Remo Stohler

Asymmetric Metal-Catalyzed [3+2] Cycloadditions of Azomethine Ylides

Cuvillier Verlag Göttingen

Asymmetric Metal-Catalyzed [3+2] Cycloadditions of Azomethine Ylides

Inauguraldissertation

zur
Erlangung der Würde eines Doktors der Philosophie

vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
der Universität Basel

von

Remo Stohler
aus
Basel und Ziefen/ Basel und Baselland

Basel 2006

Bibliografische Information Der Deutschen Bibliothek
Die Deutsche Bibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über http://dnb.ddb.de abrufbar.
1. Aufl. - Göttingen : Cuvillier, 2007
Zugl.: Basel, Univ., Diss., 2006

978-3-86727-171-4

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von:

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Basel, den 19.12.2006

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Nonnenstieg 8, 37075 Göttingen
Telefon: 0551-54724-0
Telefax: 0551-54724-21
www.cuvillier.de

1. Auflage, 2007
Gedruckt auf säurefreiem Papier

978-3-86727-171-4

dedicated to my parents

Acknowledgments

I would like to express my gratitude to my supervisor, Professor Dr. Andreas Pfaltz for giving me the opportunity of joining his group, for his constant support and his confidence as well as for the liberty I was given to work at my project.

Special thanks to Professor Dr. Wolf-Dietrich Woggon for co-examing this thesis and the organization of a laboratory course I enjoyed at Kingston University.

Furthermore I would like to thank Professor Dr. Marcel Mayor for chairing the examen.

A big thanks goes to Florentine Wahl whose excellent work opened the door to intramolecular [3+2] cycloadditions. Dominik Frank is acknowledged for his synthetic work during his Wahlpraktikum.

I am grateful to Markus Neuburger and Dr. Silvia Schaffner as well as to Eva Neumann and Stefan Kaiser for recording X-ray data and for refining X-ray structures. Dr. Klaus Kulicke, Axel Franzke and Aurélie Toussaint are acknowledged for their countless hours recording 2D NMR spectra and their help on the interpretation of the data. Dr. Heinz Nadig recorded the EI and FAB mass spectra and Antje Teichert is acknowledged for measuring the ESI mass spectra. Werner Kirsch determined all the elemental analyses. I would also like to thank all the members of the staff who run the department and make the work efficient and enjoyable.

Special thanks to Aurélie Toussaint, Antje Teichert, Dr. Matthias Maywald, Dr. Stephen Roseblade, Dr. Geoffroy Guillemot and David Woodmansee for proof-reading the manuscript.

A big thanks goes to the past and present members of the Pfaltz group for the good working atmosphere and the helpful discussions. I especially like to thank my colleagues from lab 208 for an enjoyable time.

Contents

Abbreviations

3-NBA	3-nitro-benzyl alcohol (matric for FAB-MS)
Å	Ångström (10^{-10} m)
Ar	aryl
$B(ArF)_4$	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-bis-(diphenylphosphino)-1,1'-bi-naphthalene
BOX	bisoxazoline
br	broad (NMR)
c	concentration
cat.	catalyst
COD	1,5-cyclooctadien
Conv.	conversion
COSY	correlation spectroscopy (NMR)
Cy	cyclohexyl
δ	chemical shift
DCM	dichloromethane
de	diastereomeric excess
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron impact ionization (MS)
eq	equivalent
ESI	electronspray ionization
EtOAc	ethyl acetate
FAB	fast atom bombardment
FTIR	fourier transform infrared
GC	gas chromatography
HMBC	heteronuclear multiple-bond correlation (NMR)
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
Hx	hexane
Hz	Hertz
J	coupling constant
M	molar (mol/L)
m.p.	melting point
MS	mass spectroscopy
2-Naph	2-naphthalin
n.d.	not determined
NMR	nuclear magnetic resonance
NOESY	nuclear overhause effect spectroscopy
Pe	pentane
Ph	phenyl
PHOX	phoshinooxazoline
ppm	parts per million
Py	pyridine
rac.	racemic
R_f	retention factor
rt	room temperature
tert	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
TOCSY	total correlated spectroscopy
Tol	toluene
t_r	retention time
w	weak
$\tilde{\upsilon}$	wave number (IR)
	used to illustrate relative stereochemistry
	used to illustrate absolute stereochemistry

