olefins for which the original systems were ineffective.

5.2 PHOX ligands

In the early 1990s, a new class of highly selective ligands was developed independently in the laboratories of Helmchen, Pfaltz, and Williams.[107] These ligands were bidentate and they combined the concept of the widely used C_2-symmetrical bis(oxazolines) ligands[15-16, 18, 29, 31, 108] with the very effective bis(phosphine) ligands[109] used in asymmetric hydrogenation (*Figure 27*). They were named phosphinooxazolines (abbr. PHOX) due to the presence of the phosphine and oxazoline ligand within one unit. They extended the possibilities in field of metal-catalyzed asymmetric transformations for many reactions that were not selective with the known systems.

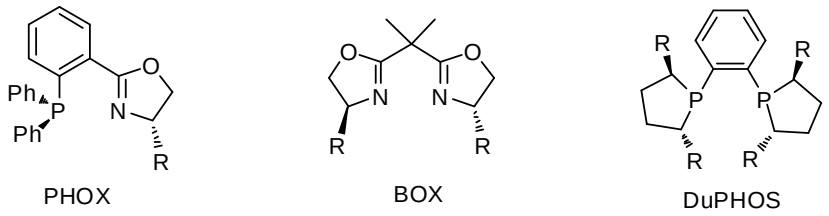
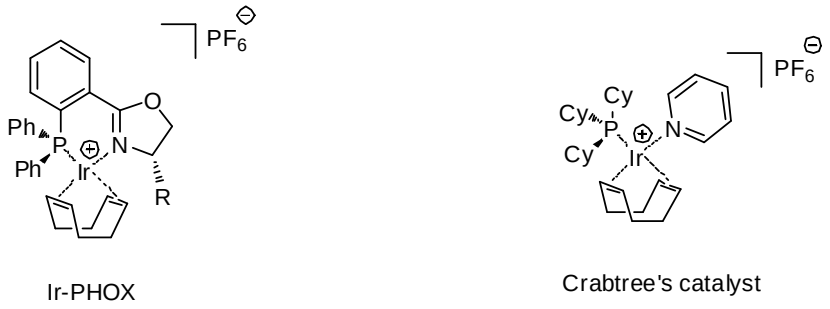


Figure 27: Phosphinooxazoline ligands (PHOX) and examples of related BOX and DuPHOS ligands.

Those P,N-ligands were originally designed for the asymmetric palladium-catalyzed allylic substitution, where they were shown to be very efficient in terms of reactivity and selectivity. Since the parent ligands were also used in various metal-catalyzed asymmetric transformations, over time researchers have found a wide range of possible applications for phosphinooxazoline ligands in the field of asymmetric catalysis.[110]

5.2.1 *Phosphinooxazoline ligands in the Iridium-catalyzed hydrogenation reactions*

The use of P,N ligands in iridium-catalyzed asymmetric hydrogenation was originally inspired by Crabtree's catalyst $[(Cy_3P)(pyridine)Ir(COD)]PF_6$, which consists of two monodentate ligands, such as phosphine and pyridine, and which was effective for the hydrogenation of olefins.[111] Therefore an analogous catalyst based on the PHOX ligand was designed that bears the chiral information in the oxazoline moiety and is therefore applicable for an asymmetric version of homogenous hydrogenation reactions (*Figure 28*).

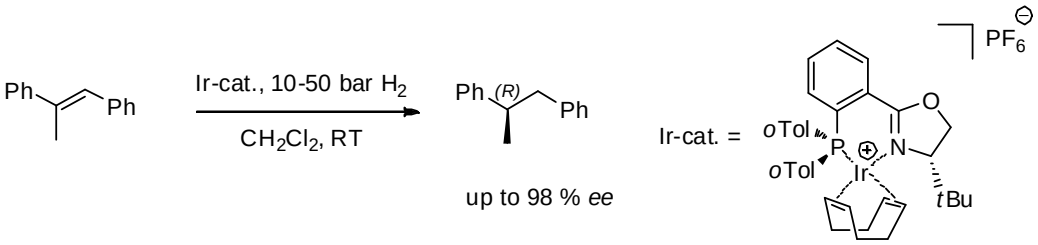


Ir-PHOX

Crabtree's catalyst

Figure 28: Comparison of Ir-PHOX with Crabtree's catalyst.

In an initial study, this Ir-PHOX was tested on a standard hydrogenation substrate, (*E*)-1,2-diphenyl-1-propene. In this hydrogenation reaction of an olefin lacking coordinating groups, it exhibited very high enantioselectivity (*Scheme 94*).



Scheme 94: Ir-PHOX in the asymmetric hydrogenation of an unfunctionalized olefin.

Even though the enantioselectivities using the chiral iridium PHOX catalyst were excellent, the turnover numbers were quite low. In order to avoid this undesired behavior, the stability of the active catalytic species was investigated and it was found that Ir-PHOX undergoes the same deactivation process[112] as Crabtree's catalyst, in which a catalytically inactive trinuclear species is formed.[111] The solution to the deactivation of the catalyst was later found by Andrew Lightfoot in our group. After testing various conditions that could possibly have an impact on the activity of the iridium catalyst, it was found that the anion of the cationic iridium catalyst plays a significant role in the deactivation process. When a weakly coordinating anion such as tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BAr_F) was used, the problem of the formation of the trinuclear species was avoided. This could be explained by the non-interfering behavior of the BAr_F anion which did not slow down the crucial step of the olefin insertion into the iridium-hydride bond as it was shown in kinetic studies of these complexes.[113] In contrast, for complexation with $PF_6^{(-)}$ or $BF_4^{(-)}$ as anions, which bind more

strongly to the Ir center or form tighter ion pairs, the insertion step was slower. This interesting observation also led us to investigate zwitterionic metal complexes, which would provide us with a direct comparison of the built-in anion with the ion pair situation. Their preparation was extensively studied in the previous chapter dealing with boron compounds, and it was also previously investigated by Clement Mazet, Valentin Kohler, and Axel Franzke.[60] The following chapter will be focused on the preparation of new chiral phosphinooxazoline ligands.

5.3 NeoPHOX ligands - Introduction

Since the development of the first chiral P,N ligands in the Pfaltz group, this field was extensively studied in order to prepare new ligands that would have the desired properties, and which would be widely applicable. In context with the development of chiral hydrogenation catalysts several classes of new P,N ligands were prepared and applied to a broad range of olefins, resulting in high selectivities. In order to satisfy the needs of potential industrial applications, it is necessary to not only reach high enantioselectivities, but also to have low catalyst loadings, in order to produce an economical process.

The synthesis of a new class of chiral phosphinooxazoline ligands called NeoPHOX was described by Marcus Schrems in our group in 2009.[114] The structural motif of the new ligands was inspired by the previously prepared P,N ligands, which were successfully applied in the iridium-catalyzed asymmetric hydrogenation of olefins (*Figure 29*).

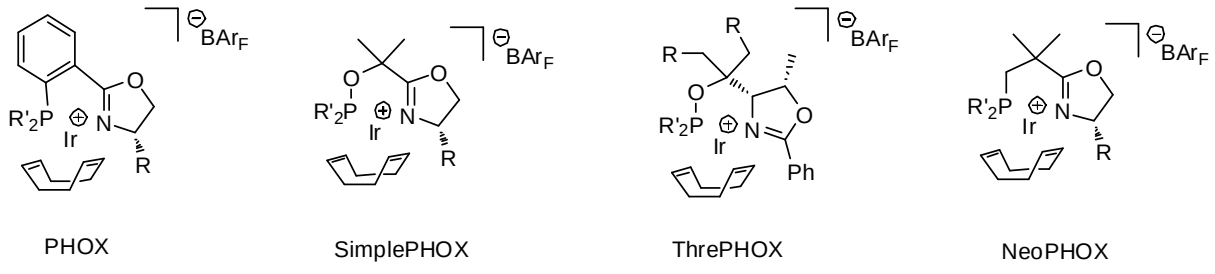
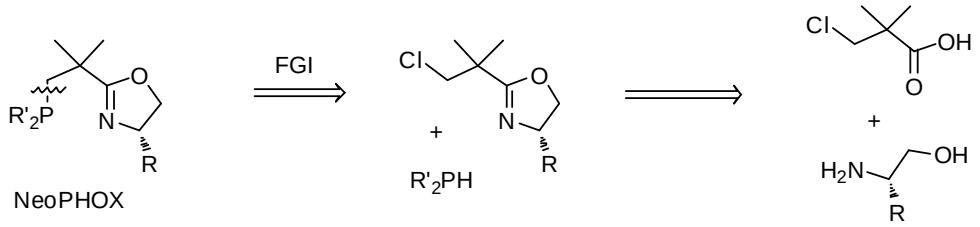


Figure 29: Structural motifs of different phosphinooxazoline ligands.

5.3.1 *Preparation of NeoPHOX ligands*

The retrosynthetic analysis of NeoPHOX ligands was based on the carbon-phosphorous bond disconnection in order to combine the phosphine and oxazoline synthons.[115] By further disconnection, a chiral aminoalcohol and a corresponding carboxylic acid are obtained as the common precursors of the oxazoline ring (*Scheme 95*).



Scheme 95: Retrosynthetic analysis for the preparation of NeoPHOX ligands.

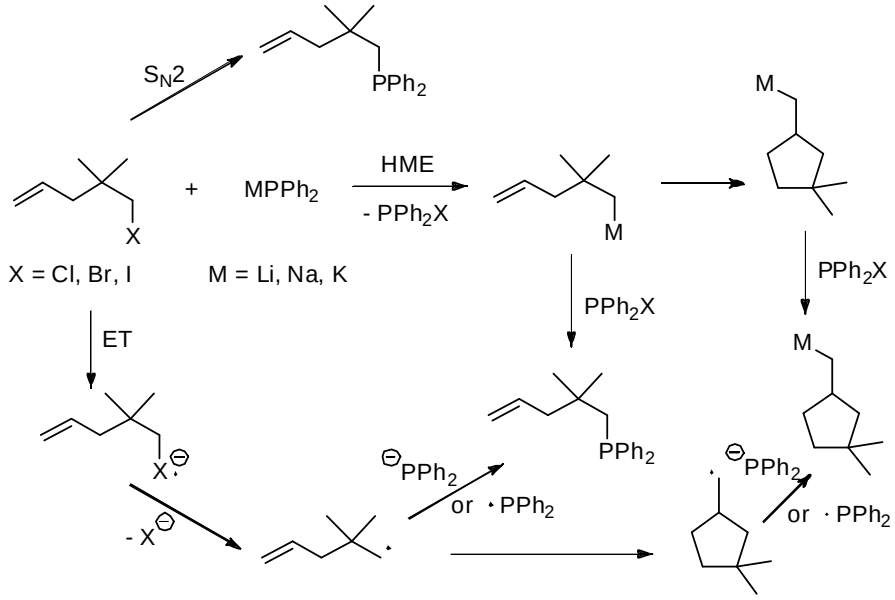
The second step of the retrosynthetic analysis, the disconnection of the oxazoline ring, is a trivial step from a synthetic viewpoint, as oxazoline formation from these precursors has been well established. However, the functional group interconversion (FGI) where the phosphine and chloro-oxazoline should react in order to deliver the target NeoPHOX ligand is not so obvious.

The final step requires a substitution reaction on a neopentyl system, which is the problematic part. In the case of a substitution reaction via an S_N1 mechanism, the formation of 1,2 rearrangement reaction products (Wagner-Meerwein rearrangement) could be expected, in order to stabilize the cation generated after the chlorine dissociation.[116]

A second mechanism possible would be an S_N2 reaction, which, in the case of a neopentyl system, is disfavored and if it does take place then it is usually very slow. However examples of the reaction of neopentyl halides with phosphines have been described by several authors and shown to proceed via a radical mechanism.[117]

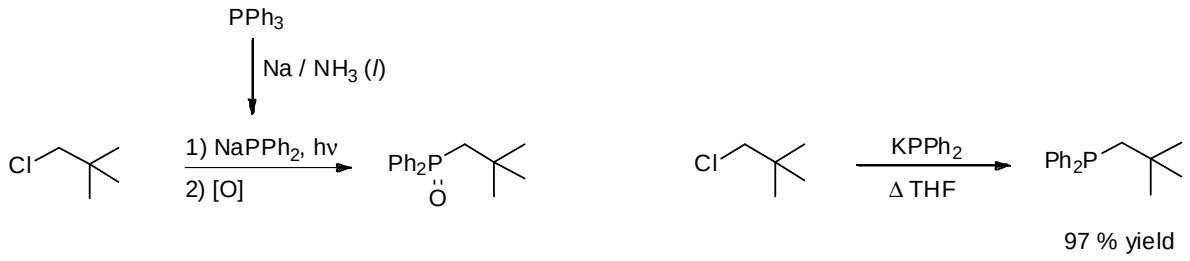
Ashby et al. investigated the reactivity of the neopentyl halide system with various metal diphenylphosphides (*Scheme 96*). They found that the reaction outcome depends on both the structure of the neopentyl halide and the nature of the phosphide salt. To conclude their observation, the SET mechanism is favored in case of the neopentyl iodide, where the reaction is complete within one minute, which is not in agreement with the S_N2 mechanism, which would be expected to be very slow. Also, when neopentyl iodide was used, a cyclic side product was observed, a result which cannot be explained by a simple S_N2 mechanism. In

contrast, the cyclic side product was not observed in the reaction using neopentyl bromide or chloride, and these reactions were also much slower than the analogous reaction with neopentyl iodide. The probability of a SET mechanism for the reaction with neopentyl iodide or bromide with $MPPh_2$ follows the order K > Na > Li. A halogen-metal exchange (HME) does not seem to play a role in this reaction.[117b]



Scheme 96: Plausible mechanism for the phosphide reaction with a neopentyl system by Ashby.[117b]

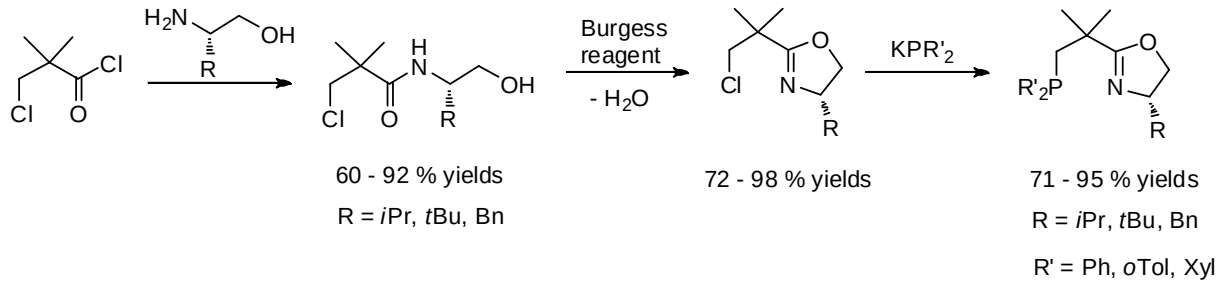
As a model system for the reaction planned fo the synthesis of NeoPHOX ligands, the reaction of neopentyl chloride in tetrahydrofuran was studied by Marcus Schrems[114] and compared to compare the results obtained by Rossi et al. in liquid ammonia (*Scheme 97*).[117a] The reaction in THF was promoted by heat, whereas the reaction in ammonia was stimulated by UV irradiation and followed by an oxidative workup to obtain the substitution products.



Scheme 97: Reaction of neopentyl chloride with diphenylphosphide under different reaction conditions by Rossi[117a] and Schrems.[114]

Marcus Schrems found that the reaction proceeds without photoactivation with UV light and at elevated temperature delivers the desired substitution product in good yield.

These reaction conditions were then applied to the ligand synthesis. In the first step, the amide was formed from 3-chloropivaloyl chloride and the corresponding chiral aminoalcohol. In the second step, a standard ring oxazoline closure starting from the amide using the Burgess reagent[118] was used for the dehydration step.[119] The crucial nucleophilic substitution proceeded well and afforded the desired NeoPHOX ligands in good yields (*Scheme 98*).



Scheme 98: Synthesis of 1st generation NeoPHOX ligands by Marcus Schrems.[115]

The synthesis of new chiral P,N ligands could be done in three steps from readily available starting materials and all steps of the synthesis provide products in high yields. The final phosphinooxazoline ligands were stable in air, without any significant oxidation of the phosphine even after several months of storage. The free ligands were then complexed with $[Ir(COD)Cl]_2$ and tested in the asymmetric hydrogenation of selected olefins (*Figure 30*).[115]

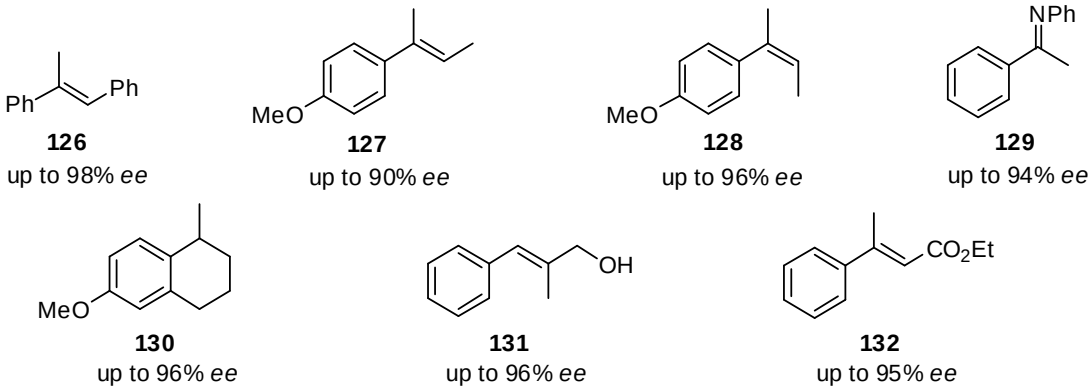


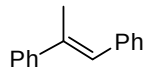
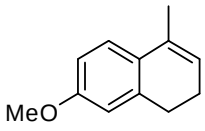
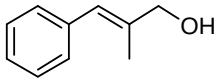
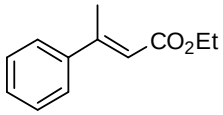
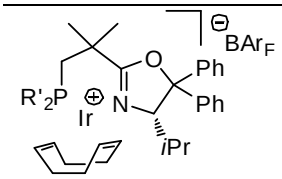
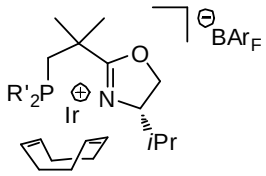
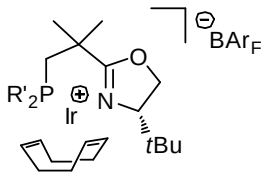
Figure 30: Enantioselectivities of the NeoPHOX iridium complexes in asymmetric hydrogenation reactions with selected substrates.

In the hydrogenation of a series of standard substrates the enantioselectivities were 90% *ee* or higher in all cases. With such high enantioselectivities on for a broad substrate range the NeoPHOX ligands outperform many related phosphinooxazoline ligands. Therefore, the new NeoPHOX ligands have two important advantages: they are easily accessible in a three step synthesis from commercially available starting materials, and the results achieved in the asymmetric hydrogenations were excellent. However, there is still one aspect that could be improved: the cost of the starting materials. The downside of the most selective phosphinooxazoline ligands is that they are almost exclusively derived from the amino acid *tert*-leucine which is very expensive. In this regard, several modifications of the NeoPHOX backbone were done by Marcus Schrems in order to decrease the final cost of these very efficient chiral ligands (*Figure 31*).

Figure 31: Employing L-valine as a starting material plus C5 modification on the oxazoline and a price comparison with the amino acid *tert*-leucine.

The initial idea was to introduce sterically demanding substituents into the position C5 of the oxazoline in order to balance the loss of steric hindrance incurred when replacing the *tert*-butyl group of the *tert*-leucine with the isopropyl group of the valine. The difference in cost of the primary starting material for the NeoPHOX ligand preparation would be almost 40 times lower in the case of valine. The results of the hydrogenation screening using the valine-based NeoPHOX ligand are summarized in the *Table 10*.[114]

Table 10: The C5 modified NeoPHOX ligand derived from L-valine compared to the previously tested NeoPHOX ligands.[114]

	 **126**	 **130**	 **131**	 **132**
	19% *ee* (*R*) 93% yield	35% *ee* (*S*) >99% yield	84% ee (–) >99% yield	63% *ee* (*R*) 41% yield
	74% *ee* (*R*) >99% yield	53% *ee* (*S*) 89% yield	88% ee (–) >99% yield	85% *ee* (*R*) >99% yield
	97% *ee* (*R*) >99% yield	92% *ee* (*S*) >99% yield	83% ee (–) >99% yield	95% *ee* (*R*) >99% yield

Reaction conditions: 50 bar, 2h, 1mol% catalyst, 0,1mmol substrate, 0,5 mL CH_2Cl_2.

From the results of the hydrogenation screening it can be seen that changing the amino acid source from L-*tert*-leucine to L-valine caused a significant drop in enantioselectivities. When sterically demanding phenyl substituents were introduced into the C5 position of the oxazoline, the drop in enantioselectivity was even higher. Therefore, it was concluded that modification of the NeoPHOX structure is quite sensitive to conformational changes in the oxazoline ring and that this modification cannot be used to prepare a selective, but the significantly cheaper ligand.

5.4 2nd Generation NeoPHOX ligands

Due to the unsuccessful attempts to prepare NeoPHOX ligands starting from the cheaper amino acid L-valine,[114] we proposed another modification involving the amino acids L-threonine and L-serine as starting materials. The chiral amino acid serine was used by Axel Franzke for modification of the PHOX ligands.[120] Promising results were obtained and so we decided evaluate both L-serine and L-threonine as starting materials with the goal of maintaining the selectivity attained by the most effective *tert*-leucine NeoPHOX derivatives but employing a significantly cheaper precursors.

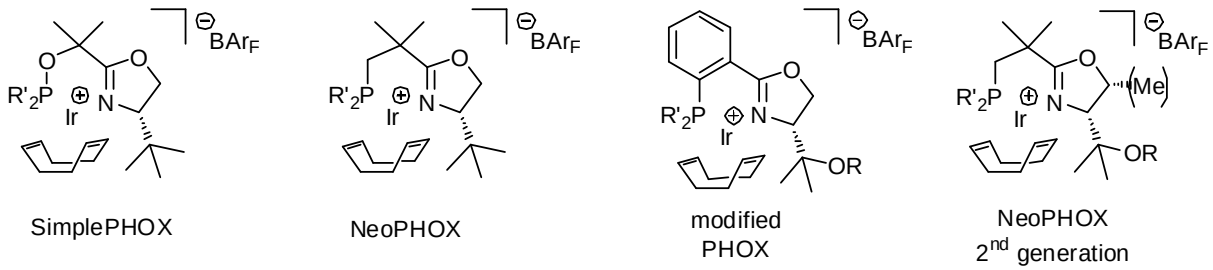
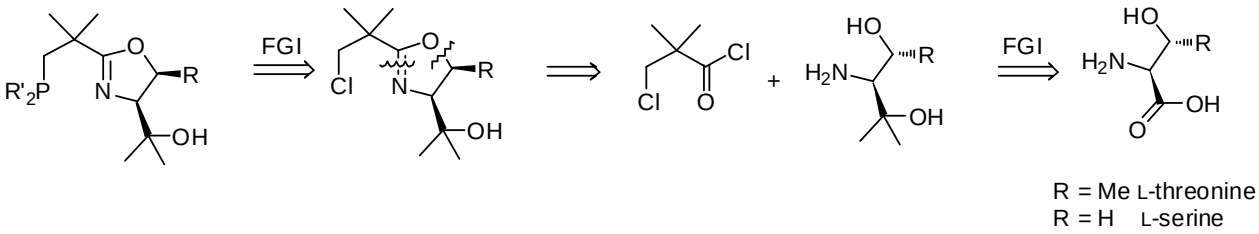


Figure 32: Comparison of the phosphinooxazoline ligands with the structural motifs implemented in the 2nd generation NeoPHOX ligands.

Structural motifs of several ligands were considered while designing the second generation NeoPHOX ligands (*Figure 32*). The basic idea behind the ligand design was to leave the neopentyl backbone interconnecting the phosphine and the oxazoline moieties unchanged because any changes in this part of the ligand would probably affect the geometry of the 6-membered iridacycle. The geometry of the metallacycle is one of the most important factors, because this part of the catalyst is the closest to the reaction center. The second most important factor for stereocontrol through catalyst-substrate interaction is the presence of a adjacent sterically demanding group, which helps to restrict the geometry of the transition states.

5.4.1 *Retrosynthetic analysis*

The first FGI transformation and the second step disconnection of the oxazoline are analogous to those used for the 1st generation NeoPHOX ligands. These transformations will also include the same synthetic transformations: oxazoline closure and the neopentyl chloride substitution reaction with the diarylphosphide (*Scheme 99*).

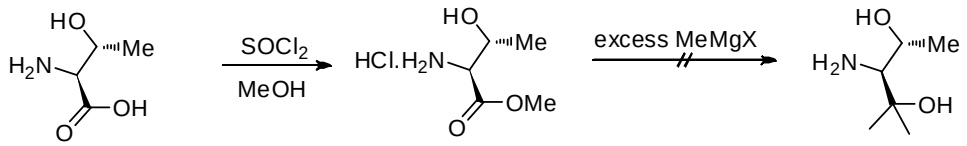


Scheme 99: Retrosynthetic analysis of the 2nd generation NeoPHOX ligands.

In the next retrosynthetic transformation the bulky tertiary alcohol substituent originates from the carbonyl group of L-threonine and L-serine.

5.4.2 *Synthesis of the threonine-derived NeoPHOX ligands*

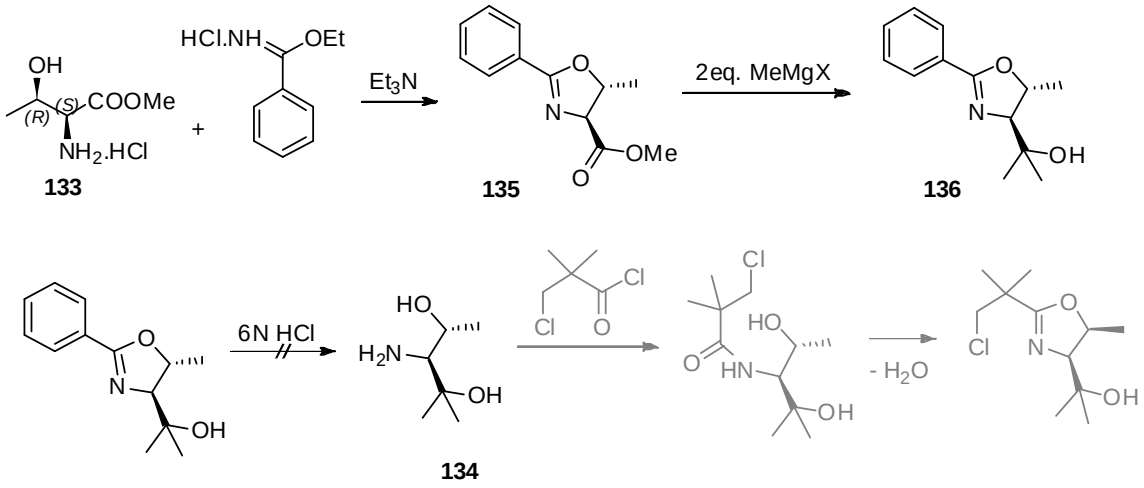
The obvious first step of the synthesis a threonine-derived NeoPHOX ligand would be the transformation of L-threonine into the methylester **133**. The ester can then be treated with methyl Grignard reagent to deliver aminoalcohol **134**, which would be the reagent of choice for the condensation with 3-chloropivaloyl chloride (*Scheme 100*).



Scheme 100: Preparation of chiral aminoalcohol **134** via direct reaction of methylester **133** with a methyl Grignard reagent.

The direct transformation of ester **133** with an excess of various methyl Grignard reagents under different reaction conditions did not lead to desired aminoalcohol **134**, only mixtures of unidentified products were obtained.

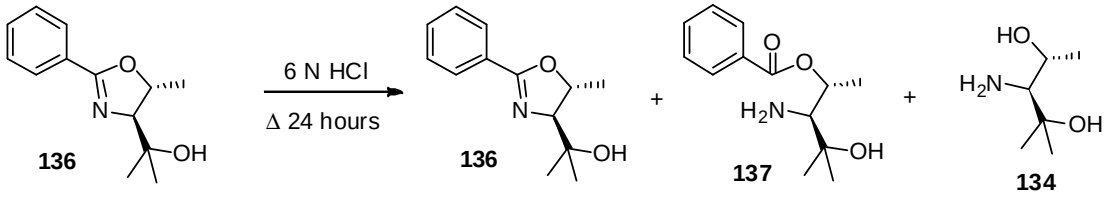
This result can be explained by the formation of unreactive intermediates by deprotonation of the amido and alcohol functions. Therefore the alcohol and amino groups were protected by introduction of an oxazoline ring (*Scheme 101*).



Scheme 101: Synthetic strategy for NeoPHOX ligand preparation involving temporary oxazoline ring formation in order to prepare starting aminoalcohol **134**.

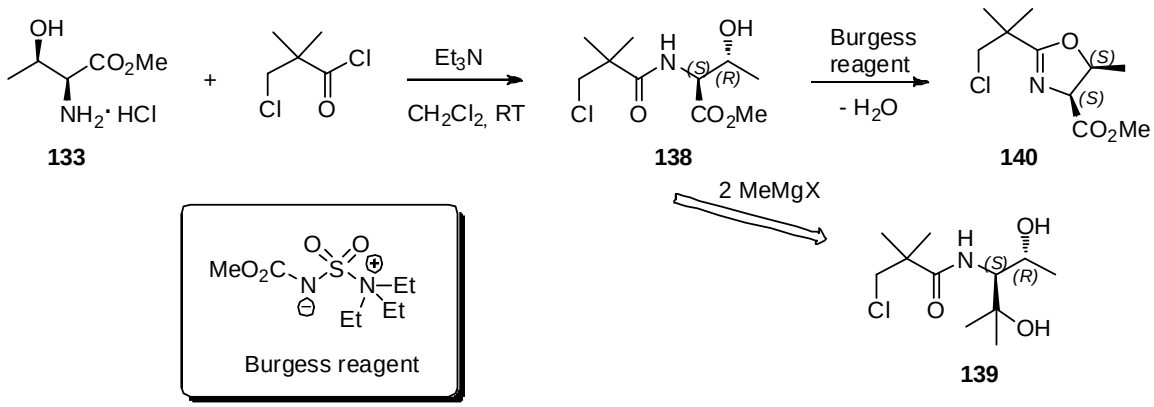
This synthetic strategy was previously used by Gisela Umbricht in our group to obtain a serine-derived tertiary alcohol analogous to aminoalcohol **134** for the preparation of BOX ligands.[121] In our case, protection of the threonine methylester **133** proceeded very cleanly and **135** was delivered in high yield The following transformation with two equivalents of the methyl Grignard reagent proceeded also well.

In the case of the serine derivative, the desired aminoalcohol was readily obtained by hydrolysis with aqueous acid.[121] However, in the case of the threonine derivative, a mixture of partially hydrolyzed oxazoline **137**, starting material **136**, and also the desired aminoalcohol **134** was obtained (*Scheme 102*).



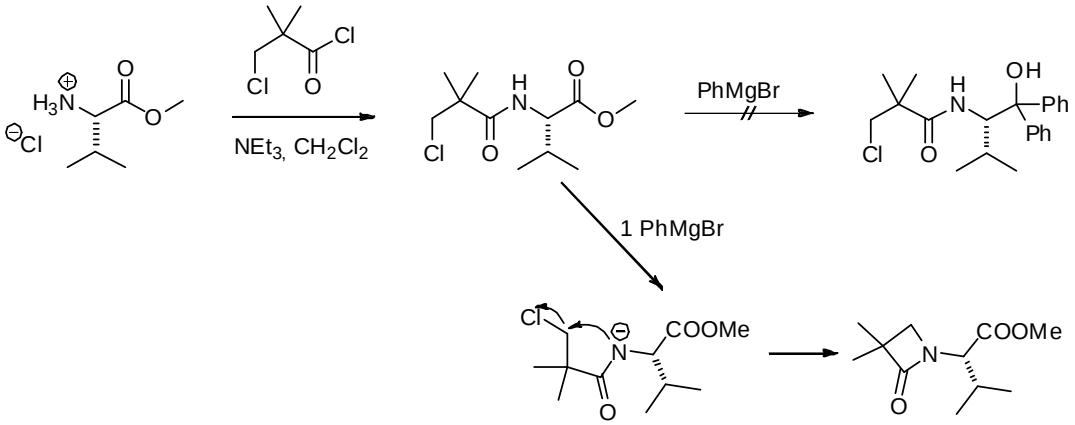
Scheme 102: Acidic hydrolysis of the threonine-derived phenyloxazoline **136** with hydrochloric acid.

In the case of threonine derivative **136**, the stability of the oxazoline ring towards acidic conditions was much higher compared to the analogous serine derivative and it was not possible to obtain the desired aminoalcohol **134**, even after applying harsh reaction conditions, such as elevated temperature, or extended reaction time. Therefore it was necessary to reconsider the synthetic strategy (*Scheme 103*).



Scheme 103: Revisited synthetic strategy for the preparation of a threonine-based NeoPHOX ligand.

In the alternative strategy shown in *Scheme 106*, amide **138** is formed from 3-chloropivaloyl chloride and threonine methylester **133** in the first step. Via this reaction the amide **138** was obtained in 96% yield. We had two options for continuing the synthesis: either to achieve the oxazoline cyclization first with the Burgess reagent, or to form the tertiary alcohol from the methylester of **138**. The second option, which would lead to **139**, was not performed because a similar transformation of the amide was unsuccessfully attempted by Marcus Schrems in the development of the C5-disubstituted NeoPHOX ligand synthesis (*Scheme 104*).



Scheme 104: Undesired 4-membered aza-lactone formation by Schrems.[114]

In this reaction, all of the amide was consumed in an undesired cyclization reaction of the deprotonated amide and therefore no tertiary alcohol could be obtained.

Thus the first option was chosen and oxazoline **140** was successfully prepared via the cyclization protocol using the Burgess reagent. There are three electrophilic centers in the molecule, the ester group, the oxazoline π-system and the C-Cl bond. To get an estimate at the reactivity order of these three centers quantum chemical calculations were carried out. In nucleophilic substitution the primary interaction occurs between the HOMO orbital of the nucleophile and the LUMO orbital of the electrophile. Therefore the orbital analysis of oxazoline **140** in its optimized geometry was calculated using NLMO analysis[79] (*Figure 33*).

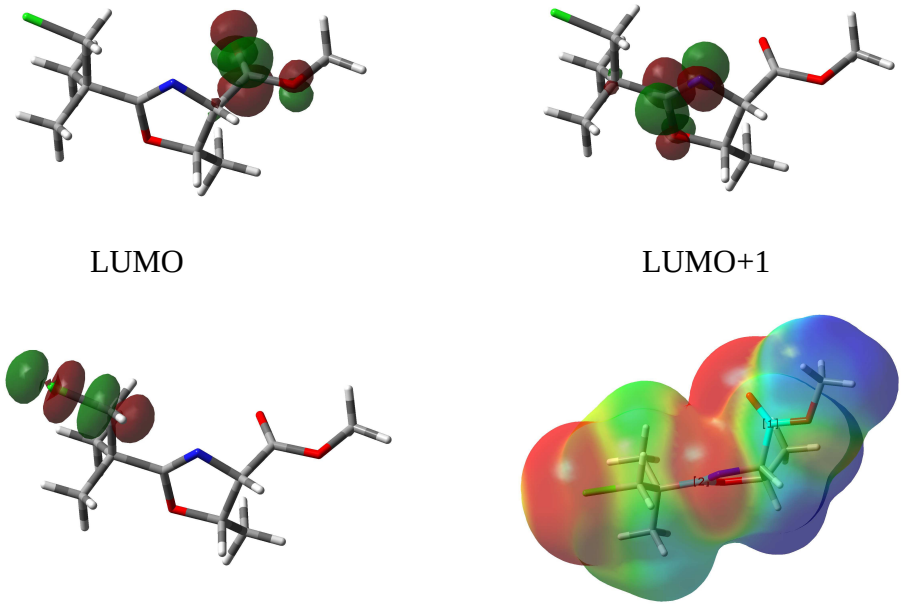
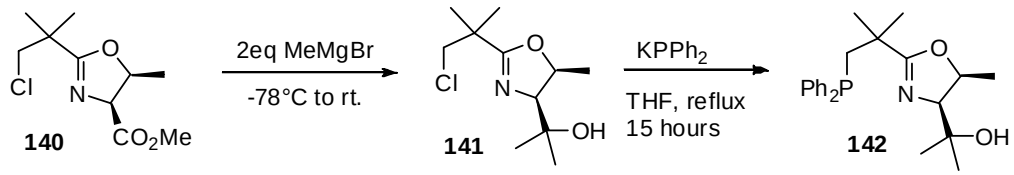


Figure 33: Natural Localized Molecular Orbital analysis and Molecular Electrostatic Potential (MEP) map by ChelpG calculated in Gaussian 09, B3LYP/6-311+g(d,p) for oxazoline **140**.

The results show that the LUMO orbital is located on the carbonyl group of the methylester function, which also exhibits the lowest electron density of the analyzed reaction centers. In the other pictures the LUMO+1 and LUMO+2 orbitals are displayed as well. The energy order is retained after the transformation of the methylester into tertiary alcohol **141**, but due to the electron density distribution in the molecule the next most reactive center is placed on the LUMO+2, which is the C-Cl σ* orbital that will react further with another nucleophile.

Taking into an account the results from computer modeling, the transformation of the ester function of the oxazoline **140** was preferentially selected for the next step in order to successfully complete synthesis of the threonine NeoPHOX ligand. With respect to the possible undesired interaction of neopentyl chloride with the methyl Grignard, the addition was performed at -78 °C, which was expected to still be a sufficient temperature for the reaction with the carbonyl group (*Scheme 105*).

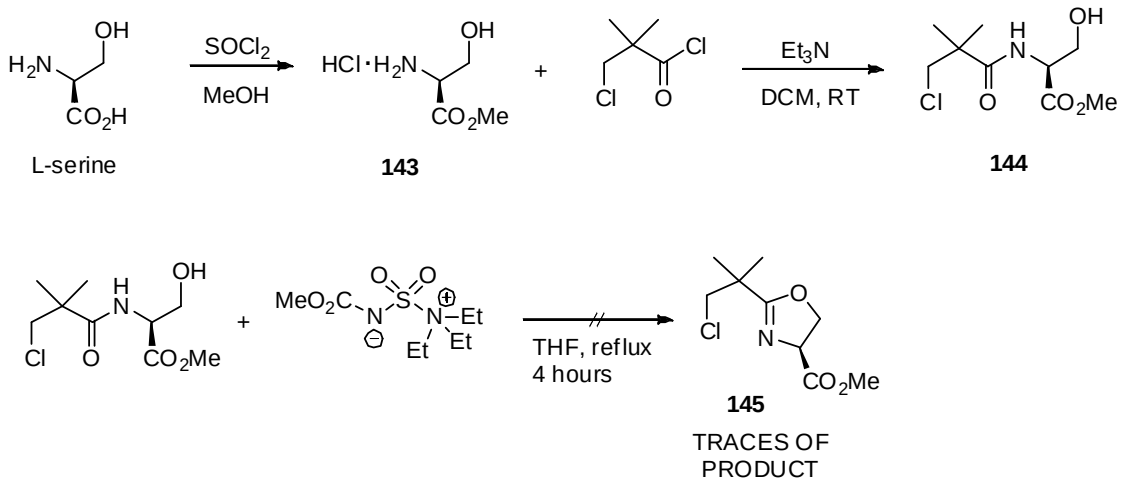


Scheme 105: Transformation of the methylester of **140** into a tertiary alcohol followed by the incorporation of diphenylphosphide

This reaction sequence proceeded as planned and the desired oxazoline **141** bearing a tertiary alcohol moiety could be obtained in 80% yield. The obtained oxazoline **141** was then subsequently transformed into the phosphinooxazoline ligand **142** using established methods.[115] This new threonine-derived NeoPHOX ligand **142** was then evaluated in asymmetric metal-catalyzed reactions.

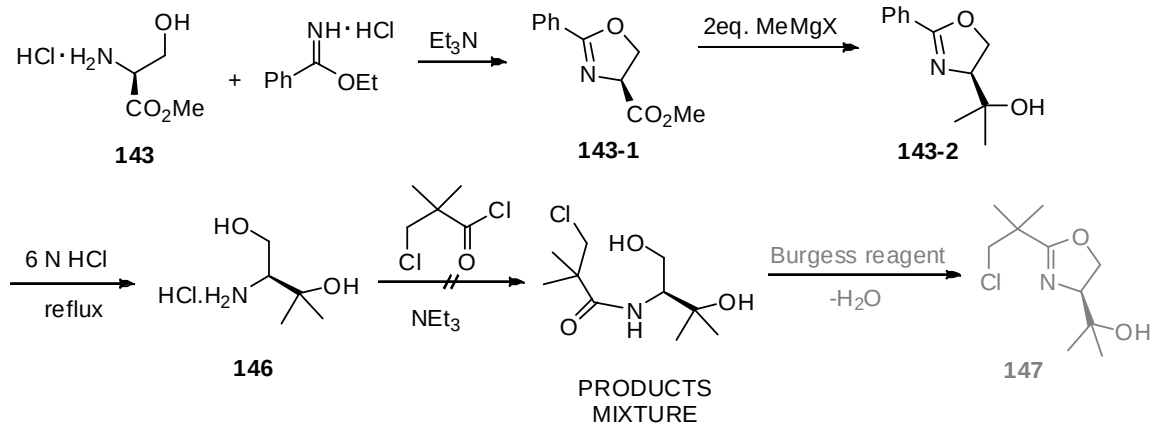
5.4.3 *Synthesis of the serine-derived NeoPHOX*

Having established the synthesis of the threonine-derived NeoPHOX ligand **142**, we planned the synthesis of the serine based NeoPHOX accordingly. However, while the formation of amide **144** from serine methylester **143** worked well as for the threonine analog, the second step, which involved the cyclization of the amide using the Burgess reagent, did not produce the desired oxazoline **145** (*Scheme 106*).



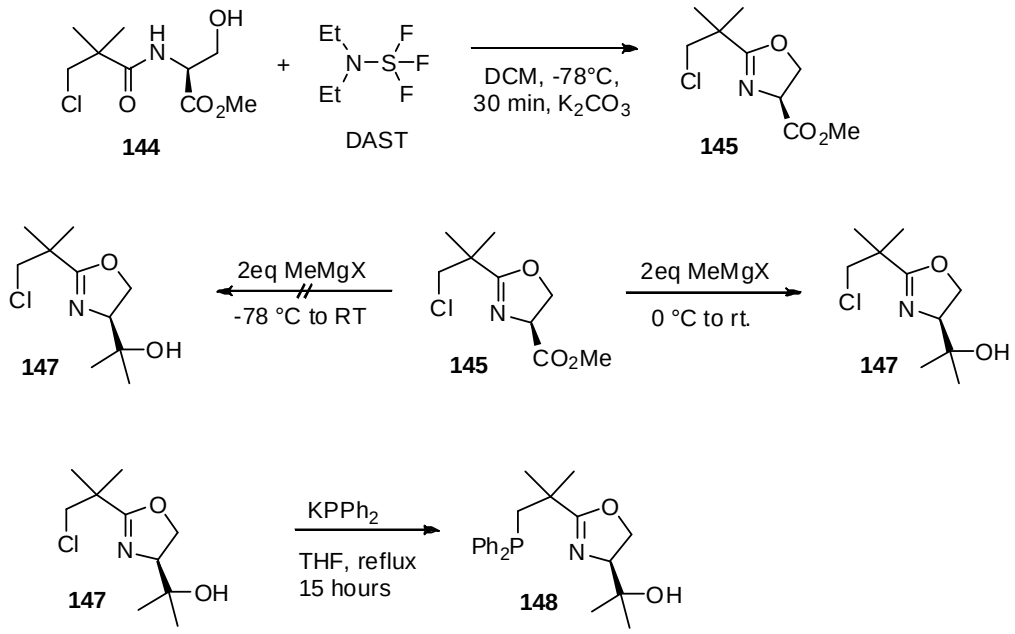
Scheme 106: Synthetic strategy for the synthesis of the serine-derived NeoPHOX ligand.

After several unsuccessful trials to reproduce the established step of the oxazoline ring closure using the Burgess reagent, a modified synthetic approach was considered. We decided to employ an extra oxazoline protection step in order to prepare the serine analog, **146**.[121] However, the reaction of **146** with 3-chloropivaloyl chloride was unexpectedly unselective and a mixture of products was obtained. Therefore, this approach was abandoned (*Scheme 107*).



Scheme 107: Revisited synthetic strategy employing an oxazoline protection step .[121]

As a consequence, we decided to continue developing the first synthetic strategy. In order to solve the problem of the oxazoline ring closure, we decided to use a method employing diethylaminosulfurtrifluoride (DAST) (*Scheme 108*).[122] Using DAST for the oxazoline ring closure delivered the desired oxazoline, **145**, within 30 min in more than 90% yield. The next step was the transformation of the ester group into a tertiary alcohol. Using low temperature for this reaction, as was used for the threonine derivative, led to an unidentified mixture of products. Surprisingly, increasing the temperature for the reaction with the Grignard reagent helped to overcome this issue. (*Scheme 108*).



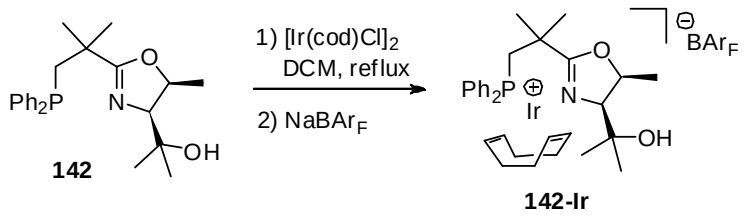
Scheme 108: Preparation of the serine-derived NeoPHOX ligand **148**.

Carrying out the Grignard addition at 0°C and subsequently warming to room temperature provided the desired product **147** in 78% yield.

Having resolved all of the problematic parts of the serine-based NeoPHOX synthesis, it was successfully completed, including the last step involving conversion of neopentyl chloride **147** into diphenylphosphine derivative **148** (*Scheme 108*).

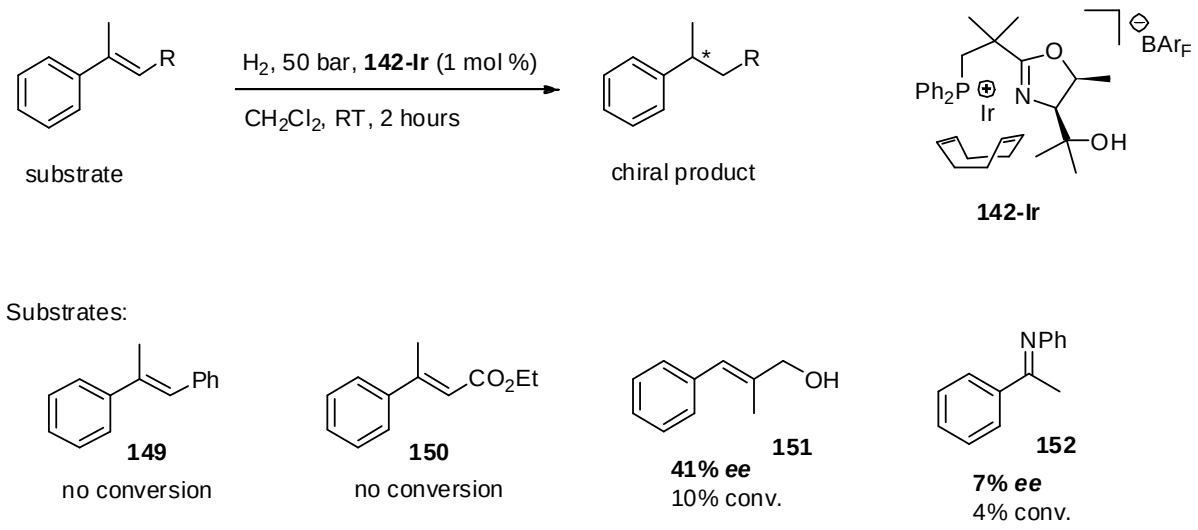
5.4.4 *Initial hydrogenation tests with the threonine-derived NeoPHOX ligand*

The iridium complex required for the hydrogenation studies were prepared by reaction of **142** with $[Ir(COD)Cl]_2$ under reflux in dichloromethane followed by anion exchange with sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate ($NaBAr_F$). The corresponding complex, **142-Ir**, was obtained in almost quantitative yield after column chromatography on silicagel (*Scheme 109*).



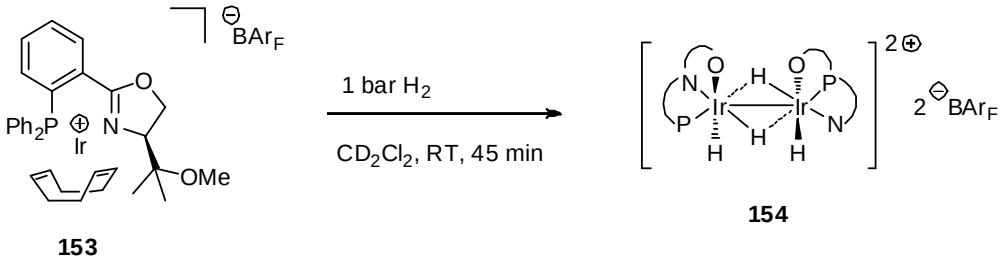
Scheme 109: Preparation of iridium complex **142-Ir**.

With iridium complex **142-Ir** in hand, we selected several standard substrates, such as unsubstituted olefin **149**, imine **152**, and two olefins with a coordinating group, **150** and **151**. Those substrates were then subjected to the hydrogenation reaction in the presence of chiral iridium complex **142-Ir** under 50 bar of hydrogen pressure (*Scheme 110*).



Scheme 110: Initial hydrogenation screening with the unprotected threonine-derived NeoPHOX ligand

The results of this initial screening showed only very low conversions and, in the case of substrates **149** and **150**, no hydrogenated products were observed. Since iridium complex **142-Ir** showed only low catalytic activity it was evident that there must be an iridium-deactivation process involved. It had been found by Axel Franzke in our group that the serine-based PHOX complex **153** can undergo an undesired dimerization process under the hydrogenation conditions to form a catalytically inactive iridium dinuclear complex (*Scheme 111*).[120b] This undesired dimerization process likely takes place after the cyclooctadiene is hydrogenated off from precatalyst **153**, which makes the coordination space on the iridium center accessible.



Scheme 111: Deactivation of the methoxy-derived serine-based PHOX ligand by Franzke.[120b]

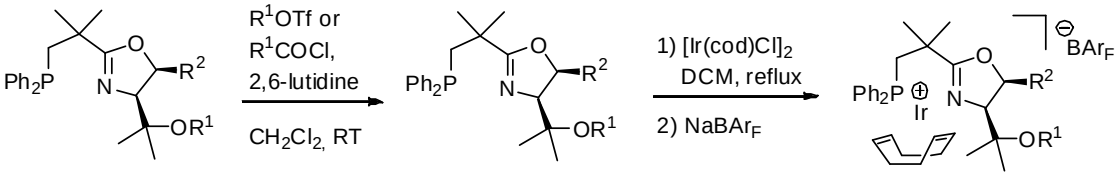
The formation of dinuclear complexes similar to **154** with serine-derived PHOX ligands was one possible reason for their low reactivities.[120b]

5.4.5 *Derivatization of the threonine- and serine-based NeoPHOX ligands, followed by preparation of the corresponding iridium complexes*

In order to avoid this undesired catalyst deactivation process, we decided to protect tertiary alcohols **142** and **148** with different protecting groups and then study the effects of this substitution. Another argument for the use of different protecting groups was the possibility of tuning the steric bulk near the metal center in the corresponding metal complexes and thus improve the enantioselectivity.

Modified PHOX ligands derived from the amino acid L-serine were recently prepared in our group and they were also investigated in the asymmetric iridium-catalyzed hydrogenation reaction of olefins.[120b] These ligands were derivatized with different substituents on the tertiary alcohol via ether or ester bonds. In order to form these derivatives potassium hydride was used for deprotonation of the tertiary alcohol followed by reaction with alkyl or acyl halides.

When this method was applied to L-threonine-derived NeoPHOX ligand **142**, only unreacted starting material was recovered. Therefore, we tested several alternative bases for the deprotonation of the tertiary alcohol, namely triethylamine, pyridine, and 2,6-lutidine. Of the amines tested, the only successful one was 2,6-lutidine, which was subsequently used for derivatization of the tertiary alcohol groups of all L-threonine- and L-serine-derived NeoPHOX ligands. Those derivatized ligands were then complexed with bis(1,5-cyclooctadiene)diiridium(I) dichloride (*Scheme 112*).



142 R^1 = H, R^2 = Me
148 R^1 = H, R^2 = H

142-TMS R^1 = Me_3Si, R^2 = Me
142-TES R^1 = Et_3Si, R^2 = Me
142-TBDMS R^1 = tBu$(Me)_2Si$, R^2 = Me
142-OAc R^1 = COMe, R^2 = Me
148-TBDMS R^1 = tBu$(Me)_2Si$, R^2 = H

142-Ir-TMS R^1 = Me_3Si, R^2 = Me
142-Ir-TES R^1 = Et_3Si, R^2 = Me
142-Ir-TBDMS R^1 = tBu$(Me)_2Si$, R^2 = Me
142-Ir-OAc R^1 = COMe, R^2 = Me
148-Ir-TBDMS R^1 = tBu$(Me)_2Si$, R^2 = H

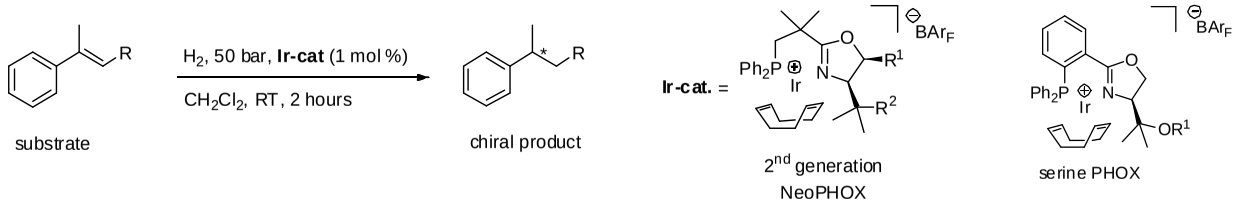
Scheme 112: Derivatization of the 2nd generation NeoPHOX ligands and formation of their iridium complexes.

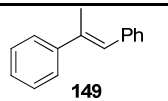
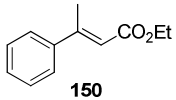
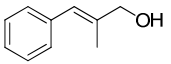
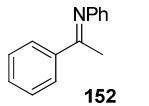
5.4.6 *Asymmetric iridium-catalyzed hydrogenations using 2nd generation NeoPHOX ligands*

The new NeoPHOX derivatives of L-threonine and L-serine ligands were tested in the iridium-catalyzed hydrogenation reaction on selected standard substrates. Good enantioselectivities were expected because the triethylsilyl protecting group of the tertiary alcohol is quite sterically demanding.

After the initial unsuccessful hydrogenation test employing threonine-derived NeoPHOX complex **142-Ir** with an unprotected tertiary alcohol function, a triethylsilyl protected derivative **142-Ir-TES** was found to exhibit very high enantioselectivities with standard substrates **149** and **150**. These selectivities were comparable with those obtained from the analogous NeoPHOX ligand derived from the *tert*-leucine (*Table 11*). However, although the selectivities were around 90 %, the conversions were quite low.

Table 11: Hydrogenation of standard substrates employing the 2nd generation NeoPHOX ligands.



	NeoPHOX							serine PHOX[120b]			
	1st generation[115]	2nd generation									
Substrate	R^1=H, R^2=CH_3 ee [%] conv.	R^1=CH_3, R^2=OH ee [%] conv.	R^1=CH_3, R^2=OAc ee [%] conv.	R^1=CH_3, R^2=$OSiMe_3$ ee [%] conv.	R^1=CH_3, R^2=$OSiEt_3$ ee [%] conv.	R^1=CH_3, R^2=OTBDMS ee [%] conv.	R^1=H, R^2=OTBDMS ee [%] conv.	R^1=OMe ee [%] conv.	R^1=Bn ee [%] conv.	R^1=Ac ee [%] conv.	R^1=Bz ee [%] conv.
 **149**	**97** (*R*) >99	*n.d.*	**87** (*S*) 59	**92** (*S*) 38	**97** (*S*) / 96* 59 / 87*	**96** (*S*) >99	**90** (*S*) >99	*n.d.* 1	**92** (*S*) 27	**92** (*S*) 90	**92** (*S*) 88
 **150**	**95** (R) >99	*n.d.*	**90** (*S*) 44	**82** (*S*) 40	**90** (*S*) / 90* 87 / 98*	**94** (*S*) >99	**92** (*S*) >99	**32** (*S*) 3	**46** (*S*) 34	**56** (*S*) 70	**69** (*S*) 91
 **151**	**94** (-) >99	**41** (+) 10	**90** (+) 92	**88** (+) 82	-	***91*** (+) >99	**84** (+) >99	**57** (+) 9	**79** (+) 43	**91** (+) >99	**92** (+) >99
 **152**	**79** (R) 99	**7** (*S*) 4	**16** (*S*) 73	**67** (*S*) 5	-	**49** (*S*) 79	**77** (*S*) 79	**5** (*R*) 2	**21** (*S*) 1	**56** (*R*) 99	**53** (*R*) >99

Reaction conditions: 1mol% catalyst, 0,1 mmol substrate, 0,5 mL CH_2Cl_2. *reaction time 16 hours

Keeping in mind the deactivation process shown in *Scheme 111*, it was considered that this could also be the reason for lower reactivity observed with our NeoPHOX catalyst. To prove that the catalyst **142-Ir-TES** is still active even after the standard reaction time of 2 hours, we extended the reaction time to 16 hours under otherwise identical reaction conditions. The outcome of this experiment was quite satisfying. While enantioselectivities remained unchanged, conversions after the extended reaction time were significantly higher. This shows that at least part of the catalyst remains active during this time.

In order to see the effect of altered steric bulk on enantioselectivity we prepared the smaller, trimethylsilyl-derived NeoPHOX, **142-Ir-TMS**. This modification had only a small impact on the selectivities obtained, but a large impact on reactivity in the hydrogenation process. Phosphino oxazoline iridium complexes were recently studied by Burgess et al. and it was found that the corresponding active catalyst, an iridium hydride of the phosphinooxazoline catalyst, has a significant acidic character.[123] The fact that the iridium hydrides of our NeoPHOX complexes are acidic could explain the different reactivities of our silylated derivatives. The trimethylsilyl ether is more readily cleaved by acid than the triethylsilylether. Cleavage would lead to the tertiary alcohol that shows very low activity. We thus prepared **142-Ir-TBDMS**, a derivative that should have the superior properties in terms of acid stability and steric bulk. The results from the hydrogenation experiment confirmed our expectations and the conversions of the tested olefins reached completion within the standard reaction time of 2 hours (*Table 11*). No less important was the finding that the acid-stable protecting group did not have a negative impact on the selectivities of the hydrogenation reactions, as they remained as high as those of the acid-labile protecting groups.

For comparison with the previously studied serine-derived PHOX ligands[120b] threonine-derived NeoPHOX ligand **142-Ac**, which possesses an acetyl protecting group, was prepared. This was one of the most effective derivatives of the serine-derived PHOX.[120b] The obtained results more less fulfilled our expectations in terms of reactivity, which was similar to the serine-PHOX based catalyst, and the enantioselectivities of the olefin hydrogenations were still high, around 90 % *ee* (*Table 11*). The serine-derived **148-Ir-TBDMS** also was highly active but somewhat less enantioselective than the corresponding threonine derived catalyst **142-Ir-TBDMS**.

The newly prepared threonine- and serine-derived NeoPHOX ligand with a TBDMS ether group exhibited very high enantioselectivities in the hydrogenation of functionalized and unfunctionalized olefins, similar to the most successful first-generation *tert*-leucine-derived

NeoPHOX analogs. It was found that the presence of an acid-stable alcohol protecting group is necessary in order to avoid undesired catalyst deactivation. The presence of an additional methyl group on the oxazoline ring in the threonine-derived NeoPHOX ligands seemed to have a positive effect, probably due to the increased rigidity of the oxazoline ring.

5.4.7 *Crystallographic analysis of Ir NeoPHOX complexes*

The three dimensional structures of several threonine- and serine-derived NeoPHOX iridium complexes were determined by X-ray analysis and compared with known phosphino-oxazoline complexes. Our interest was to see the differences in the steric shielding of the coordination sphere by protecting groups on the tertiary alcohol function and to correlate this feature with the hydrogenation results. From the obtained crystal structures, it can bee seen that the conformations of the threonine- and serine-derived NeoPHOX iridium complexes are essentially the same as those of the 1st generation NeoPHOX[114] with respect to the geometry of the 6-membered iridacycle, which retains a V-shaped conformation (*Figure 34*).

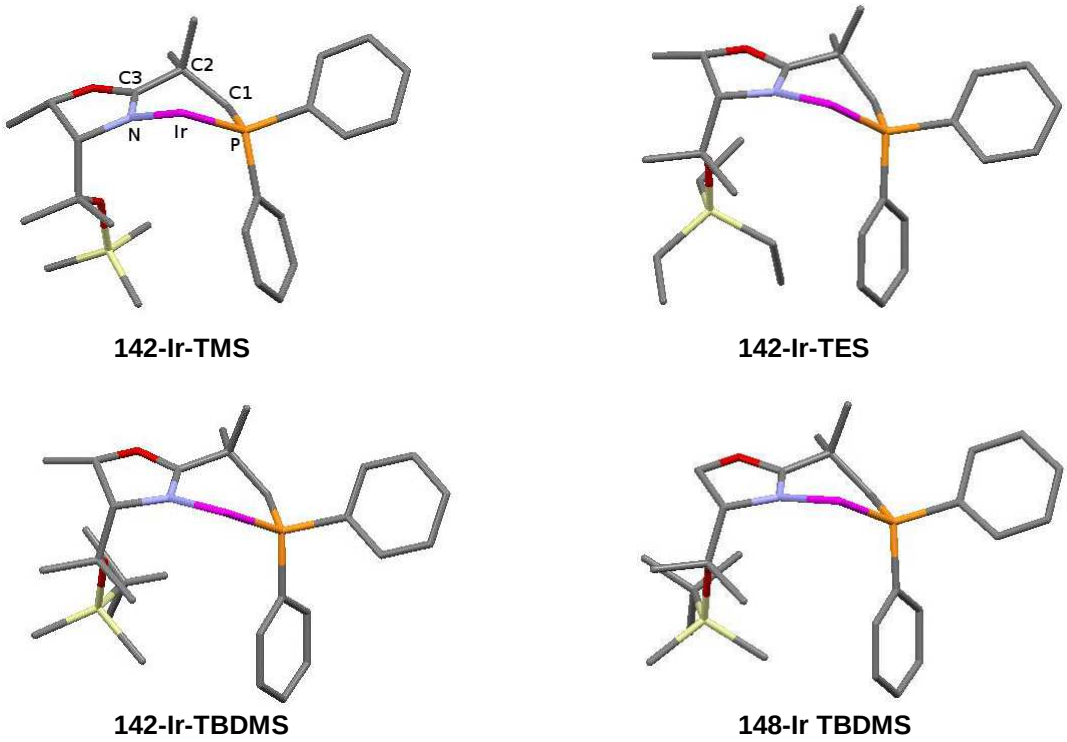
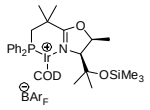
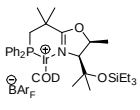
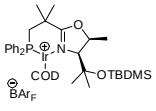
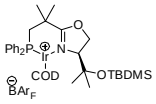
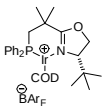
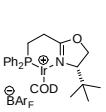
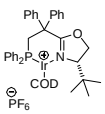
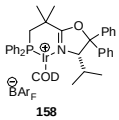


Figure 34: Crystal structures of 2nd generation NeoPHOX iridium complexes. Hydrogen atoms, COD, and BAr_F anions omitted for clarity.

Unlike the methoxy-protected serine-derived PHOX complex described by Axel Franzke, the protected tertiary alcohol group in these systems does not point towards the iridium center.[60] The interaction of the ether oxygen atom with the iridium center was the reason for the lack of reactivity of the serine-based PHOX complexes. In our case, the silyl protecting groups are all more sterically demanding than the methoxy group and thus the coordination of the tertiary alkyl ether group with the iridium center is not possible, as long as the protecting group survives the acidic reaction conditions. In the deprotected NeoPHOX ligands, the tertiary alcohol would be able rotate and coordinate to the iridium center. Unfortunately, we did not succeed in the preparation of a suitable crystal of **142-Ir** for crystallographic analysis and so we could not confirm this assumption.

To compare our new NeoPHOX iridium complexes with the 1st generation versions, complexes **155**, **157**, **158**, and the structurally related Gilbertson system **156**[124] (prepared by Marcus Schrems) were compiled in *Table 12*, which contains important crystallographic data for all these compounds.

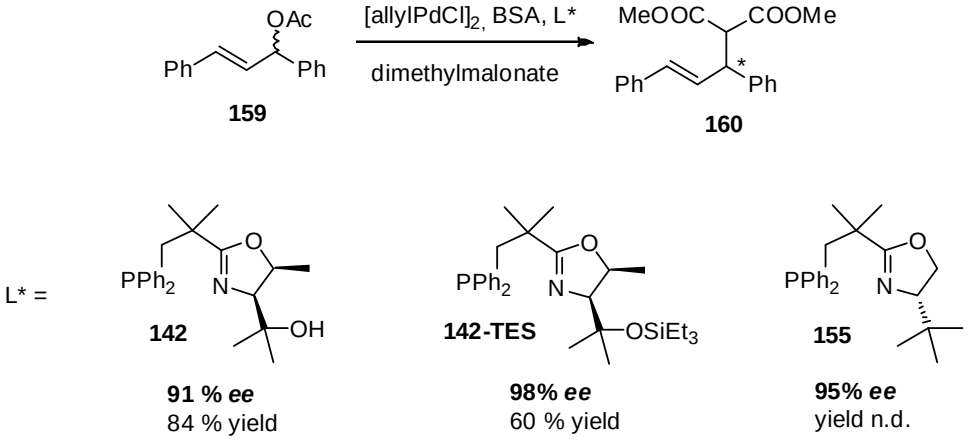
Table 12: Crystallographic bond lengths [Å] and angles [°] for selected iridium phosphinooxazoline complexes.

	 **142-Ir-TMS**	 **142-Ir-TES**	 **142-Ir-TBDMS**	 **148-Ir-TBDMS**
Ir-P	2,280	2,284	2,278	2,281
Ir-N	2,096	2,137	2.107	2,112
Ir-C2	3,430	3,462	3,473	3,459
P-C1	1,816	1,848	1,854	1,839
P-Ir-N	86,76	88,19	88,72	88,64
C1-C2-C3	111,00	110,63	111,64	111,15
	 **155**	 **156**	 **157**	 **158**
Ir-P	2,274 (2,287)	2,293	2,279	2,284
Ir-N	2,093 (2,099)	2,106	2,112	2,097
Ir-C2	3,458 (3,444)	3,340	3,463	3,425
P-C1	1,850 (1,845)	1,847	1,843	1,851
P-Ir-N	87,1 (86,78)	87,11	86,45	88,4
C1-C2-C3	111,75 (109,54)	111,56	108,82	110,15

The structural parameters of all these complexes are very similar, so no direct conclusions with respect to the observed enantioselectivities are possible.

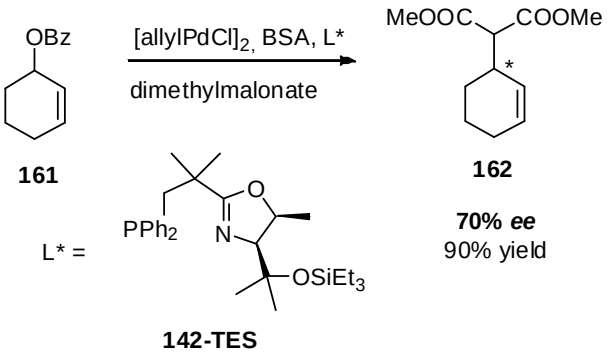
5.4.8 *Palladium-catalyzed allylic substitution employing Neophox ligands*

As the first phosphinooxazoline ligands were specifically designed for asymmetric palladium-catalyzed allylic substitutions, we wanted to test our new NeoPHOX ligands in this reaction as well. For comparison with established ligands, we decided to evaluate ligands **142** and **142-TES** on the standard substrate, (*E*)-1,3-diphenylallylacetate **159**. The anion of dimethylmalonate was used as a nucleophile for the allylic substitution (*Scheme 113*).



Scheme 113: Asymmetric palladium-catalyzed allylic substitution with *rac*-(*E*)-1,3-diphenylallylacetate **159.**

The product of this allylic substitution, **160**, was isolated in good yields, and the enantioselectivities exceeded 90% *ee*. Ligand **142-TES** was even more effective than *tert*-leucine-derived NeoPHOX ligand **155**.[114] Due to the good results obtained with substrate **159**, threonine-derived NeoPHOX ligand **142-TES** was also tested on the more demanding cyclic substrate **161** (*Scheme 114*).

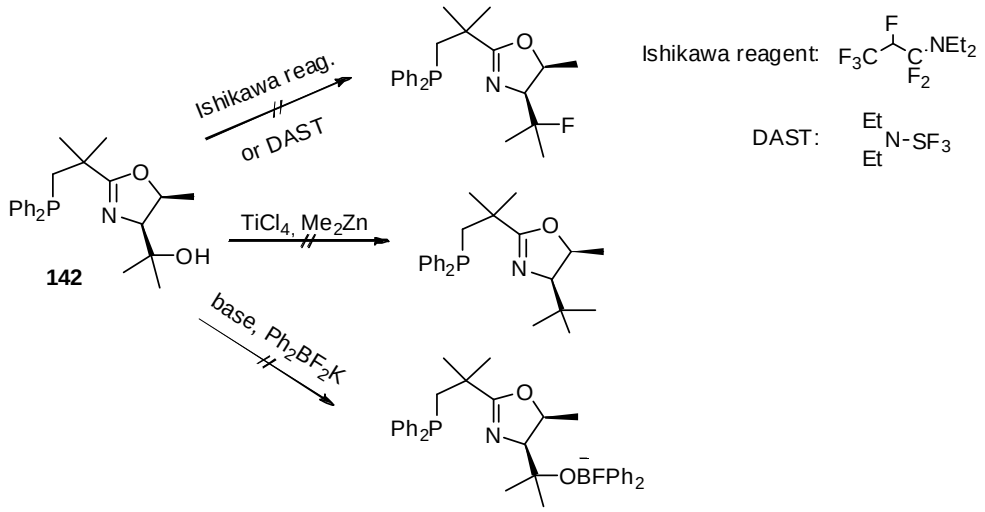


Scheme 114: Asymmetric palladium-catalyzed allylic substitution with cyclic substrate **161**

An encouraging enantioselectivity of 70% *ee* in this case was obtained and the substitution product **162** was isolated in good yield. Our result demonstrate that the 2nd generation NeoPHOX ligands possess a potential for palladium-catalyzed allylic substitutions.

5.4.9 *Attempts at modifications of 2nd generation NeoPHOX ligands*

In order to modify the backbone of NeoPHOX ligands we investigated methods that could be applied to tertiary alcohols. The first intended modification of NeoPHOX ligand **142** was the transformation of the OH group to fluorine. This change was expected to impact the electronic properties of the ligand and, from a steric point of view, the change would better resemble the isopropyl derivative due to the size of the fluorine atom, which is close to the size of a hydrogen atom. For this process we selected reagents known to be capable of converting tertiary alcohols into the corresponding fluorine compounds: the Ishikawa fluorinating reagent[125] and diethylaminosulfurtrifluoride (DAST).[126] Unfortunately, neither of them produced the desired fluorinated product from substrate **142** (*Scheme 115*).



Scheme 115: Iridium-catalyzed allylic substitution with *rac*-(*E*)-1,3-diphenylallylacetate **159.**

Another transformation considered, was a reaction reported by Manfred Reetz that employs dimethyltitanium dichloride as a methylation agent. This reagent was used to replace the hydroxy group of tertiary alcohols with a methyl group.[127] However, in this case the desired *tert*-butyl-substituted ligand was not formed. Preparation of an ionic ligand by reaction of the tertiary alcohol with Ph_2BF_2K and base also failed (*Scheme 115*).

5.5 Conclusion

The phosphinooxazoline ligands successfully used in various asymmetric transformations can be divided into several subclasses, for example PHOX, SimplePHOX, 1st generation NeoPHOX, and others. If we compare the most successful derivatives in individual subclasses we find a repeating structural motif, the oxazoline ring derived from the amino acid L-*tert*-leucine. The main restriction for the wider use of this amino acid is its price, which is about twenty times higher than the price of L-threonine and 40 times higher than that of L-serine. Therefore we decided to develop a method for the preparation of a 2nd generation of NeoPHOX ligands employing the amino acids L-threonine and L-serine.

The 2nd generation NeoPHOX ligands were tested in asymmetric iridium-catalyzed hydrogenation reactions, where they exhibited high enantioselectivities. The strctures were optimized to achieve good conversions in these reactions. The presence of an acid-stable

protecting group for the tertiary alcohol group proved to be crucial in order to avoid catalyst deactivation. The 2nd generation NeoPHOX ligands also exhibited high enantioselectivities in the palladium-catalyzed allylic substitution. The structural properties of the 2nd generation NeoPHOX ligands were investigated by crystallographic analysis. The 2nd generation NeoPHOX ligands were part of an industrial patent together with Solvias AG.[128]

Chapter 6

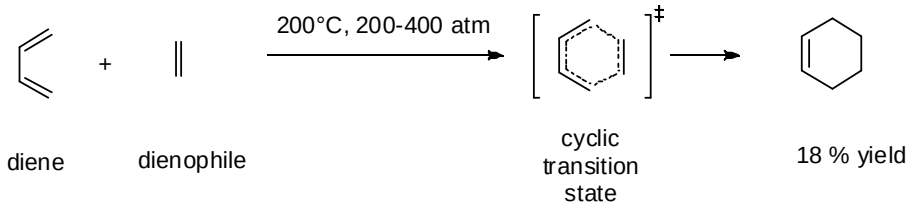
Diels-Alder products as substrates for asymmetric hydrogenation

6. Diels-Alder products as substrates for asymmetric hydrogenation

6.1 Introduction

The Diels-Alder reaction is one of the most powerful tools in organic synthesis used for construction of the cyclic compounds. This reaction was first reported by German chemists Otto Paul Hermann Diels and Kurt Alder in 1928.[129] Since its invention it has become a very popular synthetic method for the simplicity and versatility and in 1950 both chemists were awarded the Nobel Prize "for their discovery and development of the diene synthesis".