Chapter 1

Introduction

1 Introduction

1.1 Racemic Versus Enantiopure Drugs

For a long time the decision whether a drug should be developed as a racemate or as an enantiopure compound was left to the institution producing the drug. The situation changed when it was realized that there is often a significant difference between the enantiomers of chiral drugs regarding their pharmacodynamic and pharmacokinetic properties. In addition recent advances in stereoselective synthesis and analysis of chiral molecules helped to make the decision in favour of enantioselective synthesis of chemical entities. At present no regulatory institution has an absolute requirement for the development of enantiopure drugs but if a racemate is presented for marketing then its use must be justified. Arguments like the individual isomers are stereochemically unstable and readily racemize *in vitro* and/or *in vivo* or the use of a racemate produces a superior therapeutic effect than either individual enantiomer could for instance support the submission of a racemates. However, the trend towards the development of enantiopure drugs is clearly visible and therefore further development of stereoselective synthesis is highly desirable. This will be demonstrated by the following examples.

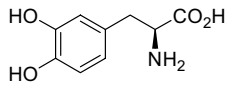
1.2 Different Pharmacokinetic Properties of Enantiomers

Since drug absorbtion, distribution, metabolism and excretion involve an interaction between the enantiomers of a drug and a chiral biological macromolecule it is hardly surprising that enantioselectivity is observed during these processes.

Absorbtion

The most important mechanism of drug absorbtion is passive diffusion through biological membranes. During this process there is generally little enantiomeric differentiation because it is dominated by the lipid and aqueous solubilities which are the same for both enantiomers.
One way of drug absorbtion which discriminates between enantiomers is the active transport process. L-dopa for instance (Figure 1), which is used in the treatment of Parkinson's disease, is rapidly absorbed from the gut by an active transport process, whereas D-dopa is slowly but

also completely absorbed by passive diffusion.[1] Large rate differences between passive and active transportation may result in a considerable difference of bioavailability.[2]

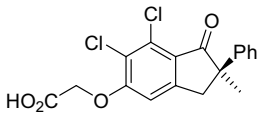


L-dopa

Figure 1.

Distribution

The majority of drugs undergo reversible binding to plasma proteins. Stereoselectivity can be observed in plasma protein binding to human serum albumin (HSA) and α_1-acid glycoprotein (AGP), the two most important plasma proteins with respect to drug binding. In general acidic drugs bind predominantly to HSA, whereas basic drugs bind predominantly to AGP, which is only present to the extent of 3% of HSA. The differences between the enantiomers in plasma protein binding are usually quite small. But also the low stereoselectivity in binding may have a significant effect on the amount of unbound drug in the plasma which is available for activity. In the case of indacrinone (Figure 2), which is used in the treatment of hypertension and congestive heart failure, the free fractions are 0.9% and 0.3% for the (*R*)- and (*S*)-enantiomer respectively.[3]



(*R*)-indacrinone

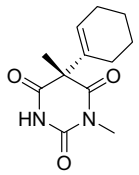
Figure 2.

Metabolism

Drug metabolism frequently shows stereoselectivity and involves the interaction with enzyme systems. Some enzymes are highly specialized whereas others like cytochrome P450 are multifunctional and accept a wide range of substrates. They usually show great substituent and stereochemical sensitivity including those systems that accept a wide range of substrates.

Examination of the stereochemistry of drug metabolism is of importance because individual enantiomers of a racemic drug may be metabolised by different routes to yield different products and they are frequently metabolised at different rates.

The (*S*)-enantiomer of barbiturate hexobarbital (Figure 3) has an elimination half-life which is three times longer than that of the (*R*)-enantiomer as a result of metabolic clearance.[4]



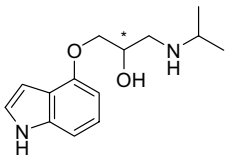
(*S*)-hexobarbital

Figure 3.

Excretion

Glomerular filtration, active secretion and passive and active reabsorbtion are the four major processes of renal excretion. In contrast to the active excretion processes no differences between the enantiomers are expected for the passive processes like glomerular filtration and passive reabsorbtion.