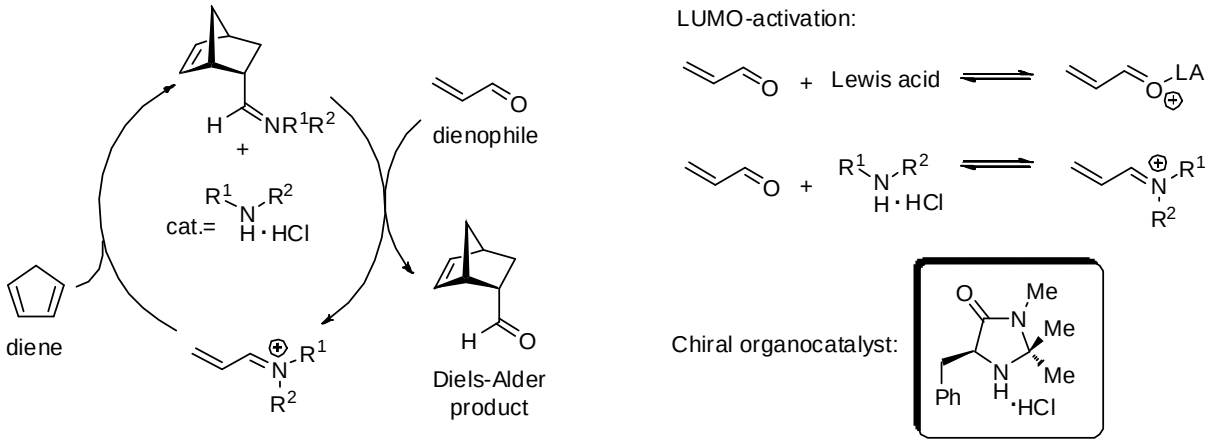
In the Diels-Alder reaction 4π electrons of the diene molecule are interacting with 2π electrons of the dienophile in a single step via a concerted mechanism and therefore this reaction also is called a [4+2] cycloaddition. The simplest reaction of this type is a reaction of 1,3-butadiene with ethylene proceeding through a cyclic transition state which finally leads to cyclohexene (*Scheme 116*).



Scheme 116: Diels-Alder reaction of 1,3-butadiene with ethylene proceeding through a cyclic transition state.

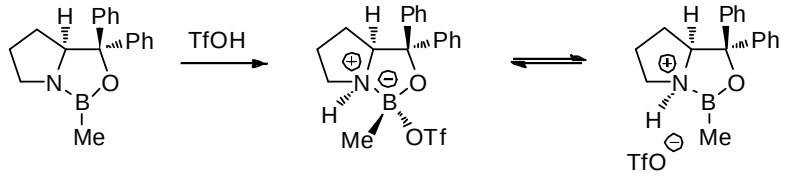
The reaction of this unsubstituted system requires elevated temperature and pressure in order to proceed even in very low yield (*Scheme 116*).[130] However, electron-withdrawing substituents in the dienophile strongly accelerate the reaction. With aldehydes or esters, e.g., Diels-Alder reactions often proceed even at room temperature. The reactivity can be furthermore increased by complexation of an electron-withdrawing substitutent (typically a carbonyl group) with a Lewis acid. Therefore Lewis acids are often used to catalyze the Diels-Alder reactions. When a chiral Lewis acid is used the Diels-Alder reaction can be rendered enantioselective.

Chiral catalysts used for that purpose are for example the earlier discussed copper bis(oxazolines).[131] Another efficient approach described by MacMillan is deploying a chiral organocatalyst based on the amino acid (*S*)-proline. This secondary amine catalyst forms a chiral iminium ion which has essentially the same effect on the dienophile as a Lewis acid. After reaction with diene the product is released by hydrolysis the catalyst is recycled (*Scheme 117*).[132]



Scheme 117: The enantioselective organocatalyzed Diels-Alder reaction by MacMillan.[132]

Another class of chiral Lewis acids, based on oxazaborolidines was investigated by E.J. Corey.[133] Very strong chiral Lewis acids are formed upon the protonation of the oxazaborolidines with strong protic acids or by N-coordination of the $AlBr_3$. Very high enantioselectivities could be achieved by using these N-activated oxazaborolidines as chiral Lewis acids in [4+2], [3+2] and [2+2] cycloadditions (*Scheme 118*).

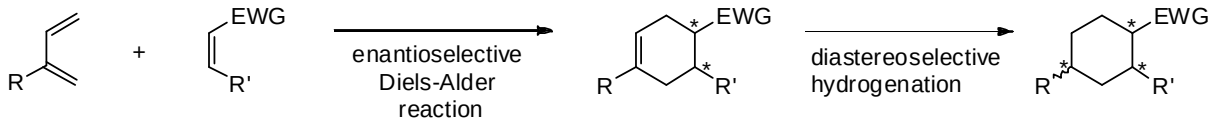


Scheme 118: Activation of the oxazaborolidines by the triflic acid by E.J. Corey[133]

Due to the weak coordination of the triflate ion to the boron, equilibrium exists between the borate complex and the trivalent boron species which can act as a chiral Lewis acid in the Diels-Alder reaction.

In this project we wanted to use chiral enantio-enriched Diels-Alder products as substrates for the asymmetric iridium-catalyzed hydrogenation reaction. If we use a diene substituted at

C(2), the product will contain a trisubstituted double bond which can be then diastereoselectively hydrogenated (*Scheme 119*).



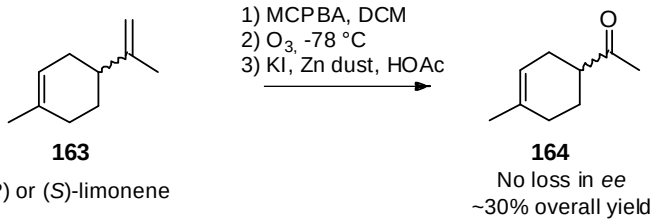
Scheme 119: Concept of the diastereoselective hydrogenation of Diels-Alder products.

If we take into an account that there could be already two stereocenters formed via the Diels-Alder reaction we can easily incorporate the third one by applying a diastreoselective hydrogenation. Therefore by using this approach we could possibly implement three stereocenters into a molecule within just two reaction steps.

The concept of the stereoselective hydrogenation of Diels-Alder products has some literature precedence in the synthesis of the biologically active compounds.[134] Hence we decided to test iridium-based catalysts developed in our group in order to develop an effective and reliable method for those synthetically useful transformations.

6.2 Initial screening of a model substrate

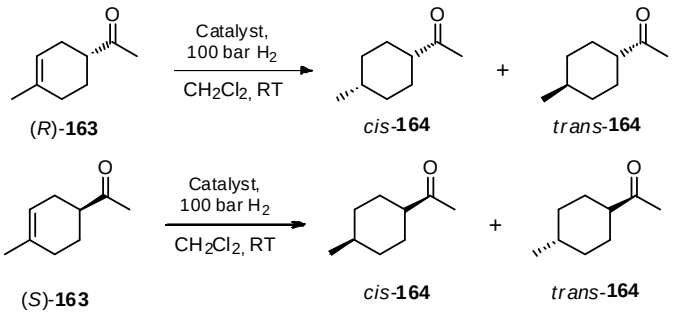
In order to optimize the conditions for the diastereoselective hydrogenation reaction of Diels-Alder products we decided to use a model substrate first. As the chiral precursor of the model substrate we selected limonene. This molecule already bears a stereogenic center and it also has a substituted double bond which can be diastereoselectively hydrogenated. Because of the directing effect in homogenous hydrogenation of related cyclohexene substrates which were previously studied by Crabree we decided to implement the ligating group into our model substrate.[135] The transformation which was necessary to perform to implement the coordinating group was the cleavage of the exocyclic double bond of the limonene. This transformation was done by the selective ozonolysis followed by a reductive workup in one pot two step synthesis (*Scheme 120*).[136]



Scheme 120: Ozonolysis of the limonene exocyclic double bond.

The substrate **164** was then used for and initial screening of various chiral iridium catalysts in the hydrogenation reaction (*Table 13*).[137]

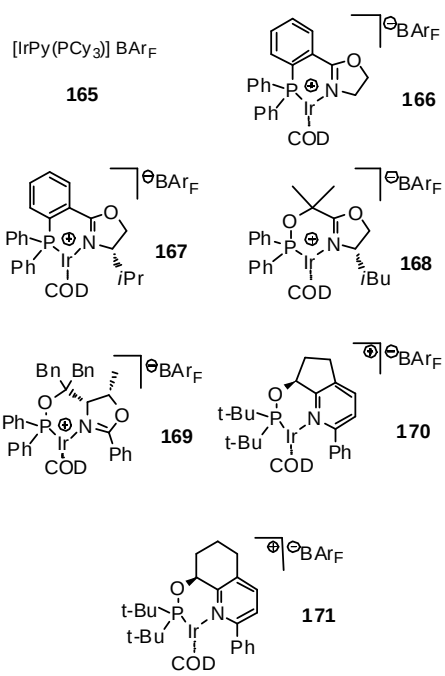
Table 13: Catalyst screening in the diastereoselective hydrogenation reaction.[137]



Catalyst	Conversion of (*R*)-**163**	**164** (*cis*/*trans*)	Conversion of (*S*)-**163**	**164** (*cis*/*trans*)
165	>99%	0.5 : 99.5	97%	0.6 : 99.4
166	95%	1 : 9.7	94%	1 : 4.6
167	76%**	1 : 23.4**	14%	1 : 3.8
168	5%	1 : 4.7	68%	4.9 : 1
169	51%	1 : 16.2	>99%	2.8 : 1
170	>99%	7.5 : 1	>99%	1 : 9.1
171	>99%**	2.6 : 1**	>99%	1 : 4.5

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

Catalysts:

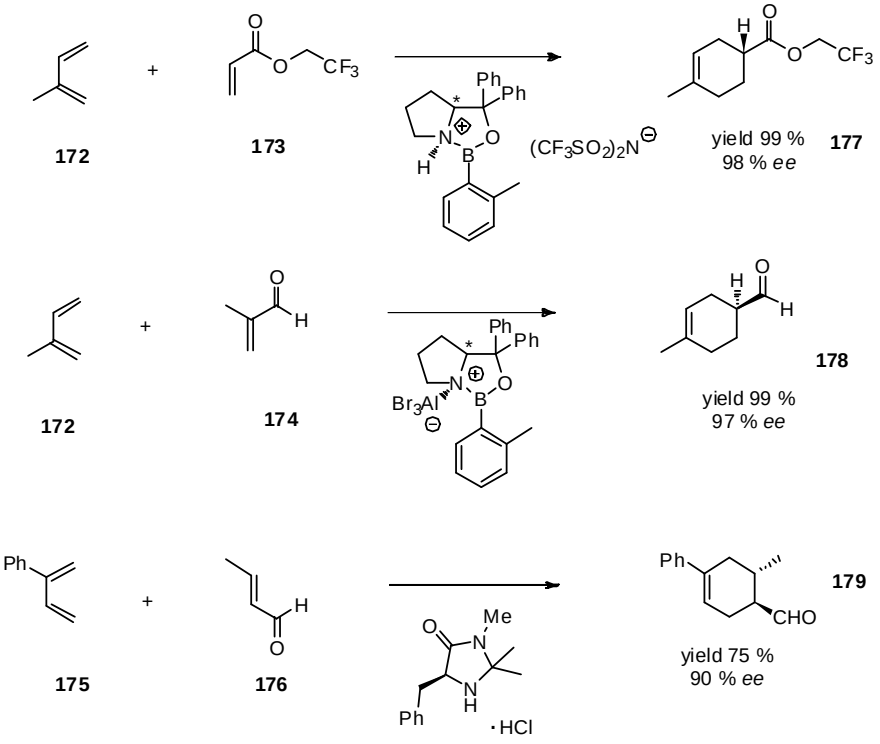


When the non-chiral iridium catalysts **165** and **166** were used the diastreoselectivities of the hydrogenation reactions favored the *trans* products and good conversions were reached. The different *cis*/*trans* ratios for the (*R*)-**163** and (*S*)-**163** for catalyst **166** can be explained by the different enantio purity of the commercial (*R*)- and (*S*)-lemonene. Using chiral Ir-PHOX **167** and Ir-SimplePHOX **168**, only moderate diastereoselectivites and low conversions were

reached. In case of the Ir-ThreoPHOX **169** either good *cis*/*trans* ratio but low conversion was obtained or high conversion and low *cis*/*trans* selectivity. The best performing catalyst was the pyridine-phosphinite derived complex **170** which gave good diastereselectivities and full conversion. The stereoselectivity is strongly catalyst-controlled as shown by the reaction of the (*R*)-enantiomer which leads to the *cis* product overriding substrate control which favors the *trans* product. Catalyst **171** also gave full conversion but lower diastereoselectivity.
Whereas in the case of achiral catalysts **165** and **166** the disastereoselectivity of the Ir-catalyzed hydrogenation was driven mainly by the ligation effect of the carbonyl group in **163** (*trans* product preferred), in the case of chiral catalyst **170** *cis* selectivity for (*R*)-**163** was preferred.

6.3 Diastereoselective hydrogenation of Diels-Alder products

Based on the results obtained from the initial screening we decided to test the most efficient catalyst **170** in the hydrogenation of substrates obtained from enantioselective Diels-Alder reactions. For this purpose we selected several compounds, structurally related to **163**. (*Scheme 121*).



Scheme 121: Syntheses of the hydrogenation substrates via Diels-Alder reaction.[132-133]

The cyclohexene derivatives **177-179** were prepared using methods described by E.J. Corey[133] and MacMillan.[132]

Due to the directing effect of the catalyst **170** with chiral substrates (*R*)-**163** and (*S*)-**163** observed in the initial screening we wanted to see whether it is also possible to control selectivity of the hydrogenation process by using different enantiomers of the chiral catalyst **170**. The results obtained in the hydrogenation using both enantiomers of the catalyst **170** are shown in *Table 14*.

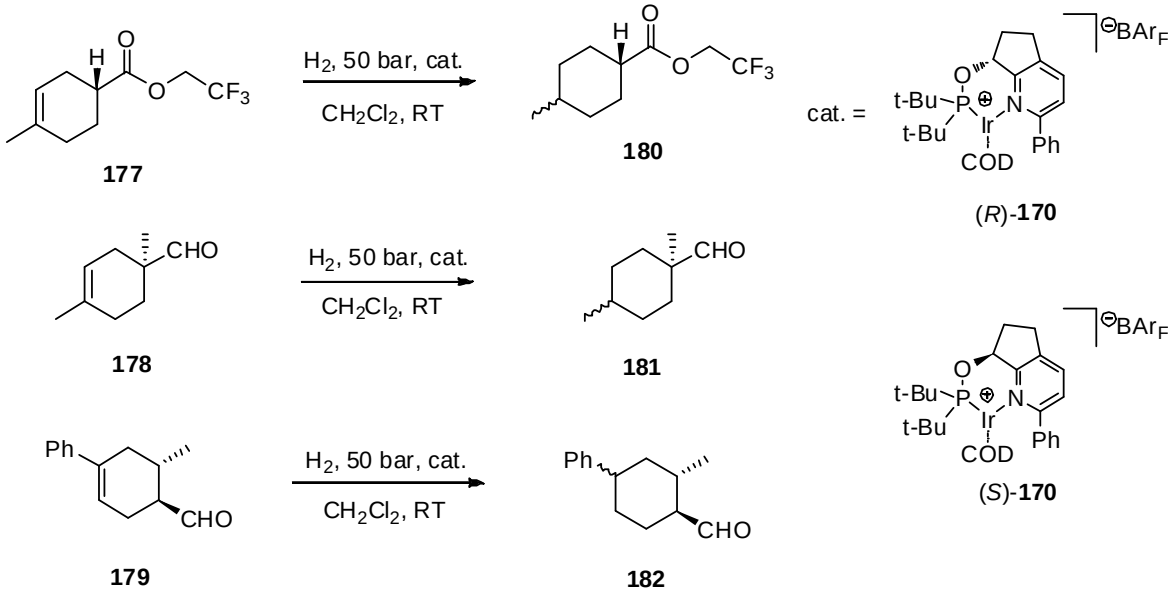


Table 14: Diastereoselective hydrogenation of Diels-Alder products **177**-**179**.

hydrogenated product	cat. (*R*)-**170**		cat. (*S*)-**170**	
	ds	conv. [%]	*ds*	conv. [%]
180	98:2	full	2:98	full
181	95:5	full	n.d.	0
182	89:11	10	4:96	10

In the diastereoselective hydrogenation of cyclohexene **177**, full conversion to product **180** was achieved and opposite diastereomers were obtained from catalysts (*R*)-**170** and (*S*)-**170** with the equal diastereoselectivities of 98:2. For substrate **178** only catalyst (*R*)-**170** led to the

desired hydrogenated product **181** while the opposite enantiomer (*S*)-**170** did not produce any product **181** and only starting **178** was observed. The same result was obtained when the hydrogenation of **178** was performed at 90 bar of H_2 under the same conditions. For the substrate **179** the reaction was selective that each enantiomer of the catalyst **170** delivered the opposite diastereomer of **182,** but only with low conversion. A possible explanation for this low reactivity might be an undesired interaction of the aldehyde functional group with the Ir-catalyst. The reaction was also performed with catalysts **167**, **168** and **171** but without any improvement.

6.4 Conclusion

We have shown that products of the enantioselective Diels-Alder reaction can be converted to saturated cyclohexene derivatives by asymmetric iridium-catalyzed hydrogenation with excellent diastereoselectivities of up to 98:2. The diastereoselectivity of the reaction is strongly catalyst-controlled, so it is possible to obtain each of the two diastereomeric products with high selectivity using either the (*R*)- or (*S*)-catalyst. It was found that the most effective catalyst in terms of diastereoselectivity and reactivity was the pyridine-phosphinite derived complex **170**.

Chapter 7

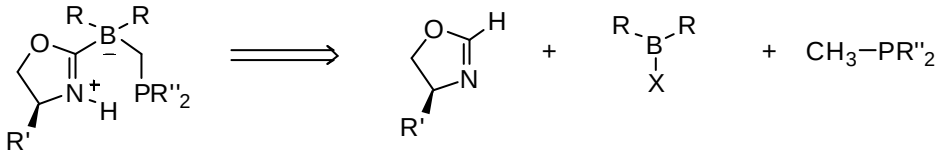
Summary

7. Summary

Borabox ligands proved to be efficient ligands for controlling the enantioselectivity of various metal-catalyzed reactions. Therefore modification of an existing borabox backbone was implemented and new borabox ligands modified on C(5) position of the oxazoline ring were prepared and tested in the copper-catalyzed asymmetric cyclopropanation. In this study high stereocontrol of the reaction was observed. However the presence of sterically demanding groups at position C(5) did not improve the results compared to the C(5) non-substituted analogs (*Figure 35*).

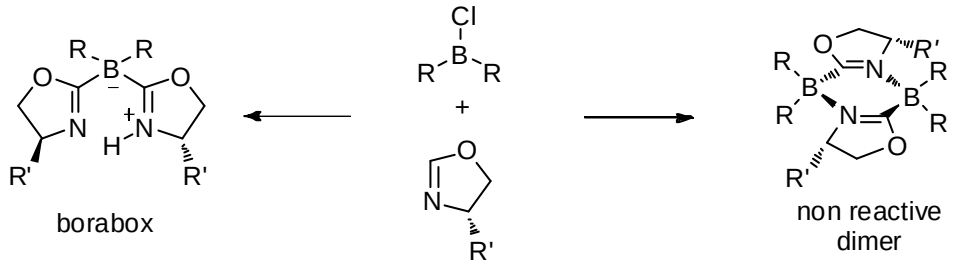
Figure 35: Borabox ligands – C(5) substituted (left), C(5) unsubstituted (right).

The synthesis of analogous boron-bridged phosphino-oxazolines was attempted via several synthetic approaches in order to prepare new zwitterionic N,P-ligands (*Scheme 122*).



Scheme 122: Retrosynthetic analysis of N,P-zwitterionic ligands.

The simple stepwise substitution by subsequent addition of lithiated oxazoline and phosphine was not possible. It either led to borabox ligands or to undesired dimeric species, which were inert towards reaction with other nucleophiles (*Scheme 123*).



Scheme 123: Reaction of chloroboranes with lithiated oxazolines.

We decided to tune the electronic properties of the boron compound by variation of the substituents in order to avoid multiple substitution or undesired dimer formation. Therefore aminochloroborates were examined due to their lower reactivity compared to chloroboranes or chloroborates. A derivative with a phosphine-aminoborate backbone was prepared but unfortunately the decreased reactivity of the nitrogen-substituted boron center did not allow another nucleophilic addition of the oxazoline moiety (*Figure 36*).

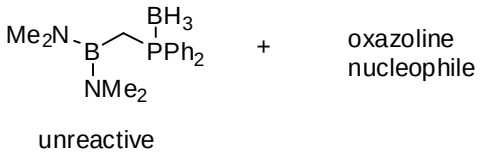
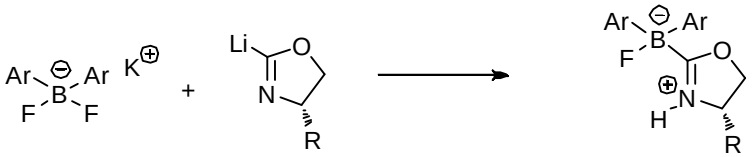


Figure 36: Unreactive aminoborate with lithiated oxazolines.

In order to avoid dimer formation the reactivity of potassium diaryldifluoroborates was investigated. These tetrasubstituted boron compounds reacted with lithium oxazolines and provided products of nucleophilic substitution at the boron center (*Scheme 124*).



Scheme 124: Nucleophilic substitution using potassium diaryldifluoroborates.

The resulting oxazoline-substituted fluoroborates could be isolated as zwitterions after protonation of the oxazoline nitrogen atom. However, the second intended substitution with the phosphine moiety failed. In addition, quantum chemistry calculations were carried out to support the experimental studies.

The synthesis of new NeoPHOX ligands derived from inexpensive chiral aminoacids L-serine and L-threonine was developed. These chiral ligands were tested in the iridium-catalyzed asymmetric hydrogenation and palladium-catalyzed allylic substitution (*Figure 37*).

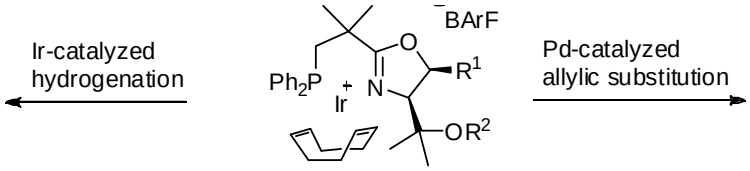
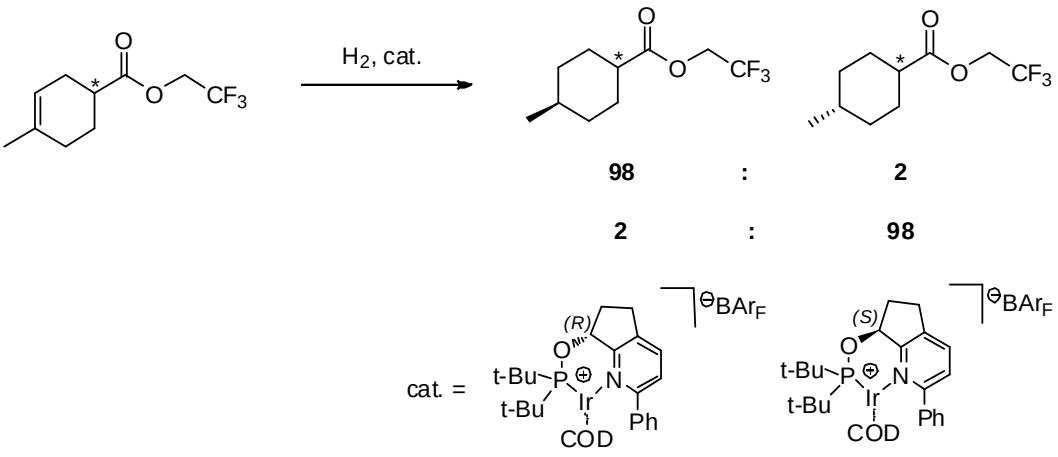


Figure 37: L-serine and L-threonine derived ligands and their applications.

In both reactions the enantioselectivities achieved were excellent for most of the substrates tested. In the iridium catalyzed hydrogenation it was found that presence of an acid-stable protecting group of tertiary alcohol (R^2) is necessary in order to achieve full conversions. The enantioselectivities obtained in the catalytic asymmetric hydrogenation and allylic substitution with the L-serine and L-threonine derived ligands were almost identical to those reported for *tert*-butyl-substituted NeoPHOX ligands, which are derived from very expensive amino acid *tert*-leucine.

The use of Ir catalysts for the diastereoselective hydrogenation of Diels-Alder products was investigated. The best results were obtained with a pyridine-phosphinite complex that afforded the saturated cyclohexane derivatives with diastereoselectivities of up to 98:2 and full conversion. The reaction is strongly catalyst-controlled, so it is possible to obtain each of the two diastereomeric products with high selectivity using either (*R*)- or (*S*)-catalyst (*Scheme 125*).



Scheme 125: Diastereoselective hydrogenation controlled by enantiomer of Ir-catalyst.

Chapter 8

Experimental part

8. Experimental part

8.1 Working techniques and reagents

Synthetic procedures involving manipulation under inert atmosphere were performed in the dried glassware under positive argon pressure using standard Schlenk techniques. For handling moisture and air sensitive compounds was used glove box (MBraun Labmaster 130). Commercially available reagents were purchased from Acros, Aldrich, Flourochem, Strem and used without further purification. Triethylamine was distilled from calcium hydride, 2,6-lutidine was distilled under reduced pressure prior to use.

Solvents were distilled from sodium/(benzophenone) (diethylether, pentane, tetrahydrofurane, toluene), obtained from the purification activated alumina columns system under nitrogen (PureSolv, Innovative Technology Inc) or obtained from Aldich or Fluka in a septum-sealed bottles under inert atmosphere and over molecular sieves. The oxygen free solvents were prepared by freeze-pump-thaw degassing technique

Column chromatography was performed on silica gel 60 (0.040-0.063 mm) or neutral alumina obtained from Aldrich or Merck. The reagents were of technical grade and were distilled prior to use.

8.2 Analytical methods

NMR-Spectroscopy: NMR spectra were recorded either on a Bruker Avance 400 (400 MHz, BBO probe head) or a Bruker Avance DRX 500 (500 MHz, BBO or BBI probe heads) NMR spectrometers. Chemical shifts δ are given in ppm and they are referenced for $CDCl_3$ to 7.26 ppm (^{1}H-NMR) and 77,16 ppm (^{13}C-NMR) for C_6D_6 to 7.16 ppm (^{1}H-NMR) and 128.1 ppm (^{13}C-NMR) and for THF-d_8 to 3.58 ppm (^{1}H-NMR) or to internal standard TMS 0 ppm. ^{31}P-NMR spectra were calibrated to an external standard of a phosphoric acid (85%) to 0 ppm. ^{19}F-NMR spectra were calibrated to the chemical shift of the most downfield isotopomer of external $CFCl_3$ to 0 ppm. ^{11}B-NMR spectra were calibrated to 0 ppm with the $BF_3{\cdot}Et_2O$ as an external standard. The assignment of ^{1}H and ^{13}C-NMR signals was accomplished with help of DEPT135 NMR experiments or by using 2D-NMR experiments (COSY, HMQC, HSQC,

HMBC). Multiplets were assigned as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and br s (broad singlet).

Mass Spectrometry: EI (Electron Impact) and FAB (Fast atom bombardment) mass spectra were recorded by Dr. Heinz Nadig (Department of Chemistry, University of Basel). Electron Impact ionization spectra were recorded on VG70-250 spectrometer and Fast Atom Bombardment spectra were recoded on Finnigan MAR312 with 3-nitrobenzyl alcohol (NBA) as matrix. Electron spray ionization (ESI) was measured on Varian 1200L Triple Quad MS/MS spectrometer with the sample concentrations between 10^{-4} and 10^{-5} M (40 psi nebulizing gas, 4.9 kV spray voltage, 18 psi drying gas at 200 °C, 38-75 V capillary voltage, 1300-1500 V detector voltage) by Dr. I. Fliescher. MALDI (Matrix-assisted laser desorption/ionization) spectra were recorded on Voyager-DE-Pro or Bruker Microflex with *p*-nitroaniline or 2,5-dihydroxybenzoic acid as matrixes.
The signals are given in mass-to-charge ratios (*m/z*) with the relative intensities in brackets.

Elementar Analysis: Elementar analyses were measured by Mr. W. Kirsch (Department of Chemistry, University of Basel) on Lenco CHN-900. The data are indicated in mass percent.

Melting Points: Melting points were determined on Büchi 535 melting point apparatus and they are uncorrected.

Optical Rotations ($[\alpha]_D^{20}$): Optical rotations were measured on a Perkin Elmer Polarimeter 341 in cuvette (l = 1 dm) at 20 °C at 589 nm (sodium lamp). The concentration c is given in g/100 mL.

Infrared Spectroscopy: Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer or on Shimadzu FTIR-8400S spectrometer (Golden Gate ATR). Liquid samples were measured as a thin layer between two sodium chloride plates and solid samples were compressed into potassium bromide pellets. The absorption bands are given in wavenumbers ($\tilde{\nu}$ [cm^{-1}]). The peak intensity is described as s (strong), m (medium), w (weak). The index br stands for broad.

Gas Chromatography: Gas chromatograms were recorded on Carlo Elba HRGC Mega2 Series 800 (HRGS Mega 2) instruments. Achiral separations were performed on a Restek Rtx-

1710 column (30 m × 0.25 mm × 0.25μm) and for chiral separations β- and γ– cyclodextrine columns (30 m × 0.25 mm × 0.25μm) were used.

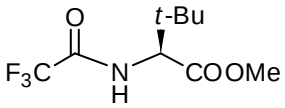
Gas Chromatography with Mass Spectrum detection: HP6890 gas chromatogram with Macherey-Nagel OPTIMA1 Me2Si (25 m × 0.2 mm × 0.35μm, 20 psi, split ca. 20:1, carrier gas: 1 mL/min helium) with HP5970A mass detector (EI). Shimadzu GC-MS-QP2010 SE equipped with Rtx-5MS (30 m × 0.25 mm × 0.25μm, 100 kPa, split ca. 40:1, carrier gas: 3 mL/min).

High-performance Liquid Chromatography: HPLC analyses were measured on Shimadzu systems with SCL-10A system controller, CTO-10AC column oven, LC10AD pump system, DGU-14a degasser. Chiracel brand chiral columns from Diacel Cheical Industries were used with models OD-H, OJ-H, AD-H in 4.6 × 250 mm size.

Thin Layer Chromatography: TLC plates were purchased from Macherey-Nagel (Polygram SIL G/UV_{254}, 0.2mm silicas with fluorescence indicator, 40 × 80 mm).

8.3 Borabox ligands

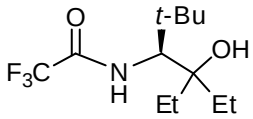
(*S*)-methyl 3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoate [138] **(BB-01)**



Triflouroacetic anhydride (1.14 mL, 8.22 mmol, 1.0 eq.) was added dropwise to a solution of L-*tert*-Leucine methylester (1.194 g, 8.22 mmol, 1.0 eq.) and triethylamin (1.26 mL, 9.05 mmol, 1.1 eq.) in CH_2Cl_2 (25 mL) at -78 °C over 5 min. After complete addition the reaction mixture was stirred at -78 °C for another 1h, then quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and allowed to warm to room temperature. Reaction mixture was then extracted with CH_2Cl_2 (3 x 15 mL), combined organic extracts were washed with brine (1 x 25 mL) and dried over $MgSO_4$. Concentration of the filtrate afforded slightly yellow oil which was then subjected to vacuum distillation (bp. 68 °C / 4 Torr) to provide 1,56 g (79% yield) trifluoroacetamide as a colorless oil[45].

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 6.80 (br s, 1H, NH), 4.49 (d, 1H, J = 9.3 Hz, CH), 3.78 (s, 3H, $COOCH_3$), 1.00 (s, 9H, $(CH_3)_3$).
^{19}F{1H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -76.9.

(*S*)-*N*-(4-ethyl-4-hydroxy-2,2-dimethylhexan-3-yl)-2,2,2-trifluoroacetamide (BB-02)



A solution of trifluoroacetamide **BB-01** (1,56 g, 6,5 mmol, 1 eq.) in THF (8 mL) was added dropwise to ethylamagnesium bromide (1,66 M in Et_2O, 19,5 mL, 32,3 mmol, 5,0 eq.) in 10 mL of THF over 1 h. The reaction mixture was heated to reflux for 6 hours and then was cooled to 0°C, quenched with saturated aqueous NH_4Cl solution (9 mL) and extracted with TBME (4 x 10 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. Concentration of the filtrate gave a yellow oil which was bulb to bulb distilled (bp. 65-70 °C / 6 Torr) to provide white paste which was further purified by

crystallization from *n*-hexane. It was obtained 1.3 g (75 % yield) of the product as white crystals.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 6.90 (d, 1H, J = 7.3 Hz, NH), 3.82 (d, 1H, J = 10.2 Hz, N-CH), 1.78 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.07 (s, 9H, $(CH_3)_3$), 0.92(t, 3H, J = 7.3 Hz, CH_3), 0.83(t, 3H, J = 7.3 Hz, CH_3).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 157.4 (q, J_{CF} = 36 Hz, C=O), 116.7 (q, J_{CF} = 288 Hz, CF_3), 79.5 (C-OH), 60.4 (CH), 36.7 (**C**$(CH_3)_3$), 30.0 (CH_2), 29.2 (CH_2), 29.1 (C(**CH_3**)$_3$), 8.6 (CH_3), 8.3 (CH_3).

^{19}F{1H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -76.9.

MS (FAB) m/z (%) 270 ([M+H]$^+$, 18), 271 (3), 252 (100), 196 (26), 137 (60).

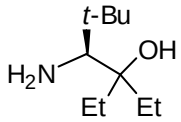
IR ($\tilde{\nu}$ [cm^{-1}]) 3465m, 3397m, 2979m, 1718s, 1541m, 1484w, 1393m, 1346m, 1270m, 1223s, 1150s, 1036w, 971w, 931w, 899w, 872w, 772w, 713w, 644w.

Elementar analysis for $C_{12}H_{22}F_3NO_2$ (269.30) calcd %: C, 53.52; H, 8.23; N, 5.20; found: C, 53.83; H, 7.96; N, 5.05.

$[\alpha]_D^{20}$ = -25.8° (c=1.00, $CHCl_3$)

M.p. 83.7 – 84.5 °C

(*S*)-4-amino-3-ethyl-5,5-dimethylhexan-3-ol (58)



To deprotect TFA protected aminolcohol BB-02 after 5 hours reflux in 5% methanolic NaOH solution overnight was observed only 50% conversion. After additional 16h reflux was conversion around 90%. Therefore formation of the aminoalcohol BB-03 was performed without N-protection of L-*tert*-leucine methylester.

To a precooled solution of EtMgBr (6,2 mL, 8,6 mmol, 1,4 M in Et_2O, 5 eq.) in 3 mL THF was dropwise added L-*tert*-Leucine methylester hydrochloride (0,25 g, 1,7 mmol, 1 eq.) in 4 mL THF at -40°C within 20 min. After the addition was complete the reaction mixture was warmed to r.t. and refluxed overnight. The reaction was quenched by sat. solution NH_4Cl at 0°C and followed by addition of 10% HCl until clear solution was obtained. Product was extracted from the mixture using TBME (6 x 15 mL) and combined organic extracts were

washed by 10 mL brine and dried over Na_2SO_4. After concentrating extracts was resulting yellow oil purified by vacuum distillation (55°C/0,15 Torr) to provide 284 mg (95% yield) of the product as a colorless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 2.53 (s, 1H, OH), 1,76 (m, 1H, CH), 1.46 (m, 2H, CH_2), 1.43 (m, 2H, CH_2), 1.00 (s, 9H, $(CH_3)_3$), 0.91 (t, 3H, J = 7.3 Hz, CH_3), 0.89 (t, 3H, J = 7.3 Hz, CH_3).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 75.6 (C-OH), 62.9 (CH), 35.5 (**C**$(CH_3)_3$), 29.8 (CH_2), 29.7 (CH_2), 29.1 (C(**CH_3**)$_3$), 8.5 (CH_3), 8.3 (CH_3).

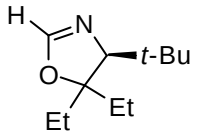
MS (FAB) m/z (%) 174 ($[M+H]^+$, 100), 175 (12), 100 (75), 57 (53).

IR ($\tilde{\nu}$ [cm^{-1}]) 3412m, 3332m, 2961s, 2882s, 2361w, 1617w, 1467m, 1398m, 1369m, 1262w, 1218w, 1146m, 1038w, 950m, 893m, 833m, 755m.

Elementar analysis for $C_{10}H_{23}NO$ (173.30) calcd %: C, 69.31; H, 13.38; N, 8.08; found: C, 69.03; H, 13.09; N, 7.92.

$[\alpha]_D^{20}$ = -26.4° (c=0.99, $CHCl_3$).

(*S*)-4-(*tert*-butyl)-5,5-diethyl-4,5-dihydrooxazole (59)



The oven dried three neck flask equipped with the reflux condenser and magnetic stir bar was charged under the inert atmosphere with aminoalcohol (1,050 g, 6,1 mmol, 1eq.), ethyl formimidate hydrochloride (0,796 g, 7,3 mmol, 1,2 eq.) and dissolved in 100 mL CH_2Cl_2 and refluxed overnight under the inert atmosphere. Then triethylamine (4,22 ml, 30,3 mmol, 5 eq.) was carefully added to a reaction mixture via syringe followed by addition of 60 mL sat. sol. $NaHCO_3$. After the extraction with 3 x 20 mL CH_2Cl_2 were the combined organic extracts dried over Na_2SO_4 and after evaporation of the volatiles in vacuum was obtained 1,198 g of the yellowish oil as a crude product which was subjected to vacuum distillation (38 °C / 0,1 Torr) to obtain 650 mg (59%) of the product as a colorless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 6.79 (d, J = 2.1 Hz, 1H, H-C=N), 3.47 (d, J = 2.3 Hz, 1H, CH-N), 1.93 (m, 1H, CH_2), 1.72 (m, 2H, CH_2), 1.57 (m, 1H, CH_2), 1.02 (s, 9H, $(CH_3)_3$), 0.95 (t, 3H, J = 7.3 Hz, CH_3), 0.86 (t, 3H, J = 7.3 Hz, CH_3).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 153.3 (HC=N), 91.6 (C-Et_2), 78.9 (CH*t*Bu), 34.4 (**C**$(CH_3)_3$), 29.6 (CH_2), 28.5 (C(**CH_3**)$_3$), 25.9 (CH_2), 8.9 (CH_3), 8.2 (CH_3).

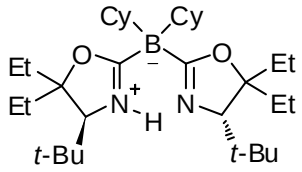
MS (FAB) m/z (%) 184 ($[M+H]^+$, 100), 83 (66), 57 (93).

IR ($\tilde{\nu}$ [cm^{-1}]) 3067w, 2968s, 2883s, 1638s, 1463m, 1365m, 1291w, 1160m, 1100s, 1026w, 926m, 885w.

Elementar analysis for $C_{11}H_{21}NO$ (183,29) calcd %: C, 72.08; H, 11.55; N, 7.64; found: C, 71.72; H, 11.25; N, 7.63.

$[\alpha]_D^{20}$ = -72.2° (c=0.93, $CHCl_3$).

Bis (2,2-diethyl-(*S*)-*tert*-butyl-oxazoline)dicyclohexylborane (57g)



To a precooled solution of the (*S*)-4-(*tert*-butyl)-5,5-diethyl-4,5-dihydrooxazole (300 mg, 1,64 mmol, 2 eq.) in 100 mL THF was dropwise added *t*-BuLi (1,1 mL 1,7 M, 2,2 eq) at -78°C and stirred for 30 min during which the colorless solution turned yellow. Then was premixed solution of the dicyclohexylchloroborane (0,82 mL, 1M in hexane, 1eq) in toluene (5 mL) added via cannula to the reaction mixture. The cooling bath was immediately removed and the reaction was leaved warm to room temperature overnight. All volatiles were removed and resulting white foam was transferred on a column (25 g SiO_2) end eluted by Hexane/EtOAc/Et_3N (10:1:0,5) mixture. The product is decomposing during the column chromatography, therefore second purification is needed on the neutral aluminium oxide column (R_f=0.85, *n*-pentane) stained by PMA solution.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 3.49 (s, 2H, CHN), 1.93-1.88 (m, 4H, $CH_{2\ Et}$), 1.88-1.80 (m, 4H, $CH_{2\ Et}$), 1.66-1.58 (m, 8H, H_{Cy}), 1.44-1.40 (m, 2H, H_{Cy}), 1,17-1,11 (m, 6H, H_{Cy}), 1,05 (s, 18H 2 x *t*Bu), 1.04 (t, J = 3.9 Hz, 6H, $CH_{3\ Et}$), 1.01 (t, J = 3.9 Hz, 6H, $CH_{3\ Et}$), 0,94-0.89 (m, 4H, H_{Cy}), 0.63-0.57 (m, 2H, H_{Cy}).

$^{13}C\{^1H\}$-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 92.3 (2C, $OCEt_2$), 74.5 (2C, CH*t*Bu), 33.9 (2C, $C(CH_3)_3$), 31.9 (4C, $CH_{2\ Cy}$), 31.7 (2C, CMe_2), 29.8 ($CH_{2\ Et}$), 29.7 ($CH_{2\ Et}$), 29,3 (2C, $CH_{\ Cy}$) 28.9 (2C, $CH_{2\ Cy}$),28.8 (4C, $CH_{2\ Cy}$), 27.7 (6C, $C(CH_3)_3$), 23.5 (2C, CH_2), 8.9 ($CH_{3\ Et}$), 8.2 ($CH_{3\ Et}$).

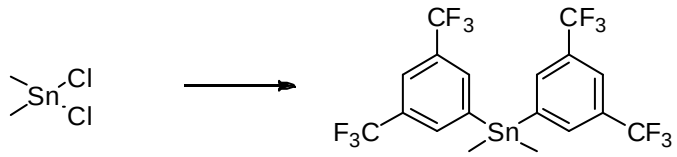
$^{11}B\{1H\}$ NMR (160.8 MHz, $CDCl_3$, 295K): δ(ppm) -11.8.

MS (FAB) m/z (%) 543 ($[M+H]^+$, 100), 542 (24), 544 (36), 278 (16), 196 (38), 83 (54).

Elementar analysis for $C_{34}H_{63}BN_2O_2$ (542.69) calcd %: C, 75.25; H, 11.70; N, 5.16; found: C, 75.27; H, 11.55; N, 5.05.

$[\alpha]_D^{20}$ = -13.4° (c=0.32, $CHCl_3$).

Bis(3,5-bis(trifluoromethyl)phenyl)dimethylstannane (60)



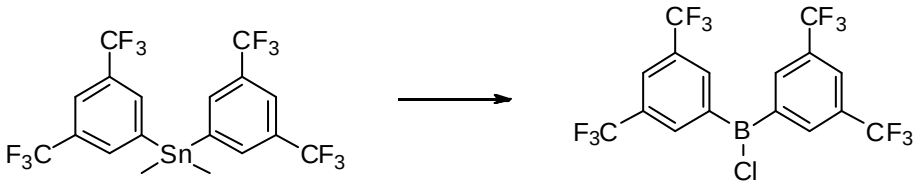
This compound was prepared according to the literature procedure[34]. Oven dried three necked flask was equipped with magnetic stir bar, dropping funnel and reflux condenser and it was cooled to room temperature under positive pressure of argon and then charged with the oven dried magnesium turnings (1,68 g, 69 mmol, 1,5 eq.) which were then activated by a small crystal of I_2. Solution of 3,5-bis(trifluoromethyl)phenylbromide (13,5 g, 46 mmol, 1 eq.) in 20 mL dry diethylether was added from the dropping funnel over course of 20 minutes in a rate to mantain gentle reflux of the reaction mixture. After the reaction heat ceased the solution of a Grignard reagent was heated[139] to a reflux for another 1 hour and stirred in addition overnight at room temperature. Then was the solution filtered under positive argon pressure through the glasswool plug over cannula to another reaction vessel for following reaction. Concentration of the final Grignard solution was recalculated according to the amount of the Mg turnings residue washed by acetone after filtration.

To a precooled solution of (3,5-bis(trifluoromethyl)phenyl)magnesium bromide (25 mL, 1,8 M in Et_2O, 46 mmol, 2 eq.) was added solid dimethyltindichloride (5g, 23 mmol, 1 eq.) *Note! Me_2SnCl_2 is highly toxic. Use appropriate precautions when handling this material*. at -78°C and stirred 2 hours and then was the reaction mixture warmed to RT and stirred overnight. The clear colorless solution was concentrated in vacuum and it was obtained 12,6 g (96 %

yield) of a white crystalline solid[140] which was used in the next experiment without further purification.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 0.72 (s, 6H, $^{2}J_{H\text{-}Sn117,\ 119}$ = 58.1, 55.5 Hz, CH_3), 7.94, 7.88, 7.83 (m, $CH_{Ar,}$ 6 H).
^{19}F{1H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -64.0.

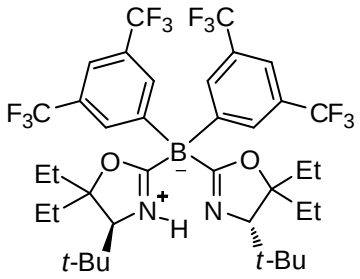
Bis(3,5-bis(trifluoromethyl)phenyl)chloroborane (61)



The oven dried thick-walled glass 100 mL Schlenk vessel equipped with the magnetic stir bar and rubber septum was after cooling to room temperature charged with the crystalline bis(3,5-bis(trifluoromethyl)phenyl)dimethylstannane (6,3 g, 11 mmol, 1 eq.) and dry *n*-heptane (25 mL). The solution of BCl_3 (11,0 mL, 1.0 M in *n*-heptane, 1 eq.) was added dropwise via syringe at rt and solution was stirred for additional 1 hour. Then was rubber septum replaced by the glass stopper equipped with the Teflon O-ring and the V-shaped metal clamp. The Schlenk flask was placed into the oil bath and it was heated to 100 °C for 48 hours. After cooling to rt was the reaction solvent removed under reduced pressure on the Schlenk line by using distillation apparatus connected to the two additional cooling traps to trap traces of the regenerated volatile dimethyltindichloride. *Note! Me_2SnCl_2 is highly toxic. Use appropriate precautions when handling this material*. The crude slightly shadow solid was then connected to the bulb to bulb distillation apparatus (also equipped with two additional cooling traps) and Me_2SnCl_2 was then sublimed (40°C / 1 Torr) from the solid crude. The residue after the sublimation was then purified by a high vacuum sublimation on a diffusion pump (55°C / 5.10^{-5} mbar) and it was obtained 2.858 g (55 % yield) of the product[140] as a white solid.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 8.06 (br s, 2H, CH_{Ar}), 7.92 (br s, 4H, CH_{Ar}).
^{19}F{1H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -63.9.

Bis(2,2-diethyl-(*S*)-*tert*-butyl-oxazoline)bis(3,5-bis(trifluoromethyl)phenyl)borane (57h)



To a precooled solution of the (*S*)-4-(*tert*-butyl)-5,5-diethyl-4,5-dihydrooxazole **(**100 mg, 546 µmol, 2 eq.) in 30 mL THF was dropwise added *t*-BuLi (0.35 mL, 1.7 M in *n*-hexane, 2.2 eq.) at -78°C and reaction mixture was stirred for 30 min while the solution turned yellow. Then Bis(3,5-bis(trifluoromethyl)phenyl)chloroborane (129 mg, 273 µmol, 1 eq.) in benzene (3 mL) was added via cannula. After addition was complete, cooling bath was removed and the reaction mixture was stirred overnight at rt. All volatiles were evaporated and resulting white foam was transferred on to a column (25 g silicagel, Hex:EtOAc:Et_3N (10:1:0,5), Rf=0.94). After the column chromatography was obtained 100mg of the product with small amounts of impurities, therefore chromatography was performed again using the same solvent mixture on silica. It was obtained 40 mg (18%) of the product as a white wax. The product seemed to be unstable and it was probably decomposing during the chromatography therefore it could not be obtained as an analytically pure sample and it was used in the next experiments without being fully characterized.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 8.75 (br s, 1H, N-H), 7.78 (br s, 4H, ArH_{ortho}), 7.69 (br s, 2H, ArH_{para}), 3.55 (s, 2H, CHN), 2.01-1.91 (m, 2H, $CH_{2\ Et}$), 1.88-1.78 (m, 2H, $CH_{2\ Et}$), 1.71-1.60 (m, 4H, $CH_{2\ Et}$), 1.04 (s, 18H 2 x *t*Bu), 0.95 (t, *J* = 7.6 Hz, 6H, $CH_{3\ Et}$), 0.82 (t, *J* = 7.6 Hz, 6H, $CH_{3\ Et}$).

^{19}F{1H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -63.8.

MS (MALDI) m/z (%) 803 ($[M+H]^+$, 100).

General procedure for the conversion protonated borabox ligands into their lithium salts[36]

n-BuLi (48 µl, 77 µmol) was added at 0°C to a solution of protonated borabox complex **BB-05** (40 mg, 74 µmol) in 4 ml of THF. After 2 hours of additional stirring at room temperature, the volatiles were removed under reduce pressure. There was isolated lithiated borabox complex (**BB-05)-Li** (40 mg, 73 µmol, 99 % yield) which was used in the further reactions.

General procedure for the cyclopropanation reaction[36]

Ligand (**BB-05)-Li** (7 mg, 0.012 mmol) and $Cu[(OTf)_2]$-0.5(C_6H_6) (2.5 mg, 0.005 mmol) were dissolved in 1 mL 1,2-dichlorethane (degassed in the ultrasonic bath) and resulting solution was stirred at room temperature for 30 minutes before styrene (115 µL, 1 mmol, freeze-pump-thaw degassed) was then added. After further 30 minutes solution of the *tert*-butyl diazoacetate (171 mg, 166 µL, 1.2 mmol) in 1 mL 1,2-dichlorethane was added over course of ~6 hours via a syringe pump. After the addition was complete the reaction was stirred for an additional 12 hours. The reaction mixture was then concentrated in vacuum to afford crude product (226 mg). Flash chromatography using hexanes-ethylacetate (9:1) (cis/trans product with R_f=0.5, and fumarate and maleate with Rf=~0,3) afforded a *cis/trans* mixture (160 mg) of the cyclopropane carboxylates. From this mixture was recorded 1H NMR and GC (1,5°/min, 50-180°C). R_t for *cis/trans* products was 69,85 min and 73,74 min (fumarate and maleate R_t = 54,54 min and 56,62 min). From GC determined *cis/trans* ratio of cyclopropane isomers was same as from the ^{1}H NMR.

Transesterification of the cyclopropanation products into the corresponding ethylesters[141]

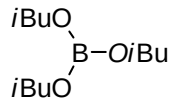
The crude reaction mixture from cyclopropanation reaction was dissolved in a neat CF_3COOH and stirred 10 minutes at rt. The CF_3COOH was evaporated in vacuum and distillation residue was furthermore several times codistilled with toluene. The crude product

was dissolved in DCM and separated by filtration from fumaric and maleic acid to afford a mixture of *cis/trans* cyclopropyl acids.

To a solution of cyclopropyl acids (100 mg, 617 µmol) were added Pyridine (3,3 mL, 0,25 M in Toluene), $SOCl_2$ (3,3 ml 0,7M in Toluene) and EtOH (3,3 ml 1,4 M in Toluene). The reaction mixture was stirred at 100°C for 1 hour, diluted with Et_2O and extracted 3 times with 0,1 M phosphate buffer (prepared form NaH_2PO_4 and (1:5) HCl in ratio 40:1 to pH = 3), followed by sat. solution $NaHCO_3$. After drying with $MgSO_4$, solvent was removed in vacuum. GC was recorded on Beta-cyclodextrine DEtButSil (SE54) 100-130°C (0,5°C/min).

8.4 Non-symetrically substituted boron compounds

Triisobutyl borate (63)

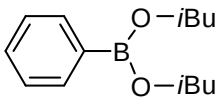


In the two necked round-bottomed flask fitted with Dean-Stark apparatus, boric acid 20g (323 mmol, 1eq.) was dissolved in isobutanol 97 mL (1,051 mol, 3,25 eq.) and refluxed under Ar for 5 hours. After removal of 17,5 ml of water was excess of the isobutanol (7,5 mL) distilled off at atmospheric pressure (bp. 108°C) and then was the reaction mixture distilled in vacuum (58°C / 3 Torr) to produce 68 g (95% yield) of the triisobutylborate **63** as a colorless liquid.

$C_{12}H_{28}BO_3$ (238,15 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 3.56 (d, J = 6.5 Hz, 6H, CH_2), 1.77 (m, 3H, CH), 0.88 (d, J = 6.7 Hz, 18H, CH_3).

Diisobutyl phenylboronate (66)



To as solution of 24 mL (48 mmol, 1.1 eq., 2 M in Et_2O) of phenylmagnesium bromide in 50 mL of diethylether was added 10 g (44 mmol, 1 eq.) of triisobutylborate in 20 mL of diethylether at -78°C in course of 30-40 minutes. The reaction mixture was then leaved warm up to room temperature and stirred overnight. Afterwadrs was reaction flask place into the oil bath and refluxed for 2 hours. After cooling to room temperature was reaction flask plugged to a source of gaseous hydrochloric acid which was bubled through the reaction mixture for 1 hour. Diethylether was evaporated, the white precipitate was filtered off and washed with benzene. The filtrate was then fractionally distilled in vacuum (68°C/4 Torr 2nd fraction) to obtain 6,32 g (64 % yield) of product **66** as colorless liquid. 1st fraction 56°C/5 Torr contained starting material (510mg) and 3rd fraction 61°C/0,07 Torr (0,732 g) containing isobutyl dipehnylborate.

$C_{14}H_{23}BO_2$ (234.14 g·mol^{-1})

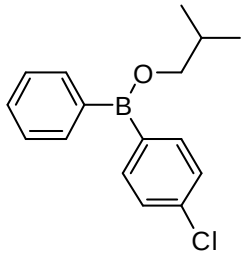
^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.69-7.67 (m, 2H, ArH), 7.43-7.38 (m, 3H, ArH), 3.86 (d, *J* = 6.5 Hz, 4H, CH_2), 1,95-1.89 (m, 2H, CH), 0.99 (d, *J* = 6.7 Hz, 12H, CH_3).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 134.0 (C_{ArH}), 130.0 (C_{ArH}), 128.1 (C_{ArH}), 71.4 (CH_2), 30.6 (CH), 19.4 (CH_3).

IR ($\tilde{\nu}$ [cm^{-1}]) 3052w, 2957s, 2878s, 2360m, 1601m, 1470s, 1435s, 1411s, 1324s, 1258s, 1173w, 1130m, 1072w, 1025s, 951w, 910w, 826w, 759w, 700m, 651m.

Elementar analysis for $C_{10}H_{16}ClNO_3$ (234.14) calcd %: C, 71.82; H, 9.90; found: C, 70.64; H, 9.65.

(4-chlorophenyl)(isobutoxy)(phenyl)borane (73)



The diisobutylphenylboronate (**66**) 0,827g (3.53 mmol, 1.0 eq.) was dissolved in 3 mL of diethyl ether and then was added with syringe pump during 2 hour of Grignard reagent 3,9 mL (3.89 mmol, 1M, 1.1 eq.) at -78°C. After addition was complete, the reaction mixture was stirred at the same temperature for another 5 hours and then leaved warm overnight in the cooling bath. Reaction was quenched with 3 mL of 5% H_2SO_4 and extracted with 3 x 25 mL of diethylether. Solvent was distilled off and 5 mL of *i*BuOH was added to the residue and co-distilled with 5 x 5 mL of *i*BuOH. The crude product (960mg) was then fractionaly distilled (68°C/0,06 Torr) to obtain 570 mg (60% yield) of the product **73** as a colorless liquid.

$C_{16}H_{18}BClO$ (272.58 g·mol^{-1})

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.63-7.60 (m, 4H, ArH), 7.49-7.39 (m, 5H, ArH), 3.94 (d, *J* = 6.4 Hz, 2H, CH_2), 2.02-1.95 (m, 1H, CH), 1.00 (d, *J* = 6.7 Hz, 6H, CH_3).

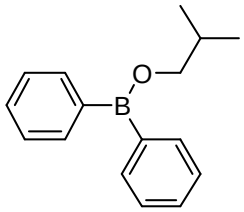
^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 136.9 (C_{Ar}), 136.3 (C_{ArH}), 134.3 (C_{ArH}), 130.5 (C_{ArH}), 128.3 (C_{ArH}), 128.1 (C_{ArH}), 74.8 (CH_2), 30.7 (CH), 19.4 (CH_3).

MS (EI, 70 eV): m/z (%): 272 (12, M^+), 199 (29), 139 (48), 105 (64), 91 (25), 78 (30), 56 (100), 41 (21).

IR ($\tilde{\nu}$ [cm^{-1}]) 3050w, 2959s, 2877m, 2361w, 1587s, 1469m, 1433m, 1385m, 1331s, 1260s, 1180w, 1130w, 1089m, 997w, 945w, 895w, 822m, 701m, 646w.

Elementar analysis for $C_{16}H_{18}BClO$ (272.58) calcd %: C, 70.50; H, 6.66; found: C, 69.35; H, 6.85.

Isobutoxydiphenylborane (64)



To a solution of 5 g (21.72 mmol, 1eq.) triisobutylborate in 20 mL of Et_2O, 23.9 mL of PhMgBr (47.79 mmol, 2M in Et_2O, 2.2 eq.) was added during 2 hours via syringe pump at -78°C and stirred at this temperature for additional 5 hours and then leaved warm overnight in the cooling bath to room temprature. Following day was the reaction mixture refluxed for 4 hours and then quenched with 25 mL of 5% HCl (aq.) and extracted with diethyl ether. Solvent was removed in vacuum and residue was co-distilled with 3 x 10 mL of isobutanol. The crude mixture was distilled on Kugelrohr at 150°C/0.1 Torr to obtain 4.764g (92% yield) of product **64** as colorless oil.

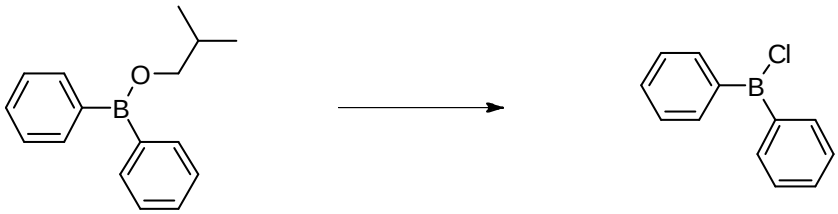
$C_{16}H_{19}BO$ (238.13 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.68-7.65 (m, 2H, ArH), 7.49-7.41 (m, 6H, ArH), 3.95 (d, J = 6.4 Hz, 2H, CH_2), 2.04-1.94 (m, 1H, CH), 1.00 (d, J = 6.7 Hz, 6H, CH_3).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 134.7 (C_{ArH}), 130.5 (C_{ArH}), 128.0 (C_{ArH}), 74.8 (CH_2), 30.8 (CH), 19.5 (CH_3).

MS (EI, 70 eV): m/z (%): 238 (4, M^+), 182 (98), 154 (24), 105 (100), 78 (92), 56 (35).

Chlorodiphenylborane (62)



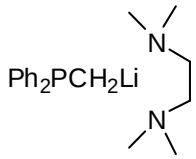
1.5 g (6.3 mmol, 1eq.) of isobutyl diphenylboronate was dissolved in 10 mL DCM and colled to 0°C then 1,38 g (6.3 mmol, 95%, 1 eq.) of PCl_5 was added in two portions. During addition the reaction was accompanied by evolution of the heat. After 15 min was the cooling bath removed and stired for another 30 minutes. The isobutylchloride (b.p. 69°C) and $POCl_3$ (b.p. 107°C) were removed by reduced pressure distillation with an additional cooling trap. The chlorodiphenylborane was distilled (80°C/0.06 Torr) to obtain 0,836 g (66% yield) of the product as an transparent oil. By recrystallization from 4 mL of *n*-heptane at -35°C was obtained 640mg a white crystalline solid.

$C_{12}H_{10}BCl$ (200.47 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 8.06-8.02 (m, 4H, ArH), 7.68-7.62 (m, 2H, ArH), 7.56-7.50 (m, 4H, ArH).

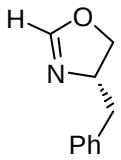
^{11}B-NMR (160.5 MHz, $CDCl_3$, 300K): δ(ppm) 62.8.

Lithim(TMEDA)methylenedipehnylphosphine (83)[64]



A solution of 3.12 mL of *n*-BuLi (1.6M in hexane) was diluted with 3 mL of *n*-pentane and 0.580 g (5 mmol, 0.75 mL, *d=0.775*) of *N,N,N′,N′*-tetramethylethylen-1,2-diamine was dropwise added. After 15 min stirring of the reaction mixture at room temperature, 1g (5 mmol, *d=1.076*) of methyldiphenylphosphine was added and continued stirring for another 48 hours. The precipitated yellow product was filtered by using Schlenk filtration apparatus and washed with 3 x 5 mL of *n*-pentane. Filtrate was then dryed in the vacuum. It was obtained 0.968g (60% yield) of **83** as a yellow solid.

(*R*)-4-benzyl-4,5-dihydrooxazole (87)

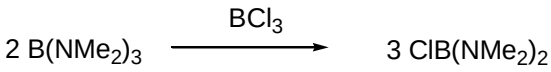


(*S*)-Phenylaninol 1.3 g (8.60 mmol, 1 eq.) was dissolved in 100 mL of dry dichloromethane and 1.036g (9.45 mmol, 1.01eq) of ethylformimidate hydrochloride was added in one portion. Reaction was refluxed overnight and after cooling to room temperature 6 mL of triethylamine was added. The reaction mixture was then diluted with 70 mL of sat. sol. $NaHCO_3$ followed by the extraction with 3 x 30 mL of diethylether. Organic extracts were dried over Na_2SO_4 and solvent was evaporated in vacuum to obtain crude product (1.305 g). By distillation on Kugelrohr (110°C/0.1 Torr) was obtained 1.150 g (83% yield) of the product **87** as colorless oil.[140]

$C_{10}H_{11}NO$ (161.2 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.34-7.28 (m, 2H, ArH), 7.25-7.19 (m, 3H, ArH), 6.81 (d, *J* = 1.7 Hz, 1H, $HC_{oxaz.}$), 4.44-4.34 (m, 1H, NCH), 4.16 (dd, *J* = 9.1 Hz, 1H, OCH_2), 3.92 (dd, *J* = 8.0 Hz, 1H, OCH_2) 3.08 (dd, *J* = 13.8, 5.8 Hz, 1H, CH_2Ph), 2.68 (dd, *J* = 13.8, 8.2 Hz, 1H).

Bis(dimethylamino)chloroborane (116)



To a precooled solution of 1.411 g (9.86 mmol, 2eq.) of $B(NMe_2)_3$ in 20 mL of *n*-pentane was dropwise added 4.93 mL of BCl_3 (1M solution in *n*-hexane, 1eq.) at -20°C. Reaction mixture was warmed to room temperature and stirred for additional 1 hour. Then the solvent was removed in vacuum and crude reaction mixture (1.035 g) was fractionally distilled. It was obtained 0.836 g (42% yield) of the product **116** as colorless air sensitive liquid. **116** has to be stored below 4°C otherwise it dimerizes to white solid $[Me_2NBCl_2]_2$ with ^{11}B-NMR shift of 10.5 ppm (in $CDCl_3$).

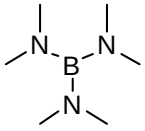
$C_4H_{12}BClN_2$ (134.42 g·mol^{-1})

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 2.72 (s, 12H, CH_3).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 300K): δ(ppm) 27.8.

MS (EI, 70 eV): m/z (%): 134 (89, M^+), 119 (53), 99 (80), 90 (81), 71 (67), 57 (57), 43 (100).

Tris(dimethylamino)borane (117) [142]



Preparation of 1,5 M etheral solution of dimethylamine

The saturated solution of NaOH (approx. 12 g NaOH in 12 mL H_2O) in Erlemayer flask was overlayed with 100 mL of diethylether and it was cooled to 0°C. Then 12.233 g of *N*,*N*-dimethylamine hydorchloride was added in several portions as a solid. The solution was after 2 hours decanted and dried overnight over KOH in the fridge and used as a stock solution.

To a precooled solution of 4.12 mL (3g, *d*=0.727, 29.7 mmol) of Et_3N in 16 mL of *n*-pentane was dropwise added 9.9 mL (9.9 mmol, 1M in *n*-hexane) of boron trichoride at -20°C. Then was the resulting suspension well stirred at room temperature for 5-10 minutes and recooled back to -20°C. In course of 2 hours 20 mL (1.5M, 30 mmol) of dimethylamine in Et_2O was dropwise added and then slowly (1,5 hour) warmed to room temperature. The reaction mixture was refluxed for 1 hour and then the voluminous white precipitate was filtered off under nitrogen. The filtration cake was several times washed with *n*-pentane. The combined filtrates were freed of solvent and distilled in vacuum (bp. 44°C/15 Torr). It was obtained 1,411g (33% yield) of the product as a colorless air sensitive liquid.

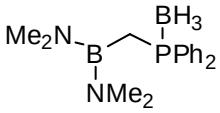
$C_6H_{18}BN_3$ (143.04 g·mol^{-1})

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 2.52 (s, 18H, CH_3).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 300K): δ(ppm) 39.6 (CH_3).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 300K): δ(ppm) 27.4.

1-((diphenylphosphino(borane))methyl)-*N,N,N',N'*-tetramethylboranediamine (119)



159 mg (0.74 mmol) of $MePPh_2 \cdot BH_3$ **84** was dissolved in 2.5 mL of THF and cooled to 0°C, then 0.51 mL of *n*-buthyllithium (1.6M in hexane, 1.1 eq.) was dropwise added via syringe. The reaction mixture was stirred for 30 min at 0°C and then warmed to room temperature and stirred for another 90min to obtain **85**. Afterwards was the reaction cooled to -78 °C and solution of 100 mg (0.74 mmol) of the $(Me_2N)_2BCl$ in 1 mL of *n*-pentane was dropwise added via syringe. Cooling bath was removed, reaction mixture discolored while warming up to the room temperature and continued stirring overnight. The solvent was removed in vacuum and 223 mg (96% yield) of the product **119** was obtained as colorless oil.

$C_{17}H_{27}B_2N_2P$ (312.01 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 295K): δ(ppm) 7.68 (dd, *J* = 9.8, 8.3 Hz, 4H, ArH), 7.47 – 7.38 (m, 6H, ArH), 2.38 (s, 12H, CH_3), 1.83 (d, *J* = 15.5 Hz, 2H, CH_2) 1.02 (br q, 3H, BH_3).

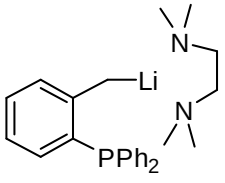
^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 295K): δ(ppm) 132.3 (d, *J* = 9.1 Hz, C_{ArH}), 132.0 (C_{Ar}), 130.6 (d, *J* = 2.4 Hz, C_{ArH}), 128.4 (d, *J* = 9.7 Hz, C_{ArH}), 40.3 (CH_3).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K): δ(ppm) 31.2 (B-N), -37.5 (m, B-P).

^{31}P-NMR (202.5 MHz, $CDCl_3$, 295K): δ(ppm) 16.8 (m, P-B).

MS (EI, 70 eV): m/z (%): 298 (20, $M^+ - BH_3$), 200.1 (100), 183 (49), 132 (18), 111 (20), 91 (13), 44 (13).

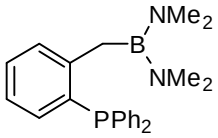
(2-(diphenylphosphino)benzyl)lithium(TMEDA)[96e]



Solution of 0.68 mL of *n*-buthyllithium (1,6M in *n*-hexane) was diluted with 3 mL of *n*-pentane and treated with 0.163 mL (1.09 mmol, *d*=0.775) of N,N,N',N'-tetramethylethylendiamine at room temperature and stirred for 15 minutes. Then 0.300 g (1.09

mmol) of diphenyl(o-tolyl)phosphine in 2 mL of *n*-pentane was added and the reaction mixture was stirred for 48 hours. The yellow precipitate **120** was isolated by filtration under Ar followed by washing with 2 x 10 mL of *n*-pentane to obtain 290 mg (67% yield) of the orange powder as product **120** which was stored in the glovebox for further transformations.

1-(2-(diphenylphosphino)benzyl)-*N,N,N′,N′*-tetramethylboranediamine[96e] (120)



98 mg of the chloroborane in 5 mL of *n*-pentane was added to a solution 290 mg of Li(TMEDA) salt in 5 ml THF at -78°C. The reaction mixture was warmed up to room temperature (from dark brown to brownish during 30min after heating to rt.) and volatiles were removed under high vacuum. The residue was extracted with 2 x 10ml of pentane and purified by crystallization at -30°C.

$C_{23}H_{28}BN_2P$ (374.27 $g \cdot mol^{-1}$)

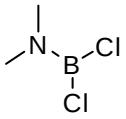
^{1}H-NMR (500.1 MHz, $CDCl_3$, 295K): δ(ppm) 7.40 – 7.25 (m, 11H, ArH), 7.10-7.07 (m, 2H, ArH), 6.84-6.82 (m, 1H, ArH), 2.57 (s, 12H, CH_3), 2.38 (s, 2H, CH_2).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K): δ(ppm) 34.5.

^{31}P-NMR (202.5 MHz, $CDCl_3$, 295K): δ(ppm) -13.7.

MS (EI, 70 eV): m/z (%): 330 (100, M^+ - NMe_2), 275 (8), 197 (6), 183 (8), 165 (5), 99 (9), 56 (6).

Dimethylaminoborane dichloride (121)



Dimethylamine 13.3 mL (20 mmol, 1,5M solution in Et_2O) was dropwise added to the precooled solution 20 mL (1M in hexane, 20 mmol) of BCl_3 in 20 mL of *n*-pentane at -20°C. After warming up to room temperature and stirring for 15 min was the reaction recooled back to -20°C and 2.78 mL (20 mmol, *d*=0.727) of triethylamine in 8 mL of *n*-pentane was added.

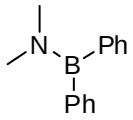
Then slowly warmed up a stirred at room temperature overnight. The white precipitate was filtered off and washed with *n*-pentane. After removing the solvent in vacuum was the crude mixture fractinally distilled at 51-53°C/90 Torr to obtain 1.02 g (41% yield) of **121** as colorless air sensitive liquid.

$C_2H_6BCl_2N$ (125.79 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 2.94 (s, 6H, CH_3).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 300K): δ(ppm) 30.5.

***N,N*-dimethyl-1,1-diphenylboranamine (122)**



Dimethylaminoboron dichloride **121** 510 mg (4.05 mmol) was dissolved in 10 mL of benzene and 4.05 mL (2M solution in Et_2O) of PhMgBr was dropwise added at 0°C. Cooling bath removed and reaction mixture was stirred overnight at room temperature. Then was the solvent removed in vacuum and after fractional distillation at 75°C / 0,08 Torr was obtained 376 mg (44 % yield) of the product **122** as a transparent liquid.

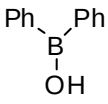
$C_{14}H_{16}BN$ (209.09 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 295K): δ(ppm) 7.28-7.26 (m, 4H, ArH), 7.22 – 7.18 (m, 6H, ArH), 2.88 (s, 12H, CH_3).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 295K): δ(ppm) 133.2 (C_{ArH}), 127.6 (C_{ArH}), 127.3 (C_{ArH}), 41.7 (CH_3).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K): δ(ppm) 41.8 (B-N).

Diphenylborinic acid (91)



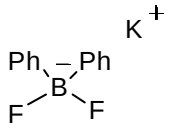
Dipehnylborinic acid was prepared by quenching isobutoxydiphenylborane **(64)** by 20 mL of 1M HCl (aq.). Followed by extraction with 3 x 15 mL of diethylether was obtained diphenylborinic acid **91** which was used for further transformations without any additional purification. The diphenylborinic acid is unstable and therefore it was prepared from its esters freshly before use.

$C_{12}H_{11}BO$ (182.03 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.94 (dd, *J* = 8.1, 1.4, 4H), 7.59 – 7.51 (m, 2H), 7.51 – 7.43 (m, 4H).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K): δ(ppm) 45.9.

Potassium diflurodipehnylborate (Ph-107)



1.5 g (8.24 mmol, 1eq.) of diphenylborinic acid **61** was dissolved in 10 mL of methanol and cooled to 0°C. Solid KHF_2 1.93 g (24.72 mmol, 3eq.) was added in one portion and the reaction was stirred for 1 hour at 0°C. Methanol was then evaporated in vacuum and the residual solid was dissolved in the acetone. Inorganic salts were decanted and sample was concentrated in vacuum. By addition of diethylether to this solution the product precipitated out. Crystals were filtered off, washed with 2 x 5 mL of Et_2O and dried in vacuum. It was obtained 1.753 g (88% yield) of the product **Ph-107** as a white crystalline solid.

$C_{12}H_{10}BF_2K$ (242.11 $g \cdot mol^{-1}$)

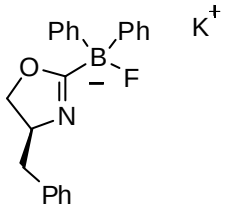
^{1}H-NMR (500.1 MHz, DMSO-d_6, 295K): δ(ppm) 7.33 (d, *J* = 6.8 Hz, 2H, ArH), 7.01 (t, *J* = 7.4 Hz, 2H, ArH), 6.93 (t, *J* = 7.3 Hz, 1H, ArH).