Since renal clearance of L-pindolol is faster than that of D-pindolol active renal secretion or renal metabolism is thought to be responsible for the differential clearance of the two enantiomers (Figure 4).[5]



Pindolol

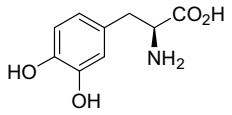
Figure 4.

1.3 Different Pharmacodynamic Properties of Enantiomers

The most important differentiation between enantiomers occurs at the level of receptor interactions. This leads to different pharmacodynamic properties of the enantiomers. Some of the possible situations are discussed below.

Only one enantiomer shows pharmacological activity

α-Methyldopa (Figure 5) is used against hypertension. The activity arises exclusively from the (*S*)-enantiomer[6] and it is therefore marketed as a single enantiomer.

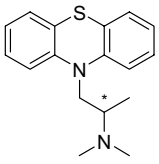


(*S*)-α-methyldopa

Figure 5.

Both enantiomers have similar activities

The enantiomers of the antihistamine promethazine (Figure 6) have similar pharmacological properties.[7]



promethazine

Figure 6.

The enantiomers have opposite effects

Dextropropoxyphene, exhibiting the (1*S*,2*R)*-configuration, is a useful painkiller whereas its enantiomer levopropoxyphene is an antitussive agent (Figure 7). Appropriately not only the molecules are mirror images but also their trade names DARVON®(dextropropoxyphene) and NOVRAD®(levopropoxyphene).[8]

dextropropoxyphene levopropoxyphene

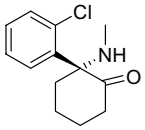
Figure 7.

One enantiomer antagonises the side effects of the other

Indacrinone (Figure 2) is an interesting example to show how the different modes of action of enantiomers can be used to create a more favourable profile of action of a drug by changing the ratio of the enantiomers. The (*R*)-enantiomer is a more potent natriuretic agent whereas the (*S*)-enantiomer is a more potent uricosuric agent. Following administration of the racemate to man the plasma half-life of the (*S*)-enantiomer is much shorter than that of the (*R*)-enantiomer (2-5 h, compared to the (*R*), 10-12 h). Hence its uricosuric activity is too short to prevent the undesirable rise in uric acid concentration. Alteration of the enantiomeric composition of the drug from the 1:1 ratio by increasing the proportion of the (*S*)-enantiomer resulted in a mixture (*S* : *R* : 4 : 1) which was isouricemic.[9] In other words one enantiomer is used to prevent the side effects caused by the other enantiomer.

Both enantiomers show activity but the adverse effects are predominantly associated with one enantiomer

Ketamine (Figure 8) is a general anaesthetic agent with painkilling properties. The drug exhibits stereoselective actions in both main-effect and the most important side-effects. The most unwanted side effects originate from the less potent enantiomer for the main-effects, the (*R*)-enantiomer.[10]



(*R*)-ketamine

Figure 8.

Chapter 2

Biological Activity of Pyrrolidines and Resulting Objectives

2 Biological Activity of Pyrrolidines and Resulting Objectives

2.1 Biological Active Pyrrolidines

Worldwide about 170 million individuals are afflicted with chronic hepatitis C[11], a viral disease that is caused by a hepatotropic virus called Hepatitis C virus (HCV). The infection can cause liver inflammation and might progress to cirrhosis or also liver cancer. The latter two are the major causes of morbidity and mortality.

The treatment of the disease with a combination of PEG-interferon-α and ribavirin is not always successful and shows severe side effects.[12] Therefore the identification of more effective treatments is essential.

Only recently it was reported that acyl pyrrolidines inhibit the Hepatits C NS5B polymerase whereas only one enantiomer showed a significant biological activity (Figure 9).[13]