^{11}B-NMR (160.5 MHz, DMSO-d_6, 295K): δ(ppm) 6.9 (br s).

^{19}F-NMR (376.5 MHz, DMSO-d_6, 300K): δ(ppm) -158.0.

IR ($\tilde{\nu}$ [cm^{-1}]) 3048w, 2995w, 1593w, 1429s, 1312w, 1266w, 1193m, 1159s, 994w, 942s, 901s, 873s, 756s, 737s, 711s, 624s.

Potassium (*S*)-(4-benzyl-4,5-dihydrooxazol-2-yl)fluorodiphenylborate (Ph-108)



To 100 mg (0.62 mmol) of oxazoline **87** in 20 mL of THF was *t*-BuLi 0.37 mL (1,7 M solution in *n*-hexane) dropwise added at -78°C and stirred for 30 min. Then 150 mg (0.62 mmol) of Ph_2BF_2K in 3 mL THF was added and leaved warm in the cooling bath overnight. Reaction progress was tracked by NMR and the reaction was complete in 16 hours. Residue was dissolved in benzene to remove inorganic salts from product by filtration. Filtrate was concentrated and *n*-pentane was added in order to precipitate the product which was filtered and washed with 3 x 5 mL of *n*-pentane. It was obtained 173 mg (72% yield) of **Ph-108** as colorless semi solid.

$C_{22}H_{20}BFKNO$ (383.31 $g \cdot mol^{-1}$)

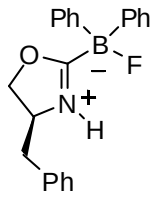
^{1}H-NMR (500.1 MHz, $CDCl_3$, 295K): δ(ppm) 7.28-7.02 (m, 15H, ArH), 4.10 (m, 2H, OCH_2), 3.79-3.78 (m, 1H, NCH), 2.71-2.68 (m, 1H, CH_2), 2.51-2.46 (m, 1H, CH_2).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K): δ(ppm) 2.6 (br s).

^{19}F-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -190.8.

MS (MALDI-TOF) m/z (%): 344 ($[M-(K^+)]^-$, 100).

Protonated (*S*)-(4-benzyl-4,5-dihydrooxazol-2-yl)fluorodiphenylborate (Ph-108-H)



Ph-108 was transferred on a silicagel column and eluted by Hex/EtOAc (9:1). The resulting colorless oil **Ph-108-H** was obtained in ca. 20% yield. The product **Ph-108-H** mass was observed as adduct with KCl by using FAB for ionization.

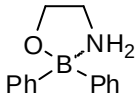
$C_{22}H_{21}BFNO$ (345.22 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 295K): δ(ppm) 10.33 (s, 1H, N-H), 7.61 – 7.40 (m, 4H, ArH), 7.40 – 7.16 (m, 9H,ArH), 7.03 (dd, *J* = 7.4, 1.9 Hz, 2H, ArH), 4.56 (t, *J* = 9.8 Hz, 1H, OCH_2), 4.41 (dd, *J* = 9.7, 7.0 Hz, 1H, OCH_2), 4.00 – 3.87 (m, 1H, NCH), 2.91 (dd, *J* = 13.9, 5.3 Hz, 1H, CH_2), 2.67 (dd, *J* = 13.9, 8.2 Hz, 1H, CH_2).

^{19}F-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -196.6.

MS (FAB NBA + KCl) m/z (%): 384 ([M+(K^+)] , 13), 326 ([M-(F)] , 100), 268 ([M-(Ph)] , 61), 200 (8), 165 (9), 117 (34), 107 (20), 91 (50), 39 (25).

2-Aminoethyl diphenylborinate (109)



Phenylmagnesium bromide 15 mL (1,86M in Et_2O, 2eq.) was diluted with 15 mL THF and solution of 2,9 g (12.6 mmol, 1 eq.) triisobutylborate in 8 mL of THF was added at 0°C then continued stirring at room temperature overnight and completed with 4 hours reflux. After cooling to room temperature was the reaction mixture quenched with 25 mL of 5% HCl (aq.). After extraction with 3 x 20 mL with diethyether was the solvent volume reduced to 15 mL and ethanolamine 0.95 mL (15.75 mmol, 1.25 eq.) in 10 ml of 50% ethanol was added. Reaction with ethanolamine was accompanied by evolution of head and during cooling back to room temperature the white crystals were formed which were allowed to crystallize for 4 hours. Crystals were then filtered of and washed by diethylether to obtain 1.922 g (68% yield) of the product **109** as fine white crystals.

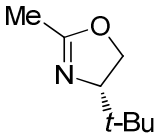
This 2-aminoethyl diphenylborinate was used as precursor of preparation of dihenylborinic acid. Apropriate amount of **109** was hydrolyzed by extraction with aq. HCl in Et_2O. Solution of the released diphenylborinic acid **91** was dried over Na_2SO_4 and then Et_2O was evaporated.

$C_{22}H_{21}BFNO$ (345.22 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, DMSO-d_6, 295K): δ 7.40 (d, *J* = 7.2 Hz, 4H, ArH), 7.13 (t, *J* = 7.4 Hz, 4H, ArH), 7.03 (t, *J* = 7.2 Hz, 2H), 6.07 (br s, 2H, NH_2), 3.76 (t, *J* = 6.4 Hz, 2H, CH_2), 2.83 (dd, *J* = 12.4, 6.2 Hz, 2H, CH_2).

^{11}B-NMR (160.5 MHz, DMSO-d_6, 295K): δ(ppm) 9.2 (br s).

(4*S*)-4-(*tert*-butyl)-2-methyl-2-oxazoline[95] (120)

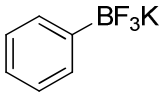


To a stirred solution of ethyl acetimidate hydrochoride 1.91g (15.46 mmol, 1.25 eq.) in 5 mL of methylene chloride at 0°C was added 1.45 g (12.36 mmol, 1 eq.) of (*S*)-*tert*-leucinol in 10 mL of DCM and allowed to slowly warm to room temperature and stirred overnight. Then was the reaction mixture was poured into 20 mL of water and extracted with 3 x 20 mL of DCM. By distillation on Kugelrohr (80°C/50 Torr) was obtained 1.491 g (86% yield) of product as transparent liquid.

$C_{22}H_{21}BFNO$ (345.22 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K) δ 4.19 – 4.09 (m, 1H, CH_2), 4.06 – 3.94 (m, 1H, CH_2), 3.88 – 3.73 (m, 1H, NCH), 1.96 (m, 3H, CH_3), 0.87 (s, 9H, *t*Bu).

Potassium phenyl trifluoroborate (110)



Phenylboronic acid 500 mg (4.10 mmol, 1 eq.) was dissolved in 7 mL of MeOH and cooled to 0°C and then 960 mg (12.3 mmol, 3eq.) of solid KHF_2 was added and stirred 2 hours at 0°C. Methanol was evaporated and the residual solid was dissolved in acetone and decanted in order to remove inorganic salts. Acetone was removed in vacuum and it was obtained 720 mg (94% yield) of **110** as white solid.

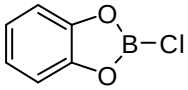
$C_6H_5BF_3K$ (184.01 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, CD_3CN, 295K) δ 7.47 (d, *J* = 7.0 Hz, 2H, ArH), 7.20 (t, *J* = 7.3 Hz, 2H, ArH), 7.14 (dd, *J* = 8.5, 6.0 Hz, 1H, ArH).

^{11}B-NMR (160.5 MHz, CD_3CN, 295K) δ 3.50 (q, 55 Hz).

^{19}F-NMR (376.5 MHz, CD_3CN, 300K) δ 143.50 (q, 49 Hz).

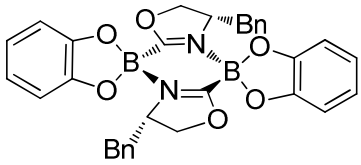
B-Chlorocatecholborane (96)



Catechol 500 mg (4.54 mmol, 1 eq.) was dissolved in 10 mL of dry dichloromethane and added to a precooled solution of o 5,2 mL BCl_3 (1M in hexane, 1.15 eq.) at -78°C. Reaction was stirred for 30 minutes and then was warmed to room temperature and solvent was removed in vacuum. Crude grey solid was then resublimed at 65°C/40 Torr to obtain 490 mg (70% yield) of **96** as white air sensitive needles.[143]

$C_6H_4BClO_3$ (154.36 $g \cdot mol^{-1}$)
^{1}H-NMR (500 MHz, $CDCl_3$, 295K) δ 7.31-7.28 (m, 2H, ArH), 7.21- 7.14 (m, 2H, ArH).
^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K) δ 28.9.

(*S*)-2-(benzo[*d*][1,3,2]dioxaborol-2-yl)-4-benzyl-4,5-dihydrooxazole dimer (98)



t-BuLi 0.37 mL (1.7 M in *n*-hexane) was dropwise added to a solution of 100 mg (0.62 mmol) of oxazoline **87** in 10 mL of THF at -78°C and stirred for 30 min. Solution of 96 mg (0.62 mmol) B-Chlorocatecholborane **96** in 2 mL THF was dropwise added at -78°C warmed up and stirred overnight at room temperature. After evaporation of the THF, the residual yellowish solid was redissolved in dichloromethane and column chromatography was performed in neat DCM to obtain 83 mg (46% yield) of the product **98** as a white crystalline solid. Crystals for X-ray analysis were prepared by dissolving product in a small amount of DCM and chloroform then overlayed with *n*-heptane and the flask inlet was covered with paper tissue and in 20 hours were obtained X-ray quality crystals of **98**.

$C_{32}H_{28}B_2N_2O_6$ (558.20 g·mol^{-1})

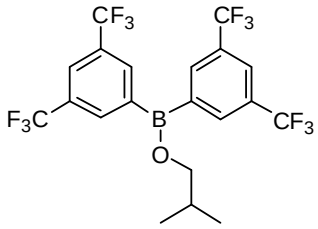
^{1}H-NMR (500.1 MHz, C_6D_6, 295K) δ 7.14 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.98 – 6.88 (m, 3H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 7.0 Hz, 2H), 4.13 – 4.04 (m, 1H), 3.59 (dd, *J* = 9.4, 6.7 Hz, 1H), 3.29 (dd, *J* = 9.6 Hz, 1H), 3.06 (dd, *J* = 13.8, 3.3 Hz, 1H), 2.35 (dd, *J* = 13.7, 10.0 Hz, 1H).

^{13}C{^{1}H}-NMR (125.8 MHz, C_6D_6, 295K): δ(ppm) 152.7 (C_{Ar}), 151.9 (C_{Ar}), 135.8 (C_{Ar}), 129.3 (C_{ArH}), 128.8 (C_{ArH}), 128.2 (C_{ArH}), 127.1 (C_{ArH}), 120.4 (C_{ArH}), 120.3 (C_{ArH}), 110.5 (C_{ArH}), 110.2 (C_{ArH}), 75.0 (OCH_2), 60.7 (NCH), 39.2 (CH_2).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K) δ 5.4.

MS (MALDI-TOF) m/z (%): 559 ([M+(H^+)], 80), 280 ([M/2+(H^+)], 100).

Bis(3,5-bis(trifluoromethyl)phenyl)(isobutoxy)borane (CF_3-64)



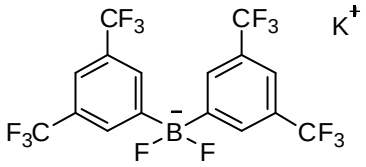
From the *3,5*-$(CF_3)_2$PhBr 1.96 g (6.69 mmol, 2.4 eq.) and 203 mg (8.37 mmol, 3 eq.) of Mg turnings was prepared 0.5M Grignard reagent in THF. This Grignard solution was cooled to -78°C and 642mg (2.79 mmol, 1 eq) of $(i$BuO$)_3$B was added in 4 mL THF dropwise via syringe. Reaction mixture was then warmed to room temperature and stirred overnight. After 30 min stirring at 60°C was the cooled reaction mixture quenched by 5% HCl (aq.). Then was performed extraction with 3 x 20 mL of Et_2O and the organic phase dried over $MgSO_4$. The crude reaction mixture was codistilled with 3 x 10 mL of isobuthanol at 40°C. Then by distillation on kugelrohr (120°C/0.08 Torr) the product 1.3 g (91% yield) was obtained as colorless oil.

$C_{10}H_{15}BF_{12}O$ (510.12 g·mol^{-1})

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 8.02 (s, 6H, ArH), 3.87 (br s, 2H, CH_2), 1.99 (br s, 1H, CH), 0.98 (d, *J* = 6.6 Hz, 6H).

^{19}F-NMR (376.5 MHz, CD_3CN, 300K) δ -64.14.

Potassium bis(3,5-bis(trifluoromethyl)phenyl)(isobutoxy)difluoroborane (CF_3-107)



Following the protocol for preparation of **Ph-107** it was used 1.3 g (2.55 mmol, 1eq.) of (*3,5*-$(CF_3)_2Ph)_2BO$*i*Bu **CF_3-64** and 0.597 g of KHF_2 in 10 mL of methanol. It was obtained 1.232 g (94% yield) of **CF_3-107** as white solid.

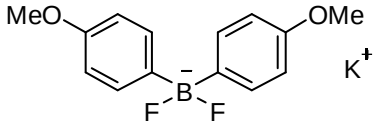
$C_{16}H_6BF_{14}K$ (514.11 g·mol^{-1})

^{1}H-NMR (400.1 MHz, DMSO-d$_6$, 300K): δ(ppm) 7.8 (s, 4H, ArH), 7.68 (s, 2H, ArH).

^{11}B-NMR (160.5 MHz, DMSO-d$_6$, 295K) δ 4.0 (br s).

^{19}F-NMR (376.5 MHz, DMSO-d$_6$, 300K) δ -62.42, -164.1.

Potassium difluoro(3-methoxyphenyl)(4-methoxyphenyl)borate (MeO-107)



Following the protocol for preparation **Ph-107** was used 1 g (4.34 mmol, 1eq.) of (*i*BuO)$_3$B and 10.5 mL (1M in THF) *p*-MeOPhMgBr. It was prepared ester **MeO-64** which was hydrolyzed to borinic acid by column chromatography on silicagel (EtOAc/Hex 1:2). Colorless oil was dissolved in MeOH and leaved react with 1.02 g (13.03 mmol, 3eq.) KHF_2. Recrystallization from chloroform/Et_2O afforded 900 mg (69% yield) of the **MeO-107** as a white solid.

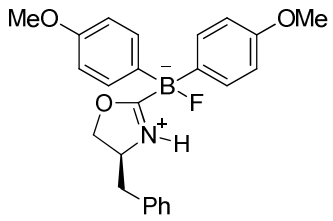
$C_{14}H_{14}BF_2KO_2$ (302.17 g·mol^{-1})

^{1}H-NMR (400.1 MHz, DMSO-d$_6$, 300K): δ(ppm) 7.16 (d, *J* = 8.3 Hz, 4H, ArH), 6.58 (d, *J* = 8.3 Hz, 4H, ArH), 3.62 (s, 6H, MeO).

^{19}F-NMR (376.5 MHz, DMSO-d$_6$, 300K) δ -155.64.

IR ($\tilde{\nu}$ [cm^{-1}]) 3016w, 2954w, 1652s, 1604s, 1512m, 1463m, 1332w, 1280m, 1238m, 1213m, 1199m, 1110s, 1031m, 1012m, 985s, 904s, 821s, 792m, 729m, 663m.

Protonated (*S*)-(4-benzyl-4,5-dihydrooxazol-2-yl)fluorobis(4-methoxyphenyl)borate (MeO-108-H)



Following procedure for **Ph-108-H** 50 mg (0.31 mmol, 1 eq.) of the oxazoline **87** was dissolved in 5 mL of THF and 0.19 mL (1.7M in *n*-hexane, 1.05 eq.) *tert*-butyllithium was added at -78°C. Followed by addition of 94 mg (0.31 mmol, 1eq.) of **MeO-107** in 2 mL THF . Then the reaction mixture was leaved warm overnight in the cooling bath to room temperature. After column chromatography on silica gel (*n*-hexane/EtOAc 2:1) was obtained 86 mg (62% yield) of the product **MeO-108-H** as a white thin needles crystals which were not suitable for X-ray analysis.

$C_{24}H_{25}BFNO_3$ (405.19 g·mol^{-1})

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 10.11 (br s, 1H, N-H), 7.39 – 7.32 (m, 4H, ArH), 7.32 – 7.23 (m, 3H, ArH), 7.07 – 7.01 (m, 2H, ArH), 6.84 (dd, *J* = 8.5, 7.1 Hz, 4H, ArH), 4.61 (dd, *J* = 9.8 Hz, 1H, OCH_2), 4.43 (dd, *J* = 9.7, 7.1 Hz, 1H, OCH_2), 4.05 – 3.95 (m, 1H, NCH), 3.78 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.91 (dd, *J* = 13.9, 5.5 Hz, 1H, CH_2), 2.70 (dd, *J* = 13.9, 8.2 Hz, 1H, CH_2).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 295K): δ(ppm) 158.3 (d, *J* = 6.4 Hz), 134.3 (C_{Ar}), 133.2 (d, *J* = 4.4 Hz, C_{ArH}), 133.1 (d, *J* = 5.1 Hz, C_{ArH}), 129.2 (C_{ArH}), 129.1 (C_{ArH}), 127.64 (C_{ArH}), 113.0 (d, *J* = 8.0 Hz, C_{ArH}), 76.3 (OCH_2), 57.1 (NCH), 55.1 (OMe), 55.0 (OMe), 39.7 (CH_2).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K) δ 1.9 (br s).

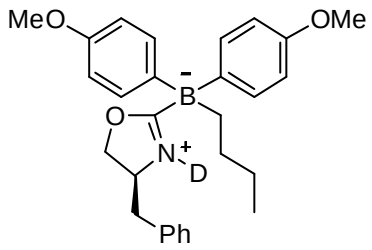
^{19}F-NMR (376.5 MHz, $CDCl_3$, 300K) δ -194.13.

MS (EI, 70 eV, 100°C): m/z (%): 244 (100, M^+ - oxaz.), 131 (13), 91 (52), 43 (5).

MS (EI, 70 eV, 250°C): m/z (%): 386 (6, M^+ - F), 296 (28), 227 (100), 176 (24), 88 (22).

MS (FAB NBA + KCl) m/z (%): 444 ([M+(K^+)] , 17), 386 ([M-(F)] , 71), 298 ([M-(Ar)] , 100), 256 (26), 222 (12), 137 (11), 91 (35), 39 (44).

(*S*)-(4-benzyl-4,5-dihydrooxazol-2-yl)fluorobis(4-methoxyphenyl)butylborate (MeO-108-Bu)



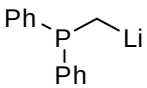
10 mg (24.67 μmol) of **MeO-108-H** was dissolved in 2 mL of THF and 31 μL (1.6M in *n*-hexane) of *n*-BuLi was added at -78°C and warmed to room temperature. After warming up the reaction mixture was stirred for 10 min. During this time color change from colorless to ocher and after quenching by methanol-d_4 it discolored again. This result was not reproducible and from the very small amount of the sample obtained in the first experiment was not possible to perform further analysis than ^{1}H, ^{11}B and ^{19}F NMR.

$C_{28}H_{33}BDNO_3$ (444.39 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.35 – 7.27 (m, 4H, ArH), 7.25 – 7.19 (m, 3H, ArH), 6.84 – 6.78 (m, 3H, ArH), 4.16 (dt, *J* = 14.5, 7.2 Hz, 1H, OCH_2), 4.03 (t, *J* = 8.9 Hz, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.77 – 3.71 (m, 1H, NCH), 3.60 (t, *J* = 6.6 Hz, 2H, CH_2(*Bu*)), 2.81 (dd, *J* = 13.8, 7.2 Hz, 1H, CH_2(*Bu*)), 2.68 (dd, *J* = 13.8, 7.2 Hz, 1H, CH_2(*Bu*)), 1.53 (dq, *J* = 8.3, 7.0 Hz, 1H, CH_2(*Bu*)), 1.37 (ddd, *J* = 17.0, 13.7, 7.3 Hz, 2H, CH_2(*Bu*)), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3(*Bu*)).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K) δ 6.7.

((Diphenylphosphino)methyl)lithium[62] (82)



To methyldiphenylphosphine 2 g (10 mmol, 1,86 mL) in 20 mL of Et_2O was dropwise added 6.24 mL (1,6M *n*-hexane solution) of *n*-BuLi at room temperature and stirred 72 hours. Then was the resulting suspension filtered under Ar and washed with 12 mL of dry *n*-pentane to obtain 404 mg (26% yield) of product **82** as a highly hygroscopic white crystals.

((Diphenylphosphino(BH_3))methyl)trimethylsilane (109)

$Ph_2P(BH_3)CH_2SiMe_3$

To a solution of 100 mg (467 µmol) $MePPh_2.BH_3$ in 1.5 mL THF was added 0.32 mL (1,6M in *n*-hexane, 1.1eq.) *n*-BuLi at 0°C stirred 0.5h then continued for 1.5 hour at room temperature. Me_3SiCl 65µl (514 µmol 1,1eq, *d*=0.856) was added and the reaction mixture was stirred for 30 minutes at room temperature. Reaction mixture was quenched with sat. sol. NH_4Cl and product was extracted into Et_2O, washed with brine and dried over $MgSO_4$. It was obtained 126 mg of the product as white solid.

$C_{14}H_{24}BPSi$ (286.23 $g \cdot mol^{-1}$)

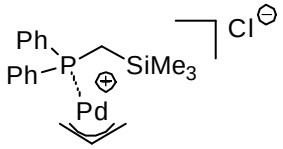
^{1}H-NMR (500 MHz, $CDCl_3$, 295K) δ ppm 7.69 (m, 4H, ArH), 7.42 (m, 6H, ArH), 1.57 (d, *J*=15.8 Hz, 2H, CH_2), -0.01 (s, 9H, Me_3Si).

^{13}C-NMR (126 MHz, $CDCl_3$, 295K) δ ppm 132.47 (d, *J* = 55.0 Hz, quart. C_{Ar}), 131.36 (d, *J* = 9.8 Hz, C_{ArH}), 130.40 (d, *J* = 2.5 Hz, C_{ArH}), 128.58 (d, *J* = 9.8 Hz, C_{ArH}), 12.50 (d, *J*=25.0 Hz, CH_2), 0.36 (s, Me)

^{31}P-NMR (202 MHz, $CDCl_3$, 295K) δ ppm 13.63 (q, *J* = 55.0 Hz).

MS (EI, 70 eV): m/z (%): 272 (100, M^+ - BH_3), 181 (7), 135 (34), 121 (8), 73 (18).

((Diphenylphosphino)methyl)trimethylsilane palladium, allyl chloride complex 109-Pd



200 mg (826 µmol) of Ph_2BF_2K was dissolved in 5 mL THF and 90 mg (826 µmol, 104 µl) Me_3SiCl was added at -78°C via syringe and stirred for 1 hour. Then solution of 170 mg $LiCH_2PPh_2$ (826 µmol) in 2.5 mL THF was added at -78°C. Solution of 156 mg (826 µmol, 1eq.) of the oxazoline **87** was dissolved in 10 mL THF and 0.57 mL *t*-BuLi (1,7M in hexane, 1eq.) was added at -78°C and stirred for 30 min. Then the reaction mixture containing Ph_2BF and phosphine was dropwise added via cannula and leaved warm in the cooling bath overnight. 15 mg (826 µmol, 1eq.) of $[Pd(allyl)Cl]_2$ was added to the reaction mixture and this

mixture was stirred for 30 min at 65°C. After column chromatography on silica gel (hexane/EtOAc 3:1->1:1) was afforded 83 mg of **109-Pd**.

$C_{22}H_{37}ClPPdSi$ (502.46 $g \cdot mol^{-1}$)

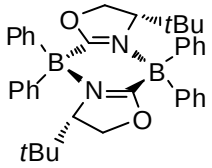
^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.63 (dd, *J* = 18.8, 11.4 Hz, 4H, ArH), 7.43 (d, *J* = 5.4 Hz, 6H, ArH), 5.62 – 5.48 (m, 1H, CH), 4.72 (t, *J* = 7.3 Hz, 1H, CH_2), 3.67 (dd, *J* = 13.7, 10.0 Hz, 1H, CH_2), 3.59 (d, *J* = 6.4 Hz, 1H, CH_2), 2.73 (d, *J* = 12.0 Hz, 1H, CH_2), 2.11 – 2.01 (t, *J* = 14.1 Hz, 1H, CH_2P), 1.94 (t, *J* = 14.1 Hz, 1H, CH_2P), -0.05 (s, 9H, Me3Si).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 135.22 (dd, *J* = 42.9, 40.2 Hz, C_{Ar}), 132.14 (dd, *J* = 35.8, 12.5 Hz, C_{ArH}), 129.69 (d, *J* = 19.1 Hz, C_{ArH}), 128.07 (d, *J* = 10.1 Hz, C_{ArH}), 116.49 (CH), 78.48 (d, *J* = 31.9 Hz, CH_2), 56.77 (CH_2), 14.17 (d, *J* = 12.0 Hz, CH_2P), -0.01 ($SiMe_3$).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 17.2.

MS (ESI): m/z (%): 422 (100, M^+ - Cl^-).

(*S*)-4-(tert-butyl)-2-(diphenylboryl)-4,5-dihydrooxazole dimer (105)



0.91 mL (1,7 M in *n*-hexane) *t*-BuLi was dropwise added to 196 mg (1,54 mmol) of oxazoline **28-*t*Bu** in 40 mL THF at -78°C and stirred 30 min. This solution was added via precooled cannula to a precooled solution of the 309 mg of Ph_2BCl in 5 mL of toluene at -78°C. Then was reaction the reaction leaved warm in cooling bath overnight. Solvent from the reaction mixture was evaporated and residue was redissolved in 5 ml of benzene. Precipitate was filtered over celite and benzene was evaporated to obtain 240mg of slightly orange foam. After chromatography on 16g of silica gel was obtained in 3rd fraction 42 mg white solid **105**.

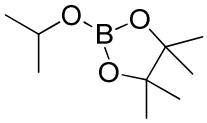
$C_{38}H_{44}B_2N_2O_2$ (502.39 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, C_6D_6, 300K): δ(ppm) 7.49-7.28 (m, 10H, ArH), 3.71-3.68 (m, 1H, CH_2), 3.49-3.46 (m, 1H, NCH), 3.20-3.17(m, 1H, CH_2), 0.36 (s, 9H, $C(CH_3)_3$).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K) δ 3.9.

MS (EI, 70 eV): m/z (%): 582 (4, M^+), 505 (43, M^+-Ph), 345 (12, M^+-Ph-oxaz.).

2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[70] (100)



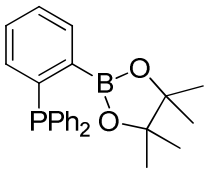
A mixture of 12 mL of triisopropylborate (52 mmol, *d*=0.818) and 6 g of dry pinacol (52 mmol) was heated for 3 h under stirring at 115°C. The isopropanol was distilled off and the residue was distilled at 174°C at atmosferic pressue to obtain 8.772 g (90% yield) of **100** as colorless liquid.

$C_9H_{19}BO_3$ (186.06 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ (ppm) 1.17 (dd, 6H), 1.23 (s, 12H), 4.31 (sept., 1H).

^{13}C{1H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 82.5 ($C(CH_3)_2$), 67.4 (CH), 24.4 (CH_3), 24.6 (CH_3),.

Diphenyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)phosphine[69] (101)



Solution of *o*-lithiated triphenylphosphine was prepared from 250 mg (0.73 mmol) of (2-bromophenyl)-diphenylphosphine which was dissolved in 5 mL THF and 0.5 mL (1,6M in *n*-hexane, 1.1eq) *n*-BuLi was added at -78°C and stirred for 15 min. To this pregenerated lithium salt was added 0.26 mL (0.81 mmol, *d*=0.916, 2eq.) of isopropylpinacolborane **100** and leaved warm overnight in the cooling bath. The reaction solvent was removed in vaccum and the residual solid was washed with 3 x 5 mL of Et_2O at -30°C to obtain 160 mg (56% yield) of **101** as white solid.

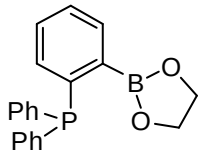
$C_{24}H_{26}BO_2P$ (388.25 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ (ppm) 7.82 - 7.74 (m, 1H, ArH), 7.34 - 7.12 (m, 12H, ArH), 6.78 - 6.68 (m, 1H, ArH), 1.05 (s, 12H, CH_3).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K) δ 31.0.

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ (ppm) -4.0.

(2-(1,3,2-dioxaborolan-2-yl)phenyl)diphenylphosphine [71] (104)



Solution of *o*-lithiated triphenylphosphine was prepared from 200 mg (0.59 mmol) of (2-bromophenyl)-diphenylphosphine which was dissolved in 5 mL THF and 0.4 mL (1,6M in *n*-hexane, 1.1eq) *n*-BuLi was added at -78°C and stirred for 15 min. To this lithium salt was added 0.81 mL (0.81 mmol, *d*=0.811, 6eq.) of triisopropylborane and leaved warm overnight in the cooling bath. Reaction was quenched with water followd by extraction with dicholomethane. Dry crude product was redissolved in 6 mL of glykol/toluene (1:5) mixture and stirred for 2 hours at 100°C. Toluene layer was speparated and evaporated. White solid residue was washed 2 x 5 mL Et_2O at -78°C to obtain 70 mg (34% yield) of **104** as white solid.

$C_{20}H_{18}BO_2P$ (332.14 $g \cdot mol^{-1}$)

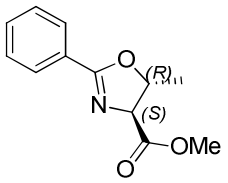
^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ (ppm) 7.84 - 7.81 (m, 1H, ArH), 7.36 - 7.29 (m, 12H, ArH), 6.93 - 6.90 (m, 1H, ArH), 4.14 (s, 4H, CH_2).

^{11}B-NMR (160.5 MHz, $CDCl_3$, 295K) δ 32.3.

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) -3.9.

8.5 NeoPHOX ligands

(4*S*,5*R*)-methyl 5-methyl-2-phenyl-4,5-dihydrooxazole-4-carboxylate[144] (135)

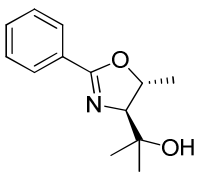


To the solution of threoninemethylester hydrochloride 10g (58.96 mmol, 1 eq.) in 50 mL DCM was added 12 g (64.86 mmol, 1.1 eq.) of ethyl phenylimidatehydrochloride and 9 mL (64.86 mmol, 1.1 eq.) of Et_3N. Reaction mixture was stirred at room temperature for 48 hours and then all solids were filtered of and the filtrate was poured into a $NaHCO_3$ and extracted with DCM. On order to remove excess of ethylbenzoate there was performed distillation under reduced pressure on Kugelrohr (90°C/0.08Torr). Distillation was continued at 125°C/0.08 Torr where product was obtained as colorless liquid 10.502 g (87% yield).

$C_{12}H_{13}NO_3$ (219.24 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.97 (dd, *J* = 5.2, 3.3 Hz, 2H, ArH), 7.52 – 7.45 (m, 1H, ArH), 7.44 – 7.35 (m, 2H, ArH), 4.98 (dq, *J* = 12.6, 6.3 Hz, 1H, OCH), 4.46 (d, *J* = 7.5 Hz, 1H, NCH), 3.80 (s, 3H, OMe), 1.52 (d, *J* = 6.3 Hz, 3H, CH*CH*$_3$).

2-((4*S*,5*R*)-5-methyl-2-phenyl-4,5-dihydrooxazol-4-yl)propan-2-ol[144] (136)

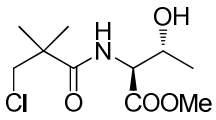


35.7 mL (3M in Et_2O, 2,5eq) MeMgBr was dropwise added to a refluxing solution of the starting 9,4 g (42.88 mmol) oxazoline **135** and then refluxed for 3 hours. After cooling to room temperature the reaction mixture was quenched by NH_4Cl (sat. sol.) and followed by extraction with 3 x 20 mL of Et_2O. All volatiles were removed under reduced pressure to obtain 6.327 g (67% yield) of **136** as slightly ochre oil. This was used for the next experiments without further purification.

$C_{13}H_{17}NO_2$ (219.28 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 8.05 – 7.90 (m, 2H, ArH), 7.59 – 7.36 (m, 3H, ArH), 4.70 (p, *J* = 6.4 Hz, 1H, OCH), 3.73 (d, *J* = 6.9 Hz, 1H, NCH), 2.22 (br s, 1H, OH), 1.46 (d, *J* = 6.3 Hz, 3H, CH*CH*$_3$), 1.34 (s, 3H, CH_3), 1.21 (s, 3H, CH_3).

(2*S*,3*R*)-methyl 2-(3-chloro-2,2-dimethylpropanamido)-3-hydroxybutanoate (138)



5 g (29.48mmol) methylthreonine hydrochloride was dissolved in 50 mL DCM and 12.5 mL (88.44 mmol, 3eq.) of Et_3N was added at 0°C then 3,8 mL (29.48 mmol, *d*=1.199) of the 3-chlorpivaloyl chloride was dropwise added and stirred overnight at room temperature. Then was the reaction mixture poured into the 10 mL $NaHCO_3$ (sat. solution) diluted by Et_2O and then water layer was extracted with 3 x 30 mL of Et_2O and combined organic phases were dried over $MgSO_4$ and distilled on the Kugelrohr (170°C/0.1 Torr). It was obtained 7,125 g (96% yield) of the colorless oily product. Analyticaly pure sample could be obtained by column chromatography on silicagel EtOAc (R_f=0.45), stained by $KMnO_4$.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 6.51 (d, 1H, *J* = 8.3 Hz, NH), 4.61 (d, 1H, *J* = 8.6 Hz, N-CH), 4.38 (m, 1H, CH-O), 3.77 (s, 3H, $COOCH_3$), 3.71 (d, 1H, *J* = 10.6 Hz, CH_2Cl), 3.57 (d, 1H, *J* = 10.6 Hz, CH_2Cl), 1.37 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.23 (d, 3H, *J* = 6,6 Hz, CH_3).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 175.4 (C=O), 171.5 (COO), 68.0 (CHOH), 57.2 (CH), 52.7 ($COOCH_3$), 52.6 (CH_2Cl), 44.5 ($C(CH_3)_2$), 23.8 ($C(CH_3)_2$), 23.2 ($C(CH_3)_2$), 20.1 (CH_3).

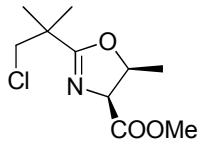
$[\alpha]^{20}_D$ -7.0 (*c* 1.01, $CHCl_3$)

MS (FAB) m/z (%) 254 (33), 253 (13), 252 ($[M+H]^+$, 100), 234 (16), 202 (8), 192 (12), 119 (7), 116 (10), 102 (22), 93 (8), 91 (22)

IR ($\tilde{\nu}$ [cm^{-1}]) 3387m, 2974m, 2956m, 2936w, 2875w, 1744s, 1648s, 1523m, 1475w, 1437m, 1391w, 1349w, 1290m, 1208m, 1083w, 1021w, 997w, 853w, 811w, 731w.

Elementar analysis for $C_{10}H_{18}ClNO_4$ (251.71) calcd %: C, 47.72; H, 7.21; N, 5,56; found: C, 47.47; H, 7.12; N, 5.54.

(4*S*,5*S*)-methyl2-(1-chloro-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (140)



1.121 g (4.45 mmol, 1eq.) of the amide **138** and 1.380g (5.79 mmol, 1.3eq.) of the Burgess reagent were dissolved in 40 mL THF and refluxed for 4 hours, then the THF was removed under reduced pressure and residue was redissolved in Et_2O and all solids were filtered off. Residual yellowish oil 1.203 g was distilled on the Kugelrohr (110°C/0.08 Torr) to obtain 924 mg (89% yield) of the product as colorless oil. By using DAST for oxazoline closure the obtained yield is 93%. Product could be purified by column chromatography EtOAc/Hex (1:5, $R_f = 0.25$).

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 4.88 (m, 1H, OCH), 4.76 (d, 1H, *J* = 10.0 Hz, N-CH), 3.73 (s, 3H, $COOCH_3$), 3.63 (m, 2H, CH_2Cl), 1.33 (s, 6H, 2xCH_3), 1.26 (d, 3H, *J* = 6.5 Hz, $CH(CH_3)$).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 173.2 (C(quart)), 170.3 (COO), 77.8 (OCH), 71.3 (NCH), 52.2 (CH_2Cl), 52.0 ($COOCH_3$), 39.0 ($C(CH_3)_2$), 23.6 ($C(CH_3)_2$), 23.6 ($C(CH_3)_2$), 16.0 (CH_3).

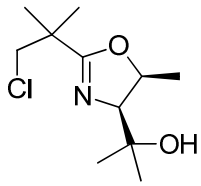
MS (EI, 70 eV): m/z (%): 233 (1, M^+), 198 (22, $[M-Cl]^+$), 174 (100, $[M-(COOMe)]^+$), 140 (9), 84 (65), 55 (15)

$[\alpha]^{20}_D$ +51,7° (*c* 1,12, $CHCl_3$)

IR ($\tilde{\nu}$ [cm^{-1}]) 2984m, 2957m, 1736s, 1655s, 1439m, 1386m, 1362w, 1321w, 1290w, 1253w, 1196s, 1174s, 1141w, 1118m, 1044s, 1000w, 973w, 945w, 917w, 892w, 832m, 751w, 634w.

Elementar analysis for $C_{10}H_{16}ClNO_3$ (233.69) calcd %: C, 51.40; H, 6.90; N, 5.99; found: C, 51.22; H, 6.82; N, 6.11.

2-((4*S*,5*S*)-2-(1-chloro-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-ol (141)



Method 1: 300 mg (1.28mmol) of the oxazoline **140** was dissolved in 7 mL Et_2O and 0.86 mL of MeMgI (3M in THF 2eq.) was added at -78°C and leaved warm overnight in the cooling bath. The reaction mixture was quenched by NH_4Cl (sat. sol.) and then extracted with 3 x 15 mL of Et_2O dried over Na_2SO_4 and solvent was evaporated. Afterwards was the oily material distilled on Kugelrohr (110°C/0.1 Torr) to obtain 120 mg of the trude product. Then was performed column chromatography on silica, EtOAc/Hex (1:1) which afforded 110 mg (37% yield) of the product **141** as colorless oil.

Method 2: 2 g (8.58 mmol, 1eq.) of the oxazoline **140** was dissolved in 30 mL THF and 5.7 mL (3M in THF, 2 eq.) MeMgCl was dropwise added at -78°C and leaved slowly warm in the dry ice cooling bath overnight. The reaction mixture was quenched by NH_4Cl and then extracted with Et_2O dried over Na_2SO_4. After solvent evaporation was obtained 1.882 g of the crude product. Then distillation on Kugelrohr (100°C/0.2 Torr) afforded 1.600 g (80%) of the product **141**.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 4.75 (m, 1H, OCH), 3.89 (d, 1H, *J* = 9.0 Hz, N-CH), 3.63 (d, 2H, *J* = 2.5 Hz CH_2Cl), 1.46 (d, 3H, *J* = 7.0 Hz, $CH(CH_3)$, 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.27 (s, 3H, CH_3)).

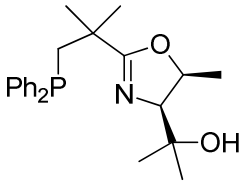
^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 171.0 (C(quart.)), 79.4 (OCH), 71.8 (NCH), 71.8 (COH(quart.)), 52.6 (CH_2Cl), 39.0 ($C(CH_3)_2$ (quart.)), 28.4 ($C(CH_3)_2$), 26.2 ($C(CH_3)_2$), 23.7 ($C(CH_3)_2$), 23.7 ($C(CH_3)_2$), 16.1 (CH_3).

MS (FAB) m/z (%) 237 (5), 236 (32), 235 (13), 234 ($[M+H]^+$, 100), 218 (13), 216 (10), 174 (15), 91 (16), 59 (12), 55 (14).

$[\alpha]^{20}_D$ +22.6° (*c* 1,15, $CHCl_3$)

IR ($\tilde{\nu}$ [cm^{-1}]) 3449m, 2977s, 2939m, 2873m, 2353w, 2343w, 1718m, 1657s, 1468m, 1444m, 1383m, 1364m, 1284m, 1227w, 1180m, 1137m, 1118m, 1076w, 1019m, 948m, 924w, 882w, 825w, 792w, 745w.

2-((4*S*,5*S*)-2-(1-(diphenylphosphino)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-ol (142)



107 mg (457 μmol) of neopentyl chloride **141** was dissolved in 5 mL THF and 0.29 mL *n*-BuLi (1.6M in *n*-hexane, 1eq.) was added at 0°C followed by addition of 0.92 mL $KPPh_2$ (0.5M in THF, 1 eq.) then was the reaction mixture warmed to room temperature and refluxed overnight (15 hours). The solvent was evaporated in vacuum and residue was redissolved in 20 mL MTBE and 6 mL NH_4Cl (sat. sol.) was added. Phases were separated and the water layer was extracted with 3 x 10 mL of MTBE then with brine and dried under Na_2SO_4. Chromatography on silica EtOAc/Hex (1:2) afforded 120 mg (68% yield) of the product as transparent oil which solidifed in the fridge within few days.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.50 (m, 2H, ArH), 7.41 (m, 2H, ArH), 7.31 (m, 6H, ArH), 4.52 (m, 1H, OCH), 3.74 (d, 1H, *J* = 9.1 Hz, N-CH), 2.72 (s, 1H, OH), 2.55 (dd, 1H, *J* = 14.3, 4.9 Hz, CH_2Cl), 2.37 (dd, 1H, *J* = 14.4, 3.3 Hz, CH_2), 1.49 (d, 3H, *J* = 6.6 Hz, $CH(CH_3)$), 1.32 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.24 (s, 3H, CH_3).

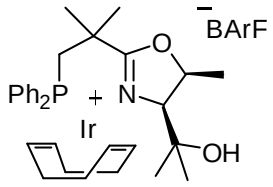
^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 173.2 (C=N), 140.0 (d, *J* = 11.0 Hz, C_{Ar}), 139.0 (d, *J* = 11.0 Hz, C_{Ar}), 133.3 (d, *J* = 20 Hz, HC_{Ar}), 132.8 (d, *J* = 20 Hz, HC_{Ar}), 128.7 (C_{ArH}), 128.45 (C_{ArH}), 128.4 (d, *J* = 2 Hz, C_{ArH}), 128.3 (d, *J* = 2 Hz, C_{ArH}), 79.2 (OCH), 75.6 (NCH), 72.2 (COH), 41.0 (d, *J* = 15 Hz, CH_2), 37.2 (d, *J* = 18 Hz, ($C(CH_3)_2$), 29.0 ($HOC(CH_3)_2$), 27.7 (d, *J* = 8 Hz, $C(CH_3)_2$), 27.4 (d, *J* = 10 Hz, $C(CH_3)_2$), 26.15 ($HOC(CH_3)_2$), 16.1 ($CHCH_3$).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) -21.3.

MS (FAB) m/z (%) 386 (4), 385 (25), 384 ($[M+H]^+$, 100), 326 (2), 325 (13), 324 (43), 306 (11), 285 (17), 284 (32), 228 (6), 227 (38), 202 (10), 201 (18), 199 (11), 185 (27), 183 (13), 136 (7), 91 (6).

$[\alpha]^{20}_D$ 16.1 (*c* 1.00, $CHCl_3$).

(142-Ir)



30 mg (78 μmol) of the free ligand **142** with 26 mg (39 μmol) of bis(1,5-cyclooctadiene)diiridium(I) dichloride dissoved in 3 mL DCM was refluxed for 2.5 hours. After that was 90 mg (1.3eq.) of $NaBAr_F$ and stirred for another 30 min at room temperature. The reaction mixutre was imobillized on silica and putted on column, washed with 100 mL Et_2O and then switched to DCM and in one fraction was isolated product **142-Ir** as orange solid. Sample was several times codistilled with $CHCl_3$ in order to remove moisture from the sample. It was obtained 119 mg (99% yield) of the product **142-Ir** as orange solid.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.82 (dd, *J* = 11.0, 7.3 Hz, 2H, ArH), 7.72 (s, 8H, $H_{ArF\text{-}o}$), 7.62-7,54 (m, 3H, ArH), 7.53 (s, 4H, $H_{ArF\text{-}p}$), 7.39 (m, 3H, ArH), 7.05-7.01 (m, 2H, ArH), 5.27 (m, 1H, COD-CH), 4.84 (m, 1H, COD-CH), 4.82 (m, 1H, OCH), 3.78 (d, *J* = 8.8 Hz, 1H, NCH), 3.50 (dd, *J* = 7.1, 3.3 Hz, 1H, COD-CH), 2.61 (m, 3H, COD-H, COD-CH_2), 2.55 (d, *J* = 10 Hz, CH_2P), 2.32 (m, 2H, COD-CH_2), 2.21 (s, 3H, $C(CH_3)_2$), 2.13 (m, 1H, COD-CH_2), 2.01 (s, 1H, OH), 1.89 (m, 1H, COD-CH_2), 1.64 (m, 1H, COD-CH_2), 1.57 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 1.49 (d, *J* = 2.5 Hz, 3H, $C(CH_3)_2$), 1.43 (m, 1H, COD-CH_2), 1.10 (s, 3H, $OC(CH_3)_2$), 0.56 (s, 3H, $OC(CH_3)_2$).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 180.3 (C=N), 161.7 (q, *J* = 50 Hz, C_{ArFi}), 134.9 (C_{ArH}), 134.8 ($HC_{ArF\text{-}o}$), 132.8 (C_{ArH}), 132.5 (d, *J* = 55 Hz, C_{Ar}), 131.3 (C_{ArH}), 131.2 (d, *J* = 10 Hz, C_{ArH}), 130.0 (d, *J* = 11 Hz, C_{ArH}), 129.1 (qq, *J* = 3 Hz, *J* = 32 Hz, $HC_{ArF\text{-}m}$), 129.1 (C_{ArH}), 128.3 (d, *J* = 54 Hz, C_{Ar}), 124.6 (q, *J* = 273 Hz, CF_3) 117.5 ($HC_{ArF\text{-}p}$), 96.1 (d, *J* = 12 Hz, COD-CH), 94.2 (d, *J* = 12 Hz, COD-CH), 82.8 (OCH), 75.00 (NCH), 70.7 ($OC(CH_3)_2$), 63.6 (COD-CH), 60.8 (COD-CH), 38.9 ($C(CH_3)_2$), 36.3 (COD-CH_2), 33.9 (d, *J* = 6 Hz, $C(CH_3)_2$), 33.5 (d, *J* = 32 Hz, CH_2P), 32.0 (COD-CH_2), 28.5 (COD-CH_2), 26.9 (d, *J* = 12 Hz, $C(CH_3)_2$), 26.4 ($OC(CH_3)_2$), 26.1 (COD-CH_2), 24.5 ($OC(CH_3)_2$), 14.8 ($CHCH_3$).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 9.5.

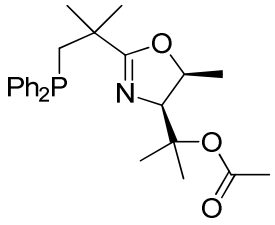
^{19}F{^{1}H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -62.6.

MS (MALDI-TOF) m/z (%): 684 ([M−(BAr_F)]$^+$, 100).

[α]$^{20}_D$ 1.3 (*c* 0.70, $CHCl_3$).

IR ($\tilde{\nu}$ [cm^{-1}]) 2971w, 1610w, 1439w, 1353m, 1271s, 1110s, 1000w, 886m, 838m, 744w, 711m, 681m, 667m

2-((4*S*,5*S*)-2-(1-(diphenylphosphino)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazol-4-yl)propan-2-yl acetate (142-OAc)



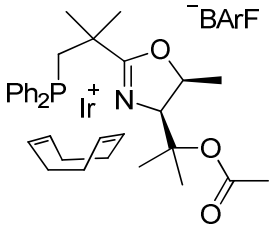
50 mg (0.13 mmol, 1 eq.) of ligand **142** was dissolved in 3 mL DCM and 76µl (0.65 mmol, 70 mg, 5 eq.) of 2,6-lutidine was dropwise added at 20°C followed by 20 µl (0.29 mmol, 2.2 eq.) AcCl and then stirred overnight (16 hours) at room temperature. Solvents were removed in vakuum and the column chromatography on silica gel (EtOAc/Hex 1:4) afforded 42mg (76% yield) of **142-Ac** as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 295K): δ (ppm) 7.45 (m, 4H, ArH), 7.31 (m, 6H, ArH), 4.30 (m, 1H, OCH), 4.08 (d, *J* = 9.1 Hz, 1H, NCH), 2.45 (ddd, *J* = 52.9, 14.3, 3.8 Hz, 2H, CH_2), 1.96 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.40 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 1.32 (s, 3H, CH_3), 1.28 (s, 3H, CH_3).

^{31}P{^{1}H}-NMR (162 MHz, $CDCl_3$, 295K): δ(ppm) 22.08.

MS (EI, 70 eV): m/z (%): 425 (1, M^+), 366 (13), 324 (31), 284 (95), 227 (100), 183 (30), 121 (20), 91 (5).

(142-Ir-OAc)



Following the general procedure as for preparation **142-Ir**. Complexation of the 42 mg (99 µmol) of the ligand **142-OAc** with 67 mg (99 µmol) of bis(1,5-cyclooctadiene)diiridium(I) dichloride in 3 mL DCM and 113 mg (128 µmol, 1.3 eq.) of $NaBAr_F$ resulted in 128 mg (82% yield) of the product **142-Ir-OAc** as orange solid.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.76 (dd, *J* = 11.0, 7.6 Hz, 2H, ArH), 7.72 (s, 8H, $H_{ArF\text{-}o}$), 7.60 (m, 1H), 7.53 (m, 6H, ArH, $H_{ArF\text{-}p}$), 7.38 (m, 3H, ArH), 7.02 (m, 2H, ArH), 4.94 (m, 1H, COD-CH), 4.87 (m, 1H, OCH), 4.81 (br s, 1H, COD-CH), 4.56 (d, *J* = 8.2 Hz, 1H, NCH), 3.62 (br s, 1H, COD-CH), 2.57 (m, 5H, CH_2P, COD-CH_2, COD-CH), 2.31 (m, 2H, COD-CH_2), 2.20 (s, 3H, $C(CH_3)_2$), 2.12 (m, 1H, COD-CH_2), 1.93 (s, 3H, Ac), 1.88 (m, 1H, COD-CH_2), 1.65 (s, 3H, $OC(CH_3)_2$, , 1H, COD-CH_2), 1.61 (d, *J* = 7.3 Hz, 3H, $CHCH_3$), 1.49 (d, *J* = 2.8 Hz, 3H, CH_3, $CHCH_3$), 1.40 (m, 1H, COD-CH_2), 0.82 (s, 3H, $OC(CH_3)_2$).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 181.0 (C=N), 170.1 (C=O) 161.7 (q, *J* = 50 Hz, C_{ArFi}), 134,9 (C_{ArH}), 134.8 ($HC_{ArF\text{-}o}$), 132.8 (d, *J* = 3 Hz, C_{ArH}), 131.9 (d, *J* = 55 Hz, C_{Ar}), 131.3 (d, *J* = 3 Hz, C_{ArH}), 131.2 (C_{ArH}), 131.1 (C_{ArH}), 129.7 (d, *J* = 11 Hz, C_{ArH}), 129.2 (d, *J* = 11 Hz, C_{ArH}), 128.9 (qq, *J* = 3 Hz, *J* = 32 Hz, $HC_{ArF\text{-}m}$), 124.6 (q, *J* = 273 Hz, CF_3), 117.5 ($HC_{ArF\text{-}p}$), 94.7 (d, *J* = 11 Hz, COD-CH), 93.5 (d, *J* = 13 Hz, COD-CH), 83.9 (OCH), 80.9 ($OC(CH_3)_2$), 70.3 (NCH), 63.7 (COD-CH), 60.6 (COD-CH), 39.0 (d, *J* = 2 Hz, $C(CH_3)_2$), 36.5 (d, *J* = 5 Hz, COD-CH_2), 33.4 (d, *J* = 6 Hz, $C(CH_3)_2$), 33.1 (d, *J* = 32 Hz, CH_2P), 32.3 (COD-CH_2), 28.3 (COD-CH_2), 27.0 (d, *J* = 12 Hz, $C(CH_3)_2$), 25.8 (COD-CH_2), 25.5 ($OC(CH_3)_2$), 22.1 ($C{=}OCH_3$), 21.9 ($OC(CH_3)_2$), 14.7 ($CHCH_3$).

MS (MALDI-TOF) m/z (%): 726 ($[M-(BAr_F)]^+$, 100).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 9.1.

^{19}F{^{1}H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -62.6.

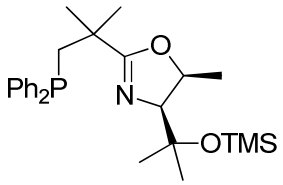
^{11}B-NMR (160.5 MHz, $CDCl_3$, 300K): δ(ppm) -6.6.

$[\alpha]^{20}_D$ -15.6 (*c* 1.00, $CHCl_3$).

IR ($\tilde{\nu}$ [cm^{-1}]) 2972w, 1739m, 1609w, 1582w, 1474w, 1437w, 1353s, 1272s, 1114s, 1049w, 1020w, 1000w, 938w, 886m, 838m, 736m, 710m, 681m, 669m

Elementar analysis for $C_{65}H_{56}NO_3BF_{24}PIr$ (1589.13) calcd %: C, 49.13; H, 3.55; N, 0.88; found: C, 48.86; H, 3.50; N, 0.93

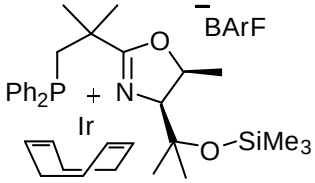
(4*S*,5*S*)-2-(1-(diphenylphosphino)-2-methylpropan-2-yl)-5-methyl-4-(2-((trimethylsilyl)oxy)propan-2-yl)-4,5-dihydrooxazole (142-TMS)



50 mg (0.13 mmol, 1 eq.) of the starting alcohol **142** was dissolved in 3 ml DCM and 76µl (0.65 mmol, 5 eq.) of 2,6-lutidine was dropwise added at 20°C. Then 67µl (0.26 mmol, 2eq, 58 mg, *d*=0,859) of TMSOTf was added and stirred for 1 hour. Solvent was evaporated on high vacuum and residue redissolved in Et_2O, the precipitate was filtered off and sample was dried in high vacuum. After column chromatography on silica EtOAc/Hex/Et_3N (1:10:0,5) was obtained 40 mg (67% yield) of the product **142-TMS** as colorless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.47 (m, 4H, ArH), 7.31 (m, 6H, ArH), 4.28 (m, 1H, OCH), 3.63 (d, *J* = 9.1 Hz, 1H, NCH), 2.46 (ddd, *J* = 51.0, 14.3, 3.7 Hz, 2H, CH_2), 1.47 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)$), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 1.23 (s, 3 H), 0.11 (s, 9 H).
^{31}P{^{1}H}-NMR (162.0 MHz, $CDCl_3$, 300K): δ(ppm) -22.3.

(142-Ir-TMS)



Following the general procedure as for preparation **142-Ir**. From 15 mg of the ligand **142-TMS** (33 µmol, 1 eq.), 11 mg of $[Ir(cod)Cl]_2$ (16 µmol, 0.5 eq.) in 3 mL DCM and 37 mg of $NaBAr_F$ (42 µmol, 1.3 eq.) was obtained 43 mg (80% yield) of **142-Ir-TMS** as orange solid. By crystallization of the product **142-Ir-TMS** in $CHCl_3$ solution which was overlayed by *n*-heptane were obtained crystals suitable for X-Ray analysis.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.75 (m, 10H, ArH), 7.58 (m, 7H, ArH), 7.37 (m, 3H, ArH), 7.01 (m, 2H, ArH), 4.80 (m, 3H, CH_2, OCH), 3.56 (m, *J* = 8.6 Hz, 2H, NCH,

COD-CH), 2.55 (m, 5H, COD), 2.28 (br s, 2H, COD-CH_2, COD-CH), 2.17 (s, 3H, $C(CH_3)_2$), 2.08 (m, 1H, COD-CH_2), 1.85 (m, 1H, COD-CH_2), 1.70 (d, *J* = 7.1 Hz, 3H, $CHCH_3$), 1.61 (m, 1H, COD-CH_2), 1.51 (d, *J* = 2.8 Hz, 3H, $C(CH_3)_2$), 1.39 (s, 3H, O-$C(CH_3)_2$), 1.30 (m, 1H, COD-CH_2), 0.85 (s, 3H, O-$C(CH_3)_2$), -0.10 (s, 9H, $Si(CH_3)_3$)

$^{13}C\{^1H\}$-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 180.3 (C=N), 161.7 (q, *J* = 50 Hz, C_{ArFi}), 135.0 (d, J = 11 Hz, C_{ArH}), 134.8 ($HC_{ArF\text{-}o}$), 132.6 (C_{ArH}), 131.2 (d, J = 5 Hz, C_{ArH}), 131.1 (C_{ArH}), 129.6 (d, *J* = 11 Hz), 129.1 (C_{ArH}), 128.8 (q, *J* = 32 Hz, $HC_{ArF\text{-}m}$), 124.6 (q, *J* = 273 Hz, CF_3), 117.5 ($HC_{ArF\text{-}p}$), 94.2 (d, *J* = 12 Hz, COD-CH), 93.1 (d, *J* = 12 Hz, COD-CH), 84.2 (OCH), 74.4 (SiO*C*$(CH_3)_2$), 74.2 (NCH), 63.0 (COD-CH), 59.7 (COD-CH), 38.8 (*C*$(CH_3)_2$), 36.3 (COD-CH_2), 33.3 (C(*C*$H_3)_2$), 32.9 (COD-CH_2) 32.2 (d, *J* = 32 Hz, CH_2P), 29.7 (SiOC(*C*$H_3)_2$), 28.3 (COD-CH_2), 27.1 ($C(CH_3)_2$), 26.6 (*C*H_3COSi), 25.8 (COD-CH_2), 15.2 (*C*H_3CH), 1.08 ($SiMe_3$).

$^{31}P\{^1H\}$-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 8.8.

$^{19}F\{^1H\}$-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -62.6.

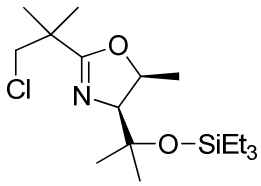
MS (MALDI-TOF) m/z (%): 756 ($[M-(BAr_F)]^+$, 100).

$[\alpha]^{20}_D$ -17.0 (*c* 0.69, $CHCl_3$).

IR ($\tilde{\nu}$ [cm^{-1}]) 2971w, 2903w, 1610w, 1588w, 1438w, 1351m, 1272s, 1159m, 1117s, 1047w, 1028w, 989m, 886m, 837m, 744w, 715m, 681m, 667s

Elementar analysis for $C_{66}H_{62}NO_2BF_{24}SiPIr$ (1619.27) calcd %: C, 48.96; H, 3.86; N, 0.87; found: C, 48.69; H, 3.92; N, 1.12

(4*S*,5*S*)-2-(1-chloro-2-methylpropan-2-yl)-5-methyl-4-(2-((triethylsilyl)oxy)propan-2-yl)-4,5-dihydrooxazole (141-TES)

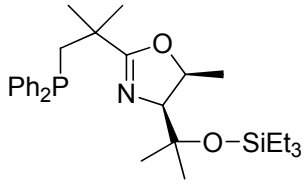


70 mg (1eq) of the alcohol (***3***) was dissolved in 3ml dry DCM and the solution was cooled to -78°C followed by addition of the 173.4 µl (160mg, *d*=0,925, 5 eq.) of the 2,6-lutidine and then 135.4 µl (158 mg, *d*=1.169, 2 eq.) of the TESOTf and stirred for 2hours at -78°C. Saturated $NaHCO_3$ was added slowly and the reaction mixture was warmed to room

temperature. Layers were separated and the organic layer was washed with water and brine. Organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromatography on silica (EtOAc/Hex 1:9) afforded 62mg of the product as colorless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 4.69 (m, 1H, OCH), 3.79 (d, *J* = 9.3 Hz, 1H, NCH), 3.62 (m, 2H, CH_2), 1.52 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)$), 1.36 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 0.94 (q, *J* = 8.1 Hz, 9H, CH_3), 0.59 (q, *J* = 8.0 Hz, 6H, CH_2).

(4*S*,5*S*)-2-(1-(diphenylphosphino)-2-methylpropan-2-yl)-5-methyl-4-(2-((triethylsilyl)oxy)propan-2-yl)-4,5-dihydrooxazole (142-TES)

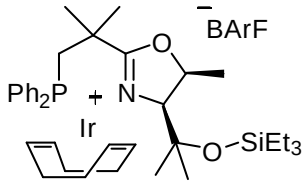


Method 1: 62 mg (0.178 mmol) of the chloride **141-TES** was dissolved in THF and cooled to 0°C, 0.36 mL of $KPPh_2$ (0,5M in THF, 1 eq.) was dropwise added at 0°C and then warmed to room temperature and refluxed overnight. The solvent was evaporated in vacuum and residue was redissolved in 20 ml MTBE and 6 mL NH_4Cl. Phases were separated and the water layer was extracted with 3 x 10 mL MTBE then with brine and dried under Na_2SO_4. After chromatography on silica (EtOAc/hex 1:20) was afforded 22 mg (25%) of the product **142-TES** as a colorless oil recalculated according to the total amount of the fraction which contained 30% starting material and was not possible to separate those two species by column. Final purification has been done in the next reaction step during complexation.

Method 2: 50 mg (0.13 mmol, 1eq) of the starting alcohol **142** was dissolved in 3 ml DCM and 76 µl (0.65 mmol, 5 eq.) of *2,6*-lutidine were dropwise added at 20°C. Then 59µl (0.26 mmol, 2eq, 69mg, *d*=1.169) of TESOTf was added and stirred for 3 hours. Solvent was evaporated on high vacuum and residue redissolved in Et_2O, the precipitate was filtered off and sample was dried on vacuum. Column chromatography on silica EtOAc/Hex (1:9) afforded 47 mg (73% yield) of the product **142-TES** as colorless oil.

^{1}H-NMR (400.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.46 (q, *J* = 7.4 Hz, 4H, ArH), 7.30 (m, 6H, ArH), 4.32 (m, 1H, OCH), 3.63 (m, 1H, NCN), 2.46 (ddd, *J* = 60.7, 14.3, 3.8 Hz, 2H, CH_2), 1.46 (d, *J* = 6.9 Hz, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (t, *J* = 8.2 Hz, 6H).
^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) -22.3.

(142-Ir-TES)



Following the general procedure as for preparation **142-Ir**. From 20 mg of the ligand **142-TES** (40 µmol, 1 eq.), 11 mg of $[Ir(cod)Cl]_2$ (20 µmol, 0.5 eq.) in 3 mL DCM and 37 mg of $NaBAr_F$ (52 µmol, 1.3 eq.) was obtained 65 mg (99% yield) of **142-Ir-TES** as orange solid. By crystallization of the product **142-Ir-TES** in $CHCl_3$ solution which was overlayed by *n*-heptane were obtained crystals suitable for X-Ray analysis.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.76 (dd, *J* = 10.9, 7.7 Hz, 2H, ArH), 7.72 (s, 8H, $H_{ArF\text{-}o}$), 7.60 (m, *J* = 7.3, 7.3 Hz, 1H, ArH), 7.54 (m, 2H, ArH), 7.52 (s, 4H, $H_{ArF\text{-}p}$), 7.39 (m, 3H, ArH), 7.01 (m, 2H, ArH), 4.84 (m, 1H, OCH), 4.76 (br s, 2H, 2 x COD-CH), 3.57 (m, 2H, NCH, COD-CH), 2.58 (m, 4H, 2 x COD-CH_2), 2.47 (m, 1H, COD-CH), 2.28 (m, 2H, CH_2P), 2.18 (s, 3H, $C(CH_3)_2$), 2.08 (m, 1H, COD-CH_2), 1.85 (m, 1H, COD-CH_2), 1.73 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 1.62 (m, 1H, COD-CH_2), 1.51 (d, *J* = 2.5 Hz, 3H, $C(CH_3)_2$), 1.41 (s, 3H, O-$C(CH_3)_2$), 1.36 (m, 1H, COD-CH_2), 0.80 (m, 12H, CH_3CH_2, O-$C(CH_3)_2$), 0.40 (m, 6H, CH_2CH_3).
^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 180.5 (C=N), 161.9 (q, *J* = 50 Hz, C_{ArFi}), 134.9 (d, *J* = 11 Hz, C_{ArH}), 134.8 ($HC_{ArF\text{-}o}$), 132.8 (C_{ArH}), 131.2 (d, *J* = 5 Hz, C_{ArH}), 131.1 (C_{ArH}), 129.6 (d, *J* = 11 Hz), 129.0 (C_{ArH}), 128.8 (q, *J* = 32 Hz, $C_{ArF\text{-}m}$), 124.6 (q, *J* = 273 Hz, CF_3), 117.5 ($HC_{ArF\text{-}p}$), 94.4 (d, *J* = 12 Hz, COD-CH), 93.1 (d, *J* = 12 Hz, COD-CH), 84.5 (OCH), 74.2 (O*C*$(CH_3)_2$), 74.0 (NCH), 63.0 (COD-CH), 59.9 (COD-CH), 38.9 (*C*$(CH_3)_2$), 36.4 (COD-CH_2), 33.4 (d, *J* = 5 Hz, C(*C*$H_3)_2$), 32.5 (d, *J* = 34 Hz, CH_2P), 30.0 (*C*H_3COSi),

28.4 (COD-CH_2), 27.1 (d, *J* = 12 Hz, $C(CH_3)_2$), 26.1 (CH_3COSi), 25.9 (COD-CH_2), 15.2 (CH_3CH), 6.9 (CH_3 ethyl), 6.5 (CH_2 ethyl).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 9.0.

^{19}F{^{1}H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -62.6.

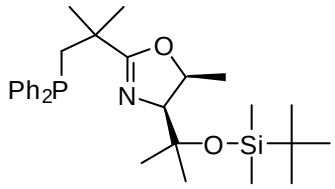
^{11}B-NMR (160.5 MHz, $CDCl_3$, 300K): δ(ppm) -6.6.

MS (MALDI-TOF) m/z (%): 798 ($[M-(BAr_F)]^+$, 100).

$[\alpha]^{20}_D$ -19.1 (*c* 0.73, $CHCl_3$).

IR ($\tilde{\nu}$ [cm^{-1}]) 2959w, 2923w, 2883w, 2855w, 1611w, 1574w, 1460w, 1439w, 1352s, 1273s, 1215w, 1158s, 1115s, 1047w, 1027w, 890m, 837m, 803w, 715m, 680m.

(4*S*,5*S*)-4-(2-((tert-butyldimethylsilyl)oxy)propan-2-yl)-2-(1-(diphenylphosphino)-2-methylpropan-2-yl)-5-methyl-4,5-dihydrooxazole (142-TBDMS)



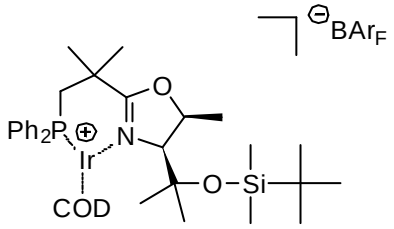
50 mg (0.13 mmol, 1eq) of the starting alcohol **142** was dissolved in 3 mL DCM and 76µl (0.65 mmol, 5 eq.) of 2,6-lutidine were dropwise added at 20°C. Then 60 µl (0.26 mmol, 69 mg, *d*=1.151, 2eq.) of TBDMSOTf was added and stirred for 1 hour. Then solvent was evaporated on high vacuum and residue redissolved in Et_2O, the precipitate was filtered off and sample was dried on vacuum. After column chromatography on silica EtOAc/Hex (1:9, R_f=0.25) was obtained 44 mg (68% yield) of the product **142-TBDMS** as colorless oil.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.56 – 7.40 (m, 4H, ArH), 7.38 – 7.23 (m, 6H, ArH), 4.43 – 4.29 (m, 1H, OCH), 3.62 (d, *J* = 9.3 Hz, 1H, NCH), 2.47 (ddd, *J* = 55.6 Hz, 14.4 Hz, 3.7 Hz, 2H, CH_2P), 1.46 (d, *J* = 6.9 Hz, 3H, $CHCH_3$), 1.34 (s, 3H, $(CH_3)_2CO$), 1.32 (s, 3H, $(CH_3)_2C$), 1.28 (s, 3H, $(CH_3)_2C$), 1.28 (s, 3H, $(CH_3)_2CO$), 0.86 (s, 9H, $(CH_3)_2t$BuOSi), 0.11 (s, 3H, $(CH_3)_2t$BuOSi), 0.10 (s, 3H, $(CH_3)_2t$BuOSi).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 172.6 (C=N), 140.1 (d, *J* = 13 Hz, C_{Ar}), 139.89 (d, *J* = 13 Hz, C_{Ar}), 133.3 (d, *J* = 20 Hz, C_{ArHo}), 133.0 (d, *J* = 20 Hz, C_{ArHo}), 128.6 – 128.2 (m, $C_{ArHm,p}$), 79.7 (OCH), 76.2 (NCH), 76.0 ($OC(CH_3)_2$), 41.1 (d, *J* = 17 Hz, CH_2P),

36.8 (d, *J* = 17 Hz, *C*(CH_3)$_2$), 30,7 (OC(*C*H_3)$_2$), 27.5 (d, *J* = 10 Hz, C(*C*H_3)$_2$), 27.1 (d, *J* = 11 Hz, C(*C*H_3)$_2$), 26.3 (OC(*C*H_3)$_2$), 26.1 (C(*C*H_3)$_3$), 18.3 (*C*(CH_3)$_3$), 16.5 (CH*C*H_3), -1.7 (Si(CH_3)$_2$), -1.7 (Si(CH_3)$_2$).

(142-Ir-TBDMS)



Following the general procedure as for preparation **142-Ir**. Complexation of the 44 mg (88 μmol, 1eq) **142-TBDMS** with 30 mg (88 μmol, 0.5eq) bis(1,5-cyclooctadiene)diiridium(I) dichloride in 3 mL DCM and reflux for 2.5 hour. After that 102 mg (115 μmol, 1.3eq) of $NaBAr_F$ was added and stirred for another 30 min at room temperature. The reaction mixture was imobillized on silica and putted on column, washed with 100 mL Et_2O and then switched to DCM and in two fractions was isolated 109 mg (75% yield) of the product **142-Ir-TBDMS** as yellow solid.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ (ppm) 7.81 – 7.75 (m, 10H, 2 x ArH, 8 x $H_{ArF\text{-}o}$), 7.60 – 7.58 (m, 1H, ArH), 7.55 – 7.52 (m, 6H, 2 x ArH, 4 x $H_{ArF\text{-}p}$), 7.40 – 7.36 (m, 3H, ArH), 7.06 – 7.02 (m, 2H, ArH), 4.88 (m 1H, OCH), 4.78 (br s, 2H, 2xCOD-CH), 3.60-3.59 (m, 1H, COD-CH), 3.56 (d, *J* = 8.3 Hz, 1H, NCH), 2.70 – 2.53 (m, 4H, CH_2P, COD-CH_2), 2.51 – 2.45 (m, 1H, COD-CH), 2.31-2.29 (m, 2H, COD-CH_2), 2.22 (s, 3H, C(CH_3)$_2$), 2.12 – 2.07 (m, 1H, COD-CH_2), 1.90-1.83 (m, 1H, COD-CH_2), 1.79 (d, *J* = 7.0 Hz, 3H, CH*C*H_3), 1.66-1.61 (m, 1H, COD-CH_2), 1.55 (d, *J* = 2.9 Hz, 1H, C(CH_3)$_2$), 1.42 (s, 3H, O-C(CH_3)$_2$), 1.40 – 1.34 (m, 1H, COD-CH_2), 0.95 (s, 3H, O-C(CH_3)$_2$), 0.74 (s, 9H, SiC(CH_3)$_3$), 0.05 (s, 3H, SiC(CH_3)$_2$), -0.28 (s, 1H, SiC(CH_3)$_2$).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 180.6 (C=N), 161.7 (q, *J* = 50 Hz, C_{ArFi}), 135.2 (d, *J* = 12 Hz, C_{ArH}), 134.8 (H*C*$_{ArF\text{-}o}$), 132.6 (d, *J* = 2 Hz, C_{ArH}), 132.2 (d, *J* = 55 Hz, C_{Ar}), 131.2 (C_{ArH}), 131.1 (C_{ArH}), 129.6 (d, *J* = 11 Hz, C_{ArH}), 129.0 (d, *J* = 10 Hz, C_{ArH}), 128.9 (q, *J* = 32 Hz, $HC_{ArF\text{-}m}$), 128.8 (d, *J* = 54 Hz, C_{ArH}), 124.6 (q, *J* = 273 Hz, CF_3), 117.5 ($HC_{ArF\text{-}p}$), 94.2 (d, *J* = 10 Hz, COD-CH), 93.0 (d, *J* = 13 Hz, COD-CH), 84.5 (OCH), 74.4 (NCH),

74.4 (O*C*(CH_3)$_2$), 62.8 (COD-CH), 59.7 (COD-CH), 38.9 (d, *J* = 2 Hz, (*C*(CH_3)$_2$), 36.4 (d, *J* = 5 Hz, COD-CH_2), 33.7 (d, *J* = 7 Hz, C(*C*H_3)$_2$), 33.0 (d, *J* = 32 Hz, CH_2P), 32.2 (COD-CH_2), 28.3 (COD-CH_2), 29.7 (O-C(*C*H_3)$_2$), 26.8 (d, *J* = 12 Hz, C(*C*H_3)$_2$), 25.7 (COD-CH_2), 25.7 (SiC(*C*H_3)$_3$), 26.1 (O-C(*C*H_3)$_2$), 17.8 (Si*C*(CH_3)$_3$), 15.0 (CH*C*H_3), -2.0 (SiC(*C*H_3)$_2$), -2.4 (SiC(*C*H_3)$_2$).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 8.6.

^{11}B-NMR (160.5 MHz, $CDCl_3$, 300K): δ(ppm) -6.6.

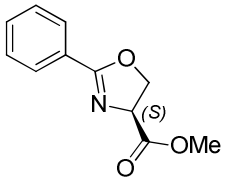
MS (MALDI-TOF) m/z (%): 798 ([M−(BAr_F)]$^+$, 100).

[α]$^{20}_D$ -21.8 (*c* 0.86, $CHCl_3$).

IR ($\tilde{\nu}$ [cm^{-1}]) 2952w, 2859w, 1610w, 1582w, 1471w, 1442w, 1353m, 1273s, 1158m, 1115s, 1047w, 1019w, 1001w, 966w, 886m, 837m, 778w, 744w, 734w, 712m, 682m, 671m.

Elementar analysis for $C_{69}H_{68}NO_2BF_{24}SiPIr$ (1661.35) calcd %: C, 49.88; H, 4.13; N, 0.84; found: C, 49.59; H, 4.19; N, 0.91

(*S*)-methyl 2-phenyl-4,5-dihydrooxazole-4-carboxylate[121] (143-1)



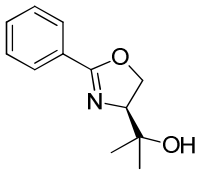
L-serine methylester hydrochloride 1.5g (9.64 mmol, 1eq) in 15 mL DCM and 1.824 g (9.64 mmol) phenylimidate hydrochloride were mixed in the flask under inert atmosphere and 1.37 mL (1eq) dry TEA was added to the reaction mixture. Resulting suspension was stirred for 48 hours at room temperature. Then all solids were filtered off and filtrate was quenched by $NaHCO_3$ and extracted by 3 x 10 mL of DCM. The crude product was distilled on Kugelrohr 125°C/0.08 Torr. It was obtained 1.286 g (65% yield) of the product as colorless oil.

$C_{11}H_{11}NO_3$ (205.21 $g{\cdot}mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.97 (d, *J* = 8.2 Hz, 2H, ArH), 7.48 (t, *J* = 7.4 Hz, 1H, ArH), 7.39 (t, *J* = 7.5 Hz, 2H, ArH), 5.00 – 4.88 (m, 1H, NCH), 4.74 – 4.65 (m, 1H, OCH_2), 4.58 (ddd, *J* = 10.4, 8.9, 1.5 Hz, 1H, OCH_2), 3.80 (s, 3H).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 171.64 (C=N), 166.30 (C=O), 131.88 (C_{ArH}), 128.60 (C_{ArH}), 128.36 (C_{ArH}), 126.94 (C_{Ar}), 69.55 (OCH_2), 68.63 (NCH), 52.72 (OCH_3).

(*S*)-2-(2-phenyl-4,5-dihydrooxazol-4-yl)propan-2-ol[121] (143-2)



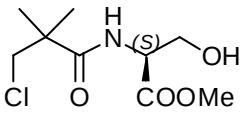
To a solution of 1.23 g (6.0 mmol, 1 eq.) of the starting ester **143-1** in 15 mL THF cooled to -78°C, was dropwise added 4 mL of MeMgCl (3M in THF, 2 eq.) and then was the reaction mixture was leaved warm overnight. After quenching by NH_4Cl (sat. sol.) was performed extraction with 3 x 10 mL of into Et_2O. Crude product was purified by column chromatography on silica gel (DCM/MeOH, 6:1, R_f=0.6). It was obtained 946 mg of the slightly ochre solid as product **143-2**.

$C_{12}H_{15}NO_2$ (205.25 $g \cdot mol^{-1}$)

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.91 (d, *J* = 7.7 Hz, 2H, ArH), 7.42 (t, *J* = 7.4 Hz, 1H, ArH), 7.34 (t, *J* = 7.7 Hz, 2H, ArH), 4.43 – 4.33 (m, 1H, OCH_2), 4.29 (t, *J* = 8.4 Hz, 1H, OCH_2), 4.17 (dd, *J* = 10.0, 8.4 Hz, 1H, NCH), 2.11 (br s, 1H, OH), 1.27 (s, 3H, CH_3), 1.12 (s, 3H, CH_3).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 165.24 (C=N), 131.71 (C_{ArH}), 128.49 (C_{ArH}), 128.37(C_{ArH}), 127.26 (C_{Ar}), 75.48 (NCH), 71.58 ($C(CH_3)_2$), 69.00 (CH_2), 26.77 (CH_3), 25.10 (CH_3).

(*S*)-methyl 2-(3-chloro-2,2-dimethylpropanamido)-3-hydroxypropanoate (144)



1 g (6.43 mmol, 1eq.) of *L*-serine methylester hydrochloride was dissolved in 10 mL DCM and 2.7 mL (19.28 mmol, 3eq) of Et_3N was added at 0°C stirred for 30 min then 0.83 mL (6.43 mmol, *d*=1.199, 1 eq.) of the 3-chlorpivaloyl chloride was dropwise added and stirred 1 hour at room temperature. Then was the reaction mixture poured into the saturated solution of $NaHCO_3$ diluted by Et_2O and then the water layer was extracted several times with Et_2O and combined organic phases were dried over $MgSO_4$. To obtain analytically pure sample the

chromatography on silicagel was performed using EtOAc (neat) as eluent (R_f=0.4). It was obtained 1.208 g (79% yield) of the product **144** as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.85 (d, *J*=7.1 Hz, 1H, NH), 4.64 – 4.57 (m, 1H, N-CH), 3.92 (ddd, *J* = 43.8, 11.3, 3.5 Hz, 2H, CH_2O), 3.80 (s, 3H, CO_2Me), 3.61 (dd, *J*=38.7, 10.8 Hz, 2H, CH_2-Cl), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 175.3 (C=O), 171.0 (COO), 62.8 (CH_2OH), 54.9 (CH), 52.7 ($COOCH_3$), 52.7 (CH_2Cl), 44.3 ($C(CH_3)_2$), 23.5 ($C(CH_3)_2$), 23.1 ($C(CH_3)_2$).

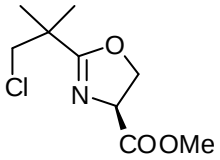
MS (FAB) m/z (%) 238 ([M+H]+, 100), 239 (10), 220 (19), 178 (14), 102 (70), 91 (28), 55 (9).

IR ($\tilde{\nu}$ [cm^{-1}]) 3382br w, 2954w, 1739m, 1651s, 1517m, 1252w, 1248w, 1286m, 1209m, 1101w, 1078m.

$[\alpha]^{20}_D$= 21.0 (*c* 1.10, $CHCl_3$).

Elem. anal.: calc.: C, 45.48; H, 6.79; N, 5.89; found: C, 45.15; H, 6.72; N, 5.80

(*S*)-methyl 2-(1-chloro-2-methylpropan-2-yl)-4,5-dihydrooxazole-4-carboxylate (145)

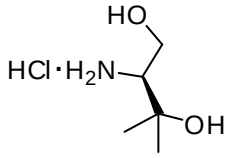


700 mg (2.95 mmol, 1 eq.) of the amide **144** was dissolved in 15 mL DCM and cooled to -78°C, then DAST 0.43 mL (3.24 mmol, *d*=1.22, 1.1 eq.). After stirring for another 1 hour was 610 mg (4.42 mmol, 1.5eq) of the solid anhydrous K_2CO_3 added and the reaction mixture was leaved warm to room temperature. The reaction was poured into the sat. solution of $NaHCO_3$ and then extracted with 3 x 20 mL DCM. After drying over $MgSO_4$ and concentrating of the sample in the vacuum was obtained 660 mg of the crude product as ochre oil. Then was the crude product distilled on Kugelrohr (110°C/0.08 Torr) to obtain 612 mg (95% yield) of the **146** as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (dd, *J* = 10.5, 7.7 Hz, 1H, CH-oxaz.), 4.50 (dd, *J* = 8.7, 7.7 Hz, 1H, CH_2-oxaz.), 4.41 (dd, *J* = 10.5, 8.7 Hz, 1H, CH_2-oxaz.), 3.77 (s, 3H, CO_2Me), 3.62 (q, *J* = 10.8 Hz, 2H, CH_2-Cl), 1.33 (s, 3H, CH_3), 1.31 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.27 (OC=N), 171.58 (C=O), 69.69 (CH_2-oxaz.), 68.14 (CH-oxaz.), 52.65 (CO_2CH_3), 52.28 (CH_2-Cl), 39.06 ($CH(CH_3)_2$), 23.73 (CH_3), 23.65 (CH_3).
MS (EI, 70 eV): m/z (%): 219 (33, M^+), 187 (30), 119 (18), 91 (100), 55 (41).
IR ($\tilde{\nu}$ [cm^{-1}]) 3406w, 2955w, 1728m, 1649s, 1633m, 1499m, 1472w, 1435m, 1387w, 1364w, 1329w, 1244m, 1171m, 1140w, 962w, 905w, 770m.
Elem. anal.: calc.: C, 49.21; H, 6.42; Cl, 16.14; N, 6.38; O, 21.85; found: C, 48.27; H, 6.13; N, 6.08

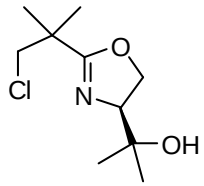
(*S*)-2-amino-3-methylbutane-1,3-diol hydrochloride (146)



To the 100 mg (487 μmol) of the oxazoline **143-2** was added 8 mL of 20% HCl (aq.) and the mixture was heated to 75°C for 4.5 hours while reaction color turns brownish. Reaction progress was tracked by TLC. After cooling to room temperature was the reaction mixture extracted 3 x 15 mL Et_2O in order to remove benzoic acid and the water residue was evaporated to dryness on the rotavap followed by 5 x 10 mL azeotropic distillation with toluene. Sample was dryied overnight on high vacuum to obtain 61 mg (79% yield) of the product **146**.

$C_5H_{14}ClNO_2$ (155.62 $g \cdot mol^{-1}$)
^{1}H-NMR (500.1 MHz, D_2O, 300K): δ(ppm) 3.95 (dd, *J* = 12.2, 3.7 Hz, 1H), 3.67 (dd, *J* = 12.1, 9.4 Hz, 1H), 3.28 (dd, *J* = 9.3, 3.5 Hz, 1H), 1.34 (s, 3H), 1.25 (s, 3H).
^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 69.30 ($C(CH_3)_2$), 61.29 (NCH), 58.43 (OCH_2), 26.60 (CH_3), 23.21 (CH_3).

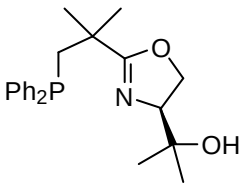
(*S*)-2-(2-(1-chloro-2-methylpropan-2-yl)-4,5-dihydrooxazol-4-yl)propan-2-ol (147)



270 mg (3.19 mmol) of the oxazoline **146** was dissolved in 15 mL THF and 0.98 mL (3M in THF, 2.4 eq.) MeMgCl was dropwise added at 0°C and stirred at this temperature for 1.5 hour and then quenched by NH_4Cl and extracted with 3 x 20 mL Et_2O, dried over Na_2SO_4 and concentrated in vacuum. It was obtained 245 mg of the yellowish oil as crude, which was subjected to column chromatography on silicagel EtOAc/MeOH (9:1, R_f=0.25) to obtain 210 mg (78% yield) of the product **147** as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (dd, *J* = 8.9, 3.8 Hz, 2H, CH_2-oxaz.), 4.04 (dd, *J* = 10.0, 7.7 Hz, 1H, CH-oxaz.), 3.65 – 3.59 (m, 2H, CH_2-Cl), 1.92 (br s, 1H, OH), 1.33 (s, 3H, $C(CH_3)_2$), 1,31 (s, 3H, $C(CH_3)_2$), 1.28 (s, 6H, HO-$C(CH_3)_2$), 1.13 (s, 3H, HO-$C(CH_3)_2$).
IR ($\tilde{\nu}$ [cm^{-1}]) 3382m, 2974m, 2963m, 2947m, 1733m, 1652s, 1644s, 1633s, 1610s, 1570m, 1470m, 1387m, 1366m, 1201w, 1179s, 1154s, 1117s, 976m, 944m, 921m, 886w, 834w, 734w, 666w.

(*S*)-2-(2-(1-(diphenylphosphino)-2-methylpropan-2-yl)-4,5-dihydrooxazol-4-yl)propan-2-ol (148)

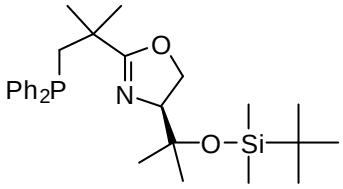


100 mg (455 µmol) of **147** was dissolved in 15 mL THF and then 1.1 mL (0,5M in THF, 1.2eq) of $KPPh_2$ was added. Then the reaction mixture was refluxed overnight. The solvent was evaporated in vacuum and residue was redissolved in 15 mL Et_2O and 3 mL NH_4Cl and 2 mL of water was also added to dissolve residual solids. Phases were separated and the water layer was extracted with 3 x 20 mL Et_2O and dried over Na_2SO_4. It was recorded NMR of the crude 210mg where was probably product about -21ppm in 31P and also $HPPh_2$. The cure

mixture (210 mg) was purified by column chromatography on silica EtOAc/Hex (1:1, R_f=0.35, 1:2, R_f=0.25) to afford 65 mg (39% yield) of the product 148 as white solid.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.51–7.58 (m, 2H, ArH), 7.43–7.40 (m, 2H, ArH), 7.34–7.28 (m, 6H, ArH), 4.26-4.24 (m, 1H, OCH),), 4.05-4.02 (m, 1H, OCH), 3.95-3,93 (m, 1H, N-CH), 2.63 (br s, 1H, OH), 2.57 (dd, 1H, *J* = 14.2, 4.9 Hz, CH_2Cl), 2.37 (dd, 1H, *J* = 14.2, 3.5 Hz, CH_2Cl), 1.32 (s, 3H, $O(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$), 1.11 (s, 3H, $O(CH_3)_2$).
^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ(ppm) 174.0 (C=N), 139.1 (d, *J* = 10.0 Hz, C_{Ar}), 138.6 (d, *J* = 10.0 Hz, C_{Ar}), 133.1 (d, *J* = 19 Hz, HC_{Ar}), 132.8 (d, *J* = 19 Hz, HC_{Ar}), 128.7 (C_{ArH}), 128.5 (C_{ArH}), 128.5 (C_{ArH}), 128.4 (C_{ArH}), 74.8 (NCH), 71.5 ($OC(CH_3)_2$), 68.7 (OCH_2), 41.2 (d, *J* = 14 Hz, CH_2P), 37.3 (d, *J* = 18 Hz, ($C(CH_3)_2$), 27.9 (d, *J* = 7 Hz, $C(CH_3)_2$), 27.4 ($HOC(CH_3)_2$), 27.3 (d, *J* = 9 Hz, $C(CH_3)_2$), 25.0 ($HOC(CH_3)_2$).
^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 21.4.

(*S*)-4-(2-((tert-butyldimethylsilyl)oxy)propan-2-yl)-2-(1-(diphenylphosphino)-2-methylpropan-2-yl)-4,5-dihydrooxazole (148-TBDMS)



45 mg (122 μmol, 1eq.) of the starting alcohol 148 was dissolved in 3 mL DCM and 70μL (610 μmol, 5 eq.) of 2,6-lutidine were dropwise added at 20°C. Then 56 μl (244 mmol, *d* = 1.151, 2. eq.) of TBDMSOTf was added and stirred for 1 hour at room temperature. Then solvent was evaporated on high vacuum and residue redissolved in Et_2O, and sample of the crude reaction mixture 60 mg was dried on vacuum. After the column chromatography on silica EtOAc/Hex (1:9, R_f = 0.25) was afforded 32 mg (54% yield) of the product **148-TBDMS**.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ(ppm) 7.48 – 7.44 (m, 4H, ArH), 7.33 – 7.28 (m, 6H, ArH), 4.20 – 4.17 (m, 1H, OCH_2), 3.77-3.69 (m, 1H, NCH, 1H, OCH_2), 2.52-2.41 (m, 2H, CH_2P), 1.35 (s, 3H, $(CH_3)_2CO$), 1.29 (s, 3H, $(CH_3)_2CO$), 1.24 (s, 3H, $(CH_3)_2C$), 1.13 (s, 3H, $(CH_3)_2C$), 0.82 (s, 9H, $(CH_3)_2$*t*BuOSi), 0.07 (s, 3H, $(CH_3)_2$*t*BuOSi), 0.07 (s, 3H, $(CH_3)_2$*t*BuOSi).

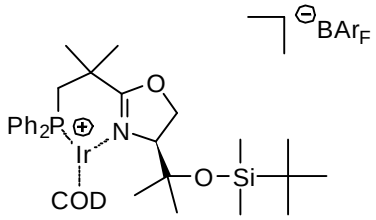
^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 173.3 (C=N), 139.7 (d, *J* = 13 Hz, C_{Ar}), 139.6 (d, *J* = 13 Hz, C_{Ar}), 133.2 (d, *J* = 20 Hz, C_{ArHo}), 132.8 (d, *J* = 20 Hz, C_{ArHo}), 128.4 – 128.3 (m, $C_{ArHm,p}$), 75.7 (O*C*$(CH_3)_2$), 74.7 (NCH), 68.7 (OCH_2), 41.1 (d, *J* = 17 Hz, CH_2P), 36.7 (d, *J* = 17 Hz, *C*$(CH_3)_2$), 28,7 (OC(*C*$H_3)_2$), 27.5 (d, *J* = 9 Hz, C(*C*$H_3)_2$), 27.1 (d, *J* = 10 Hz, C(*C*$H_3)_2$), 26.3 (OC(*C*$H_3)_2$), 25.8 (C(*C*$H_3)_3$), 18.2 (*C*$(CH_3)_3$), -2.1 ($Si(CH_3)_2$), -2.2 ($Si(CH_3)_2$).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) -23.4.

MS (EI, 70 eV): m/z (%): 483 (2, M^+), 468 (8), 426 (46), 406 (42), 310 (78), 274 (12), 227 (53), 173 (100) 121 (21), 73 (38).

IR ($\tilde{\nu}$ [cm^{-1}]) 2963m, 2947m, 2927m, 2883m, 2853m, 1733w, 1680m, 1580w, 1470m, 1437m, 1359m, 1303w, 1251m, 1186s, 1160s, 1118s, 1102m, 1051s, 1034s, 1004m, 985m, 897w, 822s, 772s, 738s, 714s, 652s.

(148-Ir-TBDMS)



Following the general procedure as for preparation **142-Ir**. Complexation of 30 mg (62 μmol, 1 eq.) **148-TBDMS** with 21 mg (31 μmol, 0.5 eq.) of bis(1,5-cyclooctadiene)diiridium(I) dichloride in 3 mL DCM. 72 mg (81 μmol, 1.3 eq.) of $NaBAr_F$ was added and stirred for another 30 min at room temperature. The reaction mixture was immobilized on silica and putted on column, washed with 100 mL Et_2O and then eluted with DCM and in two fractions. It was obtained 79 mg (77% yield) of the product **148-Ir-TBDMS** as yellow solid.

^{1}H-NMR (500.1 MHz, $CDCl_3$, 300K): δ (ppm) 7.81 – 7.72 (m, 10H, 2 x ArH, 8 x $H_{ArF\text{-}o}$), 7.60 – 7.55 (m, 1H, ArH), 7.55 – 7.49 (m, 6H, 2 x ArH, 4 x $H_{ArF\text{-}p}$), 7.41 – 7.35 (m, 3H, ArH), 7.08 – 6.96 (m, 2H, ArH), 4.88 (dd, *J* = 9.7 Hz, 4.0 Hz, 1H, OCH_2), 4.83 (m, 1H, COD-CH), 4.81 – 4.75 (m, 1H, COD-CH), 4.37 (t, *J* = 9.7 Hz, 1H, OCH_2), 3.81 (dd, *J* = 9.8, 4.0 Hz, 1H, NCH), 3.67 – 3.61 (m, 1H, COD-CH), 2.68 – 2.48 (m, 4H, CH_2P, COD-CH_2), 2.48 – 2.42 (m, 1H, COD-CH), 2.28 (m, 2H, COD-CH_2), 2.24 (s, 3H, $C(CH_3)_2$), 2.13 – 2.02 (m, 1H, COD-CH_2), 1.84 (m, 1H, COD-CH_2), 1.61 (m, 1H, COD-CH_2), 1.51 (d, *J* = 2.9 Hz, 1H, $C(CH_3)_2$), 1.43 – 1.31 (m, 1H, COD-CH_2), 1.38 (s, 3H, O-$C(CH_3)_2$) 0.84 (s, 3H, O-$C(CH_3)_2$), 0.69 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 3H, $SiC(CH_3)_2$), -0.26 (s, 1H, $SiC(CH_3)_2$).

^{13}C{^{1}H}-NMR (125.8 MHz, $CDCl_3$, 300K): δ (ppm) 180.2 (d, *J* = 2 Hz, C=N), 161.8 (q, *J* = 50 Hz, C_{ArFi}), 135.1 (d, *J* = 12 Hz, C_{ArH}), 134.8 ($HC_{ArF\text{-}o}$), 132.8 (d, *J* = 2 Hz, C_{ArH}), 132.3 (d, *J* = 55 Hz, C_{Ar}) 131.2 (d, *J* = 2 Hz, C_{ArH}), 131.1 (d, *J* = 10 Hz, C_{ArH}) 129.6 (d, *J* = 11 Hz, C_{ArH}), 129.1 (d, *J* = 10 Hz, C_{ArH}), 128.9 (q, *J* = 32 Hz, $HC_{ArF\text{-}m}$), 128.7 (d, *J* = 54 Hz, C_{ArH}), 124.6 (q, *J* = 273 Hz, CF_3), 117.5 ($HC_{ArF\text{-}p}$), 94.2 (d, *J* = 10 Hz, COD-CH), 92.1 (d, *J* = 13 Hz, COD-CH), 73.9 (NCH), 73.5 (O*C*$(CH_3)_2$), 71.6 (OCH), 63.3 (COD-CH), 60.3 (COD-CH), 38.9 (*C*$(CH_3)_2$), 36.4 (COD-CH_2), 33.8 (d, *J* = 5 Hz, C(*C*$H_3)_2$), 33.2 (d, *J* = 32 Hz, CH_2P), 32.4 (COD-CH_2), 28.7 (O-C(*C*$H_3)_2$), 28.1 (COD-CH_2), 27.0 (d, *J* = 12 Hz, C(*C*$H_3)_2$), 25.6 (COD-CH_2), 25.4 ($SiC(CH_3)_3$), 24.2 (O-C(*C*$H_3)_2$), 17.8 (Si*C*$(CH_3)_3$), -2.5 (SiC(*C*$H_3)_2$), -2.9 (SiC(*C*$H_3)_2$).

MS (MALDI-TOF) m/z (%): 784 ($[M-(BAr_F)]^+$, 100).

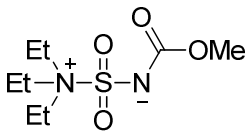
$[\alpha]^{20}_D$= -17.4 (*c* 0.70, $CHCl_3$).

^{31}P{^{1}H}-NMR (202.5 MHz, $CDCl_3$, 300K): δ(ppm) 9.2.

IR ($\tilde{\nu}$ [cm^{-1}]) 2963w, 2947w, 1610w, 1580w, 1437w, 1351m, 1271s, 1160m, 1114s, 1103s, 1199s, 1196s, 1001m, 970m, 895w, 886m, 838m, 777m, 743m, 715s, 710s, 668s.

Elem. anal.: calc.: C, 49.88; H, 4.13; N, 0.84; found: C, 49.59; H, 4.19; N, 0.91.

Burgess reagent [145]

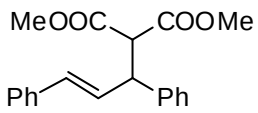


25 g of chlorosulfonylisocyanate was placed into the 250 mL three necked flask fitted with stirrbar and dropping funnel and chloro-calcium drying tube on the condenser diluted with 50

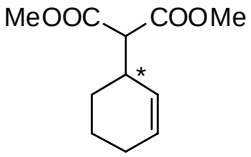
mL of dry benzene. From the dropping funnel was dropwise added 6.2 mL dry MeOH in 8 mL of benzene over 30 min and then stirred for additional 0.5 hour. Product was filtered over Schlenk filtration apparatus and dried on vacuum line. Then it was dissolved in 200 mL of dry benzene a heated by heatgun to help dissolve all crystals. This solution was added in course of 40 min to a 46 mL of Et_3N in 50 mL dry benzene at 10°C and stirred for another 30 min. Resulting mixture was then filtered under inert atmosphere and filtrate was evaporated on the rotavap and the residue was recrystallized from THF. It was obtained 12.3 g of Burgess reagent which was stored in the freezer for further experiments.

General procedure for Allylic substitution

1,8 mg of $[Pd(allyl)Cl]_2$ (0.01mmol) and 0.025 mmol of the approproate ligand in 1.2 mL DCM was in the Young tube degassed by freeze-pump-thaw and then stirred for 2 hours at 50°C. In the second Young tube containing the substrate, 252 mg (1 mmol) diphenylallylacetate (or CyOBz) in 4 mL DCM was mixed with dimethylmalonate 396 mg (3 mmol), BSA 0.73 mL (610 mg, 3 mmol, *d*=0.832) and 1 mg of the dried KOAc. This solution was also degassed by three freeze-pump-thaw cycles and then the solution of the catalyst was added. Resulting reaction mixture was stirred at room temperature 24 hours. Then was the reaction diluted by Et_2O and quenched by addition of 20 mL of NH_4Cl (sat. sol.). Aqueous layer was extracted with 3 x 15 mL Et_2O and combine organic extracts were dried over $MgSO_4$. After column chromatography on silica gel (Hexane/EtOAc/Et_3N 18:1:1) was obtained product as a white solid. Enantiomeric excess was determined by HPLC or GC.



Separation: HPLC (Diacel Chiracel AD-H, heptane/ispropanol 97:3, 0.9 mL·min^{-1}, 20°C, 254 nm): t_R = 16.3 (*R*), 17.9 (*S*) min.

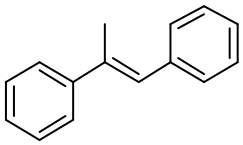


Separation: GC (β-cyclodextrine PM, 130°C, 100kPa): t_R = 21.7 (*R*), 23.7 (*S*) min.

General procedure for the hydrogenation reaction and used analytical methods

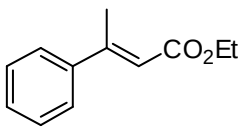
All hydrogenations reactions were performed at room temperature, 50 bar of H_2 gas, with the substrate concentration 0.2 mol/L and catalyst concentration 1 mol %. As a solvent was used crown cap dichloromethane purchased from Aldrich.

E-1,2-Diphenylpropene:



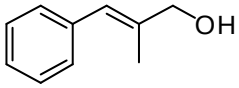
GC: Restek Rtx-1710 column (30 m × 0.25 mm × 0.25μm), 60 kPa He, (100°C - 2min -7 K / min – 250°C -10 min): t_R = 18.2 min (product), 23.8 min (starting material)
HPLC: (Diacel Chiracel OJ (2.6 × 250 mm), heptane/isopropanol 99:1, 0.5 mL/min, 20°C, 220 nm, t_R = 15.6 min (*R*), 23.8 min (*S*)

Ethyl *E*-2-methylcinnamate:



GC: Chiraldex γ-cyclodextrin TFA G-TA (30 m × 0.25 mm × 0.12μm) 60 kPa H_2, (85°C – 50 min -10 K / min – 160°C): t_R = 42.9 min ((*R*)product), 44.9 min ((*S*)product), 57.0 min (starting material)

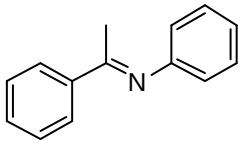
E-2-Methyl-3-phenylprop-2-enol:



GC: Restek Rtx-1710 column (30 m × 0.25 mm × 0.25µm), 60 kPa He, (100°C - 2min -7 K / min – 250°C -10 min): t_R = 14.6 min (product), 16.5 min (starting material)

HPLC: (Diacel Chiracel OD-H (2.6 × 250 mm), heptane/isopropanol 95:5, 0.5 mL/min, 40°C, 200 nm, t_R = 15.3 min (+), 17.5 min (-)

E-Phenyl-(1-phenylethylidene)amine:

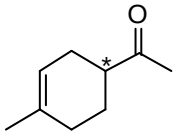


GC: Restek Macherey-Nagel Optima 5-Amin (30 m × 0.25 mm × 0.5µm), 60 kPa He, (150°C -7 K / min – 250°C -10 min): t_R = 12.8 min (product), 13.2 min (starting material)

HPLC: (Diacel Chiracel OD-H (2.6 × 250 mm), heptane/isopropanol 99:1, 0.5 mL/min, 20°C, 210 nm, t_R = 24.6 min (*S*), 33.0 min (*R*)

8.6 Diastereoselective hydrogenation of Diels-Alder products

1-(4-methylcyclohex-3-en-1-yl)ethanone (164)



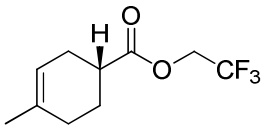
Solution of (*R*) or (*S*) limonene 5 mL (4.21g, 30.9 mmol) in 50 mL of DCM was cooled to -78°C under N_2 and *m*CPBA 6.93 g (30.9 mmol, 77%) was added as a solid. After stirring for 30 min was the cooling bath removed and the reaction mixture was warmed and stirred another 2 hours at room temperature. Then was the mixture recooled back to -78°C and ozon was bubled through the glass bubler into the reaction flask until the blue color was observed (20-30min). Resulting solution was purged by bubling O_2 at -78°C and then with N_2 while warming up to 0°C. Then Zn dust 20 g (309 mmol, 10 eq.) was added followed by addtion of 6.2 g (37.1 mmol, 1.2 eq.) of KI and 25 mL of glacial acetic acid. This suspension was well stirred overnight at room temperature and then decanted. Residual solids were repeatedly washed with Et_2O and continued with neutralization by Na_2CO_3 (sat. sol.) and subsequent extraction with 3 x 30 mL of Et_2O. Combined organic extracts were dried over $MgSO_4$ and concentrated in vacuum. Column chromatography on silica gel (5% Et_2O/*n*-pentane) afforded 1.315 g (31% yield) of the product as a yellowish oil.

$C_9H_{14}O$ (138.21 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 295K): δ (ppm) 5.39 (s, 1H,C=CH), 2.60 – 2.43 (m, 1H, CHC=O), 2.21 – 2.10 (m, 4H, $COCH_3$, CH_2), 2.05 – 1.90 (m, 3H, CH_2), 1.65 (s, 3H, CH_3), 1.62 – 1.51 (m, 1H, CH_2).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 295K): δ (ppm) 212.07 (C=O), 134.00 (*C*=CH), 119.41 (C=*C*H), 47.40 (*C*H-C=O), 29.66 (CH_3), 28.16 (CH_2), 27.21 (CH_2), 25.06 (CH_2), 23.57 (CH_3).

(*R*)-2,2,2-trifluoroethyl 4-methylcyclohex-3-enecarboxylate[146] (177)



0.32 mL (0.5M in Tol, 0.16mmol) oxazaborolidine was added to a precooled solution of 37 mg $(CF_3SO_2)_2NH$ (0.133 mmol) in 0.7 mL tolueme at -25°C and stirred for 10 minutes. Then isoprene 74µl (50 mg, *d* = 0.681) and 84µl (102 mg, *d* = 1.216) of 2,2,2-trifluoroethylacrylate in 0.7 mL toluene was added. The reaction mixture was stirred for 8 hours at 0°C and then quenched with 20 µL of triethylamine and warmed to room temperature. By column chromatography on silica gel in 2% Et_2O/*n*-pentane (R_f=0.45) was obtained 129 mg (88% yield) of the product as a colorless low boiling liquid.

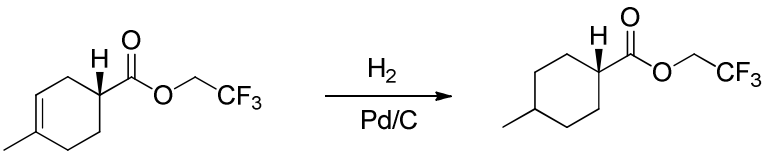
$C_{10}H_{13}F_3O_2$ (222.20 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 295K): δ (ppm) 5.46 – 5.29 (m, 1H), 4.64 – 4.26 (m, 2H), 2.68 – 2.52 (m, 1H), 2.35 – 2.15 (m, 2H), 2.15 – 1.89 (m, 3H), 1.83 – 1.68 (m, 1H), 1.65 (s, 3H).

^{19}F{1H}-NMR (376.5 MHz, $CDCl_3$, 300K): δ(ppm) -73.9.

GC-MS: (EI, 70 eV, R_t=12.7 min): m/z (%): 222 (15, M^+), 122 (32), 94 (100), 79 (54), 67 (29), 55 (15).

2,2,2-trifluoroethyl 4-methylcyclohexanecarboxylate (180)

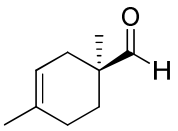


Substrate **177** 15 mg was reduced with Pd/C in 0.5 mL of MeOH at 1 bar of H_2 at room temperature. There was observed also about 10% of the trasesterified product as methylester.

$C_{10}H_{15}F_3O_2$ (224.22 $g \cdot mol^{-1}$)

GC-MS: (EI, 70 eV, R_t=4.35 min; 4.43 min): m/z (%): 224 (23, M^+), 155 (30), 124 (39), 97 (40), 82 (67), 70 (100), 67 (25), 55 (81), 41 (23).

(*S*)-1,4-dimethylcyclohex-3-enecarbaldehyde[147] (178)



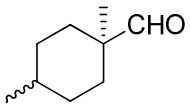
To a solution of oxazaborolidine 0.124 mL (0.5M in Tol, 0.062mmol) in 0.5 mL DCM at -40°C was added sloution of 13.7 mg $AlBr_3$ (0.05 mmol) in 0.3 mL DCM and after stirring 30 min was the temperature lowered to -78°C and then isoprene 426.4 mg (350 µl, 6.26 mmol) followed by methacroleine 87.6 mg (102 µl, 1.25 mmol) were added. After stirring 16 hours at -78°C was reaction quenched by addition of 0.2 mL Et_3N and warmed up to room temperature. After column chromatography on silica (15 cm) in 2% Et_2O in *n*-pentane R_f=0.5 ($KMnO_4$ stain), was obtained 157 mg (91% yield) of the product **178**.

$C_9H_{14}O$ (138.21 $g \cdot mol^{-1}$)

^{1}H-NMR (250.1 MHz, $CDCl_3$, 295K): δ (ppm) 9.46 (s, 1H), 5.46 – 5.29 (m, 1H), 2.43 – 2.22 (m, 1H), 2.03 – 1.90 (m, 2H), 1.90 – 1.77 (m, 2H), 1.63 (s, 3H), 1.59 – 1.45 (m, 2H), 1.03 (s, 3H).

GC-MS: (EI, 70 eV, R_t=9.88 min): m/z (%): 138 (73, M^+), 123 (45), 109 (32), 95 (95), 81 (34), 67 (100), 55 (28), 41 (27).

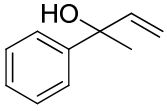
1,4-dimethylcyclohexanecarbaldehyde (181)



$C_9H_{16}O$ (140.22 $g \cdot mol^{-1}$)

GC-MS: (EI, 70 eV, R_t=8.19 min): m/z (%): 140 (5, M^+), 111 (62), 84 (9), 69 (100), 55 (38), 41 (21).

2-phenylbut-3-en-2-ol[148]

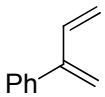


To the 36 mL (1M in THF, 1.2 eq.) vinylmagnesiumbromide was at room temperature added 3.51 mL (30 mmol, 1 eq.) of acetopehnone in a rate to keep gentle reflux of a reaction mixture. Stirring was then continued for another 1 hour. Then was reaction quenched by 10 mL of sat. sol. of NH_4Cl and extracted by Et_2O and dried over Na_2SO_4. The crude product was distilled on Kugelrohr 70°C /0.1 Torr to obtain 3.75 g (84% yield) of the product as colorless liquid.

$C_{10}H_{12}O$ (148.20 $g \cdot mol^{-1}$)

^{1}H-NMR (250.1 MHz, $CDCl_3$, 295K): δ (ppm) 7.43 – 7.31 (m, 2H, ArH), 7.30 – 7.19 (m, 2H, ArH), 7.19 – 7.08 (m, 1H, ArH), 6.05 (dd, *J* = 17.3, 10.6 Hz, 1H, C=CH), 5.17 (dd, *J* = 17.3, 1.1 Hz, 1H, C=CH_2), 5.02 (dd, *J* = 10.6, 1.1 Hz, 1H, C=CH_2), 2.23 (s, 1H, OH), 1.53 (s, 3H, CH_3).

Buta-1,3-dien-2-ylbenzene[148] (175)



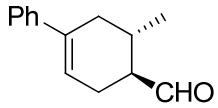
396 mg (2.28 mmol, 0.09 eq.) of aniline hydrobromide (prepared from aniline in DCM and 63% HBr and recrystalized from EtOH) 56 mg (506 μmol, 0.02 eq.) of hydrochinon and 3.75 g (25.3 mmol, 1eq.) of 2-phenylbut-3-en-2-ol were heated to 100-150°C and the product was continuously distilled over the 14 cm Vigreux column and fraction with the boiling point around 70°C/20 Torr was collected. Obtained distillate was then purified by column chromatography on silicagel in 2% Et_2O/*n*-pentane to obtain 1.23 g (37% yield) as colorless liquid.

$C_{10}H_{10}$ (130.19 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 295K): δ (ppm) 7.42 – 7.29 (m, 5H, ArH), 6.65 (dd, *J* = 17.3, 11.0 Hz, 1H, C=CH), 5.32 (d, *J* = 0.8 Hz, 1H, CH_2), 5.28 – 5.17 (m, 3H, CH_2).

^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$, 295K): δ (ppm) 148.28 (*C*-Ph), 139.75 (CH), 138.18 (C_{Ar}), 128.30 (C_{ArH}), 128.14 (C_{ArH}), 127.49 (C_{ArH}), 117.17 (CH_2), 116.91 (CH_2).

(3*S*,4*S*)-3-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbaldehyde[132] (179)



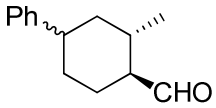
To a solution of 89 mg (683 μmol) of the phenylbutadiene in 0.7 mL CH_3NO_2/H_2O (95/5 v/v 1.0 M) was added 35 mg (137 μmol) of the catalyst at 0°C and followed by addition of *trans*-crotonaldehyde 149 mg (2.12 mmol, *d*=0.846, 176 μl). The solution was stirred at 0°C for 24 hours and then placed directly onto a silicagel column and eluted with 5% EtOAc/*n*-pentane to obtain 100 mg (73% yield) of the product (regioisomers ratio 1:4) as a colorless oil.

$C_{14}H_{16}$ (200.28 $g \cdot mol^{-1}$)

^{1}H-NMR (400.1 MHz, $CDCl_3$, 295K): δ (ppm) 9.71 (d, *J* = 3.2 Hz, 1H, CH=O), 7.39 – 7.35 (m, 2H, ArH), 7.34 – 7.29 (m, 2H, ArH), 6.16 – 6.05 (m, 1H, C=CH), 2.62 – 2.11 (m, 6H, CH, CH_2), 1.14 (d, *J* = 6.4 Hz, 3H, CH_3).

GC-MS: (EI, 70 eV, R_t=32.42 min (major); 32.48 min (minor)): m/z (%): 200 (73, M^+), 182 (15), 169 (100), 155 (51), 143 (68), 129 (68), 115 (45), 104 (15), 91 (70), 77 (24), 65 (10), 55 (11), 41 (8).

(1*S*,2*S*)-2-methyl-4-phenylcyclohexanecarbaldehyde (182)



$C_{14}H_{18}O$ (202.29 $g \cdot mol^{-1}$)

GC-MS: (EI, 70 eV, R_t=31.96 min; 32.00 min): m/z (%): 202 (55, M^+), 184 (16), 169 (17), 157 (13), 143 (14), 131 (44), 117 (44), 104 (83), 91 (100), 78 (13), 69 (13), 55 (13), 41 (19).

8.7 Crystallographic data

The X-ray structures were measured by Dr. Markus Neuburger (Department of Chemistry, University of Basel) on Bruker Nonius KappaCCD difractometer using graphite-monochromated Mo K_α-radiation and solved using Direct methods (Sir97,[149] Superflip[150] or SHELX[151]) and refined in Crystals[152] by Dr. Markus Neuburger. Least-squares refinement against F was carried out on all non-hydrogen atoms. Chebychev polynomial weights were used to complete the refinement.[153] The absolute configuration and enantiopurity could be determined by definement of the flack parameter.[154] Data were recorded at 123 K. Crystals were usually grown by dissolving a compound in dichloromethane or chloroform and carefully ovelayed with *n*-heptane. Then they were mounted with paraffin on a glas fibre gomiometer head.

compound	**98-catechol**	**98**
formula	$C_{38}H_{34}B_2N_2O_8$	$C_{32}H_{28}B_2N_2O_6$
formula weight ($g \cdot mol^{-1}$)	668.32	558.21
shape	block	block
color	colorless	colorless
temperature [K]	123	123
crystal size [mm^3]	0.070 · 0.090 · 0.270	0.070 · 0.120 · 0.330
crystal system	orthorhombic	orthorhombic
space group	P 2_1 2_1 2_1	P 2_1 2_1 2_1
a [Å]	8.4230(2)	8.5678(3)
b [Å]	10.6624(2)	12.6340(4)
c [Å]	36.6293(8)	26.1131(8)
α [°]	90	90
β [°]	90	90
γ [°]	90	90
volume [Å]^3	3289.66(12)	2826.63(16)
Z	4	4
density (calc.) [$g \cdot cm^{-1}$]	1.349	1.312
μ(Mo K_α) [mm^{-1}]	0.094	0.090
transmission (min/max)	0.99 / 0.99	0.99 / 0.99
Θ range for data collection [°]	1.989 - 30.251	1.791 - 40.262
radiation (λ [Å])	0.71073	0.71073
F(000)	1400	1168
measured reflections	56135	123904
independent reflections	5468 (merging r = 0.051)	9730 (merging r = 0.057)
observed reflections	4684 (I>2.0σ(I))	6330 (I>2.0σ(I))
parameters refined	451	452
R	0.0449	0.0501
R_w	0.0630	0.0784
goodness of fit on F	1.0467	1.1201
flack parameter	-	-

compound	**142-Ir-TES**	**142-Ir-TMS**
formula	$C_{70}H_{69}BCl_3F_{24}IrNO_2PSi$	$C_{67}H_{63}BCl_3F_{24}IrNO_2PSi$
formula weight ($g \cdot mol^{-1}$)	1780.72	1738.64
shape	block	block
color	orange	orange
temperature [K]	123	123
crystal size [mm^3]	0.060 · 0.130 · 0.240	0.070 · 0.150 · 0.240
crystal system	orthorhombic	orthorhombic
space group	P 2_1 2_1 2_1	P 2_1 2_1 2_1
a [Å]	14.8070(10)	15.1113(5)
b [Å]	17.4577(12)	17.7434(7)
c [Å]	28.8726(19)	27.3178(10)
α [°]	90	90
β [°]	90	90
γ [°]	90	90
volume [Å]^3	7463.5(9)	7324.6(5)
Z	4	4
density (calc.) [$g \cdot cm^{-1}$]	1.585	1.577
μ(Mo K_α) [mm^{-1}]	2.038	2.075
transmission (min/max)	0.77 / 0.88	0.73 / 0.86
Θ range for data collection [°]	1.546 - 27.899	1.770 - 29.136
radiation (λ [Å])	0.71073	0.71073
F(000)	3560	3464
measured reflections	68593	113578
independent reflections	17796 (merging r = 0.028)	19676 (merging r = 0.032)
observed reflections	16608 (I>2.0σ(I))	16944 (I>2.0σ(I))
parameters refined	938	1022
R	0.0239	0.0252
R_w	0.0286	0.0329
goodness of fit on F	1.0808	1.1085
flack parameter	-0.010(2)	-0.008(2)

compound	**142-Ir-TBDMS**	**148-Ir-TBDMS**
formula	$C_{69}H_{68}BF_{24}IrNO_2PSi$	$C_{68}H_{66}BF_{24}IrNO_2PSi$
formula weight ($g \cdot mol^{-1}$)	1661.35	1647.32
shape	block	block
color	orange	orange
temperature [K]	123	123
crystal size [mm^3]	0.060 · 0.170 · 0.220	0.070 · 0.180 · 0.210
crystal system	orthorhombic	orthorhombic
space group	P 2_1 2_1 2_1	P 2_1 2_1 2_1
a [Å]	13.0330(3)	12.9974(3)
b [Å]	19.5152(4)	19.2190(4)
c [Å]	27.7197(6)	27.4554(5)
α [°]	90	90
β [°]	90	90
γ [°]	90	90
volume [Å]^3	7050.3(3)	6858.3(2)
Z	4	4
density (calc.) [$g \cdot cm^{-1}$]	1.565	1.595
μ(Mo K_α) [mm^{-1}]	2.042	2.098
transmission (min/max)	0.71 / 0.88	0.69 / 0.86
Θ range for data collection [°]	1.727 - 37.789	1.733 - 37.789
radiation (λ [Å])	0.71073	0.71073
F(000)	3328	3296
measured reflections	297104	296707
independent reflections	37854 (merging r = 0.044)	36782 (merging r = 0.042)
observed reflections	30699 (I>2.0σ(I))	31942 (I>2.0σ(I))
parameters refined	1031	930
R	0.0246	0.0222
R_w	0.0326	0.0265
goodness of fit on F	1.0931	1.0944
flack parameter	-0.0085(19)	-0.0087(15)

9. References

[1] M. E. Franks, G. R. Macpherson, W. D. Figg, *The Lancet* **2004**, *363*, 1802-1811.

[2] a) T. Eriksson, S. Bjorkman, B. Roth, A. Fyge, P. Hoglund, *Chirality* **1998**, *10*, 223-228; b) T. Eriksson, S. Bjorkman, P. Hoglund, *Eur. J. Clin. Pharmacol.* **2001**, *57*, 365-376; c) S. K. Teo, W. A. Colburn, W. G. Tracewell, K. A. Kook, D. I. Stirling, M. S. Jaworsky, M. A. Scheffler, S. D. Thomas, O. L. Laskin, *Clin. Pharmacokinet.* **2004**, *43*, 311-327.

[3] W. Winter, E. Frankus, *The Lancet* **1992**, *339*, 365.

[4] a) M. M. Midland, A. Tramontano, *The Journal of Organic Chemistry* **1978**, *43*, 1470-1471; b) M. M. Midland, J. I. McLoughlin, J. Gabriel, *The Journal of Organic Chemistry* **1989**, *54*, 159-165.

[5] D. Mansuy, M. Lange, J. C. Chottard, P. Guerin, P. Morliere, D. Brault, M. Rougee, *J. Chem. Soc., Chem. Commun.* **1977**, 648-649.

[6] H. J. Callot, C. Piechocki, *Tetrahedron Lett.* **1980**, *21*, 3489-3492.

[7] H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem., Int. Ed.* **1986**, *25*, 1005-1006.

[8] Y. Yamada, Miljkovi.D, P. Wehrli, B. Golding, P. Loliger, R. Keese, K. Muller, Eschenmo.A, *Angew. Chem., Int. Ed.* **1969**, *8*, 343-&.

[9] A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339-345.

[10] H. Nozaki, H. Takaya, S. Moriuti, R. Noyori, *Tetrahedron* **1968**, *24*, 3655-3669.

[11] a) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1975**, 1707-1710; b) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1982**, *23*, 685-688; c) T. Aratani, *Pure Appl. Chem.* **1985**, *57*, 1839-1844; d) A. Nakamura, A. Konishi, Y. Tatsuno, S. Otsuka, *J. Am. Chem. Soc.* **1978**, *100*, 3443-3448.

[12] a) H. Fritschi, U. Leutenegger, K. Siegmann, A. Pfaltz, W. Keller, C. Kratky, *Helv. Chim. Acta* **1988**, *71*, 1541-1552; b) M. Misun, A. Pfaltz, *Helv. Chim. Acta* **1996**, *79*, 961-972.

[13] P. Vonmatt, A. Pfaltz, *Tetrahedron: Asymmetry* **1991**, *2*, 691-700.

[14] C. Pique, B. Fahndrich, A. Pfaltz, *Synlett* **1995**, 491-492.

[15] R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005-6008.

[16] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726-728.

[17] D. Müller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta* **1991**, *74*, 232-240.

[18] E. J. Corey, N. Imai, H. Y. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728-729.

[19] E. J. Corey, K. Ishihara, *Tetrahedron Lett.* **1992**, *33*, 6807-6810.

[20] R. E. Lowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *32*, 7373-7376.

[21] C. Bolm, K. Weickhardt, M. Zehnder, T. Ranff, *Chem. Ber.* **1991**, *124*, 1173-1180.

[22] A. M. Harm, J. G. Knight, G. Stemp, *Synlett* **1996**, 677-&.

[23] I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Tetrahedron Lett.* **1996**, *37*, 813-814.

[24] G. Desimoni, G. Faita, M. Mella, *Tetrahedron* **1996**, *52*, 13649-13654.

[25] A. K. Ghosh, M. Packiarajan, J. Cappiello, *Tetrahedron Lett.* **1996**, *37*, 3815-3818.

[26] I. W. Davies, L. Gerena, L. Castonguay, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Chem. Commun. (Cambridge, U. K.)* **1996**, 1753-1754.

[27] J. K. Whitesell, *Chem. Rev. (Washington, DC, U. S.)* **1989**, *89*, 1581-1590.

[28] J. Hall, J. M. Lehn, A. Decian, J. Fischer, *Helv. Chim. Acta* **1991**, *74*, 1-6.

[29] P. Vonmatt, G. C. Lloydjones, A. B. E. Minidis, A. Pfaltz, L. Macko, M. Neuburger, M. Zehnder, H. Ruegger, P. S. Pregosin, *Helv. Chim. Acta* **1995**, *78*, 265-284.

[30] R. P. Singh, *Synth. React. Inorg. Met.-Org. Chem.* **1997**, *27*, 155-166.

[31] A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1-45.

[32] H. Nishiyama, K. Aoki, H. Itoh, T. Iwamura, N. Sakata, O. Kurihara, Y. Motoyama, *Chem. Lett.* **1996**, 1071-1072.

[33] a) W. Levason, C. A. McAuliffe, *Advan. Inorg. Chem. Radiochem.* **1972**, *14*, 173-253; b) X. Zhang, *Enantiomer* **1999**, *4*, 541-555; c) S. H. L. Kok, T. T. L. Au-Yeung, H. Y. Cheung, W. S. Lam, S. S. Chan, A. S. C. Chan, *Vol. 2*, Wiley-VCH Verlag GmbH & Co. KGaA, **2007**, pp. 883-993.

[34] J. C. Thomas, J. C. Peters, *Inorg. Chem.* **2003**, *42*, 5055-5073.

[35] a) C. Ohrenberg, P. H. Ge, P. Schebler, C. G. Riordan, G. P. A. Yap, A. L. Rheingold, *Inorg. Chem.* **1996**, *35*, 749-754; b) P. J. Schebler, C. G. Riordan, I. A. Guzei, A. L. Rheingold, *Inorg. Chem.* **1998**, *37*, 4754-4755; c) S. J. Chiou, P. H. Ge, C. G. Riordan, L. M. Liable-Sands, A. L. Rheingold, *J. Inorg. Biochem.* **1999**, *74*, 98-98; d) P. H. Ge, A. L. Rheingold, C. G. Riordan, *Inorg. Chem.* **2002**, *41*, 1383-1390; e) C. V. Popescu, M. T. Mock, S. A. Stoian, W. G. Dougherty, G. P. A. Yap, C. G. Riordan, *Inorg. Chem.* **2009**, *48*, 8317-8324; f) C. G. Riordan, *Coord. Chem. Rev.* **2010**, *254*, 1815-1825.

[36] C. Mazet, V. Kohler, A. Pfaltz, *Angew. Chem., Int. Ed.* **2005**, *44*, 4888-4891.

[37] V. Kohler, C. Mazet, A. Toussaint, K. Kulicke, D. Haussinger, M. Neuburger, S. Schaffner, S. Kaiser, A. Pfaltz, *Chemistry – A European Journal* **2008**, *14*, 8530-8539.

[38] A. I. Meyers, K. A. Novachek, *Tetrahedron Lett.* **1996**, *37*, 1747-1748.

[39] J. P. Foster, F. Weinhold, *J. Am. Chem. Soc.* **1980**, *102*, 7211-7218.

[40] Y. Matsumura, T. Maki, S. Murakami, O. Onomura, *J. Am. Chem. Soc.* **2003**, *125*, 2052-2053.

[41] S. J. Roseblade, A. Pfaltz, *Synthesis* **2007**, 3751-3753.

[42] a) S. Bell, B. Wustenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642-644; b) S. Kaiser, S. Smidt, P., A. Pfaltz, *Angew. Chem., Int. Ed.* **2006**, *45*, 5194-5197; c) W. J. Drury, III, N. Zimmermann, M. Keenan, M. Hayashi, S. Kaiser, R. Goddard, A. Pfaltz, *Angew. Chem., Int. Ed.* **2004**, *43*, 70-74.

[43] a) T. Ohkuma, M. Koizumi, M. Yoshida, R. Noyori, *Org. Lett.* **2000**, *2*, 1749-1751; b) K. Okano, K. Murata, T. Ikariya, *Tetrahedron Lett.* **2000**, *41*, 9277-9280; c) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 5675-5678; d) C. Bolm, M. Zehnder, D. Bur, *Angew. Chem., Int. Ed.* **1990**, *29*, 205-207.

[44] a) J. Uenishi, T. Hiraoka, S. Hata, K. Nishiwaki, O. Yonemitsu, K. Nakamura, H. Tsukube, *The Journal of Organic Chemistry* **1998**, *63*, 2481-2487; b) V. B. Birman, E. W. Uffman, J. Hui, X. M. Li, C. J. Kilbane, *J. Am. Chem. Soc.* **2004**, *126*, 12226-12227; c) A. C. Spivey, D. P. Leese, F. J. Zhu, S. G. Davey, R. L. Jarvest, *Tetrahedron* **2004**, *60*, 4513-4525.

[45] A. Toussaint, PhD thesis, University of Basel **2008**.

[46] A. Toussaint, A. Pfaltz, *Eur. J. Org. Chem.* **2008**, 4591-4597.

[47] D. A. Evans, K. A. Woerpel, M. J. Scott, *Angew. Chem., Int. Ed.* **1992**, *31*, 430-432.

[48] W. R. Leonard, J. L. Romine, A. I. Meyers, *The Journal of Organic Chemistry* **1991**, *56*, 1961-1963.

[49] a) A. K. El-Qisiari, H. A. Qaseer, P. M. Henry, *Tetrahedron Lett.* **2002**, *43*, 4229-4231; b) M. B. Andrus, Z. N. Zhou, *J. Am. Chem. Soc.* **2002**, *124*, 8806-8807; c) S. K. Ginotra, V. K. Singh, *Tetrahedron* **2006**, *62*, 3573-3581; d) S. K. Ginotra, V. K. Singh, *Org. Biomol. Chem.* **2006**, *4*, 4370-4374.

[50] C. Mazet, S. Roseblade, V. Koehler, A. Pfaltz, *Org. Lett.* **2006**, *8*, 1879-1882.

[51] R. D. Chambers, T. Chivers, *Journal of the Chemical Society* **1965**, 3933-3939.

[52] D. J. Parks, W. E. Piers, G. P. A. Yap, *Organometallics* **1998**, *17*, 5492-5503.

[53] H. Nöth, H. Vahrenkamp, *J. Organomet. Chem.* **1968**, *11*, 399-405.

[54] E. W. Abel, S. H. Dandegaonker, W. Gerrard, M. F. Lappert, *Journal of the Chemical Society* **1956**, 4697-4699.

[55] G. Chremos, H. Weidmann, H. Zimmerman, *The Journal of Organic Chemistry* **1961**, *26*, 1683-1683.

[56] R. Koster, Grassber.Ma, *Justus Liebigs Annalen Der Chemie* **1969**, *719*, 169-&.

[57] a) Fleck, *Justus Liebigs Annalen Der Chemie* **1893**, *276*, 138; b) K. A. Petrov, S. V. Agafonov, V. P. Pokatun, V. M. Chizhov, *Zh. Obshch. Khim.* **1987**, *57*, 299-302.

[58] B. M. Mikhailov, N. S. Fedotov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1956**, 359.

[59] B. M. Mikhailov, T. V. Kostroma, N. S. Fedotov, *Russ. Chem. Bull.* **1957**, *6*, 603-610.

[60] A. Franzke, PhD thesis, University of Basel **2006**.

[61] unpublished results.

[62] N. E. Schore, B. E. LaBelle, *The Journal of Organic Chemistry* **1981**, *46*, 2306-2310.

[63] D. J. Peterson, *J. Organomet. Chem.* **1967**, *8*, 199-208.

[64] N. E. Schore, L. S. Benner, B. E. LaBelle, *Inorg. Chem.* **1981**, *20*, 3200-3208.

[65] C. A. Jaska, A. J. Lough, I. Manners, *Inorg. Chem.* **2004**, *43*, 1090-1099.

[66] H. F. Bettinger, M. Filthaus, H. Bornemann, I. M. Oppel, *Angew. Chem., Int. Ed.* **2008**, *47*, 4744-4747.

[67] W. Gerrard, M. F. Lappert, B. A. Mountfield, *Journal of the Chemical Society* **1959**, 1529-1535.

[68] C. M. Breneman, K. B. Wiberg, *J. Comput. Chem.* **1990**, *11*, 361-373.

[69] S. Porcel, G. Bouhadir, N. Saffon, L. Maron, D. Bourissou, *Angew. Chem., Int. Ed.* **2010**, *49*, 6186-6189.

[70] R. Smoum, A. Rubinstein, M. Srebnik, *Bioorg. Chem.* **2003**, *31*, 464-474.

[71] O. Basle, S. Porcel, S. Ladeira, G. Bouhadir, D. Bourissou, *Chem. Commun. (Cambridge, U. K.)* **2012**, *48*, 4495-4497.

[72] B. M. Mikhailov, V. A. Vaver, *Russ. Chem. Bull.* **1957**, *6*, 833-837.

[73] B. M. Mikhailov, N. S. Fedotov, *Russ. Chem. Bull.* **1956**, *5*, 1561-1563.

[74] S. W. H. Nöth, B. Rasthofer, Ch. Narula, A. Konstantinov, *Pure Appl. Chem.* **1983**, *50*.

[75] a) H. Mizuno, H. Sakurai, T. Amaya, T. Hirao, *Chem. Commun. (Cambridge, U. K.)* **2006**, 5042 - 5044; b) Thierig, Umland, *Naturwissenschaften* **1967**, *54*, 563.

[76] T. Ito, T. Iwai, T. Mizuno, Y. Ishino, *Synlett* **2003**, *2003*, 1435,1438.

[77] A. D. Becke, *The Journal of Chemical Physics* **1993**, *98*, 1372-1377.

[78] J. J. A. Montgomery, M. J. Frisch, J. W. Ochterski, G. A. Petersson, *The Journal of Chemical Physics* **2000**, *112*, 6532-6542.

[79] A. E. Reed, F. Weinhold, *The Journal of Chemical Physics* **1985**, *83*, 1736-1740.

[80] U. C. Singh, P. A. Kollman, *J. Comput. Chem.* **1984**, *5*, 129-145.

[81] E. Vedejs, S. C. Fields, M. R. Schrimpf, *J. Am. Chem. Soc.* **1993**, *115*, 11612-11613.

[82] a) R. D. Holmes-Smith, R. D. Osei, S. R. Stobart, *Journal of the Chemical Society, Perkin Transactions 1* **1983**, 861-866; b) J. Cámpora, C. M. Maya, I. Matas, B. Claasen, P. Palma, E. Álvarez, *Inorg. Chim. Acta* **2006**, *359*, 3191-3196; c) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.* **1990**, *112*, 5244-5252.

[83] F. C. Nahm, E. F. Rothergy, K. Niedenzu, *J. Organomet. Chem.* **1972**, *35*, 9-17.

[84] K. Light, P. Koehler, H. Kriegsmann, *Zeitschrift für Anorganische und Algemeine Chemie* **1975**, *415*, 31-42.

[85] G. Anilkumar, S. Bhor, M. K. Tse, M. Klawonn, B. Bitterlich, M. Beller, *Tetrahedron: Asymmetry* **2005**, *16*, 3536-3561.

[86] M. K. Tse, S. Bhor, M. Klawonn, C. Döbler, M. Beller, *Tetrahedron Lett.* **2003**, *44*, 7479-7483.

[87] a) S. D. Dreher, S.-E. Lim, D. L. Sandrock, G. A. Molander, *The Journal of Organic Chemistry* **2009**, *74*, 3626-3631; b) M. Butters, J. N. Harvey, J. Jover, A. J. J. Lennox, G. C. Lloyd-Jones, P. M. Murray, *Angew. Chem., Int. Ed.* **2010**, *49*, 5156-5160.

[88] E. Alacid, C. Nájera, *The Journal of Organic Chemistry* **2009**, *74*, 8191-8195.

[89] G. A. Molander, C. R. Bernardi, *The Journal of Organic Chemistry* **2002**, *67*, 8424-8429.

[90] D. B. Llewellyn, D. Adamson, B. A. Arndtsen, *Org. Lett.* **2000**, *2*, 4165-4168.

[91] T. A. Betley, J. C. Peters, *Inorg. Chem.* **2002**, *41*, 6541-6543.

[92] H. Braunschweig, R. Dirk, B. Ganter, *J. Organomet. Chem.* **1997**, *545–546*, 257-266.

[93] R. W. Hoffmann, H. J. Zeiss, *The Journal of Organic Chemistry* **1981**, *46*, 1309-1314.

[94] G. S. Kyker, E. P. Schram, *J. Am. Chem. Soc.* **1968**, *90*, 3672-3677.

[95] A. I. Meyers, M. Shipman, *The Journal of Organic Chemistry* **1991**, *56*, 7098-7102.

[96] a) H. C. Soeyleyici, E. Firinci, F. Eyduran, F. Akbulat, Y. Ahin, *Spectrochim. Acta, Part A* **2011**, *78*, 1139 - 1142; b) M. Suginome, A. Yamamoto, M. Murakami, *Angew. Chem., Int. Ed.* **2005**, *44*, 2380 - 2382; c) A. Goswami, H. Pritzkow, F. Rominger, W. Siebert, *Eur. J. Inorg. Chem.* **2004**, 4223 - 4231; d) A. Goswami, H. Pritzkow, F. Rominger, W. Siebert, *Eur. J. Inorg. Chem.* **2004**, 4223 - 4231; e) H. Braunschweig,

R. Dirk, U. Englert, *Zeitschrift für Anorganische und Algemeine Chemie* **1997**, *623*, 1093 - 1097; f) G. E. Herberich, B. Schmidt, U. Englert, *Organometallics* **1995**, *14*, 471 - 480; g) R. W. Hoffmann, U. Weidmann, *J. Organomet. Chem.* **1980**, *195*, 137 - 146.

[97] a) S. R. Neal, A. Ellern, A. D. Sadow, *J. Organomet. Chem.* **2011**, *696*, 228 - 234; b) H.-A. Ho, J. F. Dunne, A. Ellern, A. D. Sadow, *Organometallics* **2010**, *29*, 4105 - 4114; c) J. F. Dunne, J. Su, A. Ellern, A. D. Sadow, *Organometallics* **2008**, *27*, 2399 - 2401; d) J. F. Dunne, K. Manna, J. W. Wiench, A. Ellern, M. Pruski, A. D. Sadow, *Dalton Trans.* **2010**, *39*, 641 - 653; e) B. Baird, A. V. Pawlikowski, J. Su, J. W. Wiench, M. Pruski, A. D. Sadow, *Inorg. Chem.* **2008**, *47*, 10208 - 10210.

[98] G. E. Coates, J. G. Livingstone, *Journal of the Chemical Society* **1961**, 1000-1008.

[99] H. Noeth, W. Regnet, H. Rihl, R. Standfest, *Chem. Ber.* **1971**, *104*, 722 - 733.

[100] J. J. Eisch, B. Shafii, J. D. Odom, A. L. Rheingold, *J. Am. Chem. Soc.* **1990**, *112*, 1847-1853.

[101] K. M. Cooke, T. P. Kee, A. L. Langton, M. Thornton-Pett, *J. Organomet. Chem.* **1991**, *419*, 171-180.

[102] W. S. Knowles, *Angew. Chem., Int. Ed.* **2002**, *41*, 1998-2007.

[103] N. Bodor, K. B. Sloan, T. Higuchi, K. Sasahara, *J. Med. Chem.* **1977**, *20*, 1435-1445.

[104] J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *Journal of the Chemical Society A: Inorganic, Physical, Theoretical* **1966**, 1711-1732.

[105] S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402-1411.

[106] M. G. Schrems, E. Neumann, A. Pfaltz, *Heterocycles* **2008**, *76*, 771-781.

[107] a) J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769-1772; b) P. Vonmatt, A. Pfaltz, *Angew. Chem., Int. Ed.* **1993**, *32*, 566-568; c) G. J. Dawson, C. G. Frost, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.* **1993**, *34*, 3149-3150.

[108] G. Desimoni, G. Faita, P. P. Righetti, *Tetrahedron Lett.* **1996**, *37*, 3027-3030.

[109] a) M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518-8519; b) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125-10138.

[110] a) E. C. Linton, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 16162-16163; b) D. Liu, F. Xie, X. Zhao, W. Zhang, *Tetrahedron* **2008**, *64*, 3561-3566; c) Y. Wang, D. Liu, Q. Meng, W. Zhang, *Tetrahedron: Asymmetry* **2009**, *20*, 2510-2512; d) M. Lenze, S. L. Sedinkin, N. P. Rath, E. B. Bauer, *Tetrahedron Lett.* **2010**, *51*, 2855-2858; e) K. S. Petersen, B. M. Stoltz, *Tetrahedron* **2011**, *67*, 4352-4357.

[111] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331-337.

[112] S. P. Smidt, A. Pfaltz, E. Martinez-Viviente, P. S. Pregosin, A. Albinati, *Organometallics* **2003**, *22*, 1000-1009.

[113] S. P. Smidt, N. Zimmermann, M. Studer, A. Pfaltz, *Chemistry – A European Journal* **2004**, *10*, 4685-4693.

[114] M. G. Schrems, PhD thesis, University of Basel **2009**.

[115] M. G. Schrems, A. Pfaltz, *Chem. Commun. (Cambridge, U. K.)* **2009**, 6210-6212.

[116] H. Meerwein, *Justus Liebigs Annalen Der Chemie* **1914**, *405*, 129-175.

[117] a) J. S. Duca, M. H. Gallego, A. B. Pierini, R. A. Rossi, *The Journal of Organic Chemistry* **1999**, *64*, 2626-2629; b) E. C. Ashby, R. Gurumurthy, R. W. Ridlehuber, *The Journal of Organic Chemistry* **1993**, *58*, 5832-5837.

[118] G. M. Atkins, E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744-4745.

[119] a) P. Wipf, C. P. Miller, *The Journal of Organic Chemistry* **1993**, *58*, 1575-1578; b) E. Aguilar, A. I. Meyers, *Tetrahedron Lett.* **1994**, *35*, 2477-2480; c) P. Wipf, C. P. Miller, C. M. Grant, *Tetrahedron* **2000**, *56*, 9143-9150; d) M. Benaglia, T. Benincori, P. Mussini, T. Pilati, S. Rizzo, F. Sannicolo, *The Journal of Organic Chemistry* **2005**, *70*, 7488-7495.

[120] a) A. Franzke, A. Pfaltz, *Chemistry – A European Journal* **2011**, *17*, 4131-4144; b) A. Franzke, F. Voss, A. Pfaltz, *Tetrahedron* **2011**, *67*, 4358-4363.

[121] G. Umbricht, PhD thesis thesis, University of Basel **1993**.

[122] A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, D. R. Williams, *Org. Lett.* **2000**, *2*, 1165-1168.

[123] Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249-6253.

[124] a) S. R. Gilbertson, C.-W. T. Chang, *Chem. Commun. (Cambridge, U. K.)* **1997**, 975-976; b) S. R. Gilbertson, C.-W. T. Chang, *The Journal of Organic Chemistry* **1998**, *63*, 8424-8431.

[125] T. Kubota, *J. Fluorine Chem.* **2000**, *105*, 193-196.

[126] P. Liu, A. Sharon, C. K. Chu, *J. Fluorine Chem.* **2008**, *129*, 743-766.

[127] M. T. Reetz, J. Westermann, R. Steinbach, *J. Chem. Soc., Chem. Commun.* **1981**, 237-239.

[128] A. Pfaltz, M. G. Schrems, B. Pugin, Solvias A.-G., Switz., patent No. WO2010072746A1, **2010**, p. 48pp.

[129] O. Diels, K. Alder, *Justus Liebigs Annalen Der Chemie* **1928**, *460*, 98-122.

[130] L. M. Joshel, L. W. Butz, *J. Am. Chem. Soc.* **1941**, *63*, 3350-3351.

[131] J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325-335.

[132] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

[133] E. J. Corey, *Angew. Chem., Int. Ed.* **2009**, *48*, 2100-2117.

[134] a) J. Ramharter, J. Mulzer, *Eur. J. Org. Chem.* **2012**, *2012*, 2041-2053; b) M. E. Jung, T.-H. Zhang, R. M. Lui, O. Gutierrez, K. N. Houk, *The Journal of Organic Chemistry* **2010**, *75*, 6933-6940; c) H. M. Lima, R. Sivappa, C. J. Lovely, American Chemical Society, **2010**, pp. ORGN-599.

[135] R. H. Crabtree, M. W. Davis, *The Journal of Organic Chemistry* **1986**, *51*, 2655-2661.

[136] V. J. Davisson, C. D. Poulter, *J. Am. Chem. Soc.* **1993**, *115*, 1245-1260.

[137] A. Wheatherwax, in *Unpublished results*, University of Basel, **2010**.

[138] S. E. Denmark, R. A. Stavenger, A.-M. Faucher, J. P. Edwards, *The Journal of Organic Chemistry* **1997**, *62*, 3375-3389.

[139] J. L. Leazer, R. Cvetovich, F. R. Tsay, U. Dolling, T. Vickery, D. Bachert, *The Journal of Organic Chemistry* **2003**, *68*, 3695-3698.

[140] V. Köhler, PhD thesis, University of Basel **2005**.

[141] H. Fritschi, U. Leutenegger, A. Pfaltz, *Helv. Chim. Acta* **1988**, *71*, 1553-1565.

[142] R. J. Brotherton, A. L. McCloskey, *J. Am. Chem. Soc.* **1960**, *82*, 6242-6245.

[143] R. B. Coapes, F. E. S. Souza, M. A. Fox, A. S. Batsanov, A. E. Goeta, D. S. Yufit, M. A. Leech, J. A. K. Howard, A. J. Scott, W. Clegg, T. B. Marder, *Journal of the Chemical Society, Dalton Transactions* **2001**, 1201-1209.

[144] H. Aït-Haddou, O. Hoarau, D. Cramailére, F. Pezet, J.-C. Daran, G. G. A. Balavoine, *Chemistry – A European Journal* **2004**, *10*, 699-707.

[145] H. R. P. Edward M. Burgess, Jr., E. Alan Taylor, and W. Michael Williams, *Org. Synth.* **1988**, *6*, 788.

[146] D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 6388-6390.

[147] D. Liu, E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 1498-1499.

[148] C. S. Marvel, R. G. Woolford, *The Journal of Organic Chemistry* **1958**, *23*, 1658-1660.

[149] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, *J. Appl. Crystallogr.* **1993**, *26*, 343-350.

[150] L. Palatinus, G. Chapuis, *J. Appl. Crystallogr.* **2007**, *40*, 786-790.

[151] G. Sheldrick, *Acta Crystallographica Section A* **2008**, *64*, 112-122.

[152] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[153] J. R. Carruthers, D. J. Watkin, *Acta Crystallographica Section A* **1979**, *35*, 698-699.

[154] H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143-1148.

10. Attachments

Curriculum Vitae

First name: Jaroslav Surname: Padevět

Date of birth: 31st January, 1982

Nationality: Czech

Education:

2006 – 9/2012

University of Basel, Switzerland, PhD work thesis "Synthesis of new phosphino-oxazoline ligands for asymmetric catalysis" under supervision of Prof. Andreas Pfaltz

2001-2006

Institute of Chemical Technology Prague, Czech Republic. MSc degree in organic chemistry under supervision of Prof. Dalimil Dvorak (Enantioselective catalysis of Fischer chromium carbene complexes)

1997-2001

Technical College Specializing in Chemistry and Pharmacy in Prague, Czech Republic, (with first class honours)

Professional experience:

2006-current position

Laboratory teaching Assistant

Chemistry Department, University of Basel, Switzerland,

2007-current position

Assistant to PD Dr. Daniel Häussinger

Hardware and software maintenance of Bruker NMR spectrometers.

2005, 1 month

RE&D VÚFB Drug Research and Development Company, Czech Republic

Practical training experience as a member of research group

1998-2001

Institute of Chemical Technology Prague, Czech Republic

Member of research group under the supervision of Prof. Dalimil Dvorak

Professional Interests:

Synthetic Organic, Organometallic and Inorganic Chemistry, Structural Analysis, Stereochemistry, Pharmaceutical Chemistry, Pharmacology, Computational Chemistry

Professional skills:

- Practical experimental chemistry with air and moisture sensitive chemicals
- Resolving X-Ray crystal structures (Crystals)
- Computational chemistry (Gaussian, PC-GAMESS)
- Programming in HTML, CSS, PHP, SQL, BASH.
- UNIX system administration (FreeBSD, IRIX, GNU Linux): LAMP, DHCP, backup, networking in LAN (TCP/IP).

Conferences:

August 28th- September 1st, 2010, CUSO Summerschool 2011, Villars sur Ollon, Switzerland, (Poster)

June 10-11, 2010, Workshop of the International Research Training Group (CCROS), Basel, Switzerland, (Organization committee)

November 25-27, 2005, 40th Conference on Organic and Pharmaceutical Chemistry, Nymburk, Czech Republic, (Poster)

July 17-21, 2005, 13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 13th), Geneva, Switzerland, (Poster)

Memberships and awards:

- 3rd award in the 2005 poster section, Conference on Organic and Pharmaceutical Chemistry, (Nymburk, Czech Republic)
- 1st prize in the 2005 Student research activities competition (SVK in Czech Republic)
- 3rd prize in the 2004 Student research activities competition (SVK in Czech Republic)
- Member of the Czech Chemical Society since 1998