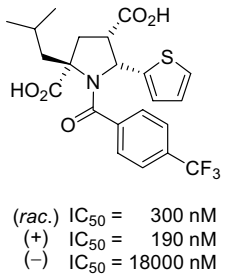
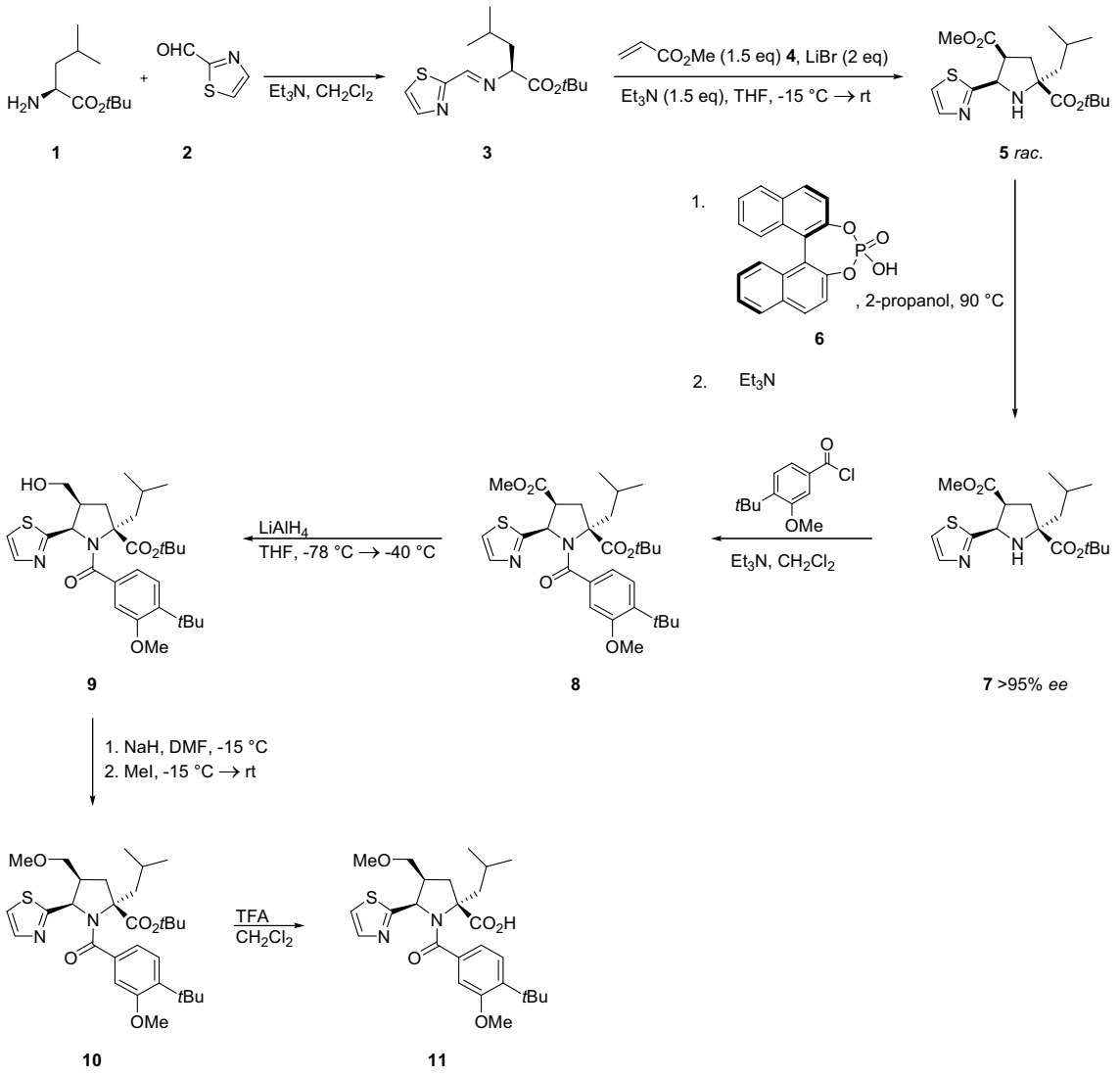


Figure 9.

Optimization of the substitution –pattern further increased the compounds' potency.[14] The synthesis of such an optimized pyrrolidine moiety **11** is illustrated in Scheme 1.[15] Subsequent to the formation of the imine **3** 2 equivalents of lithium bromide were used to promote the 1,3-dipolar cycloaddition reaction between the imine **3** and methyl acrylate **4** under basic conditions in THF. The racemic *endo* pyrrolidine species **5** was resolved into its enantiomers by diastereomeric salt formation using the chiral acid, *R*-BINAP phosphate **6.** The resulting salt was treated with triethylamine to obtain the chiral pyrrolidine **7** with a yield of 82% and an enantioselectivity of >95%. Further transformations led to the desired pyrrolidine moiety **11** with an overall yield of >25% in a 7 step sequence.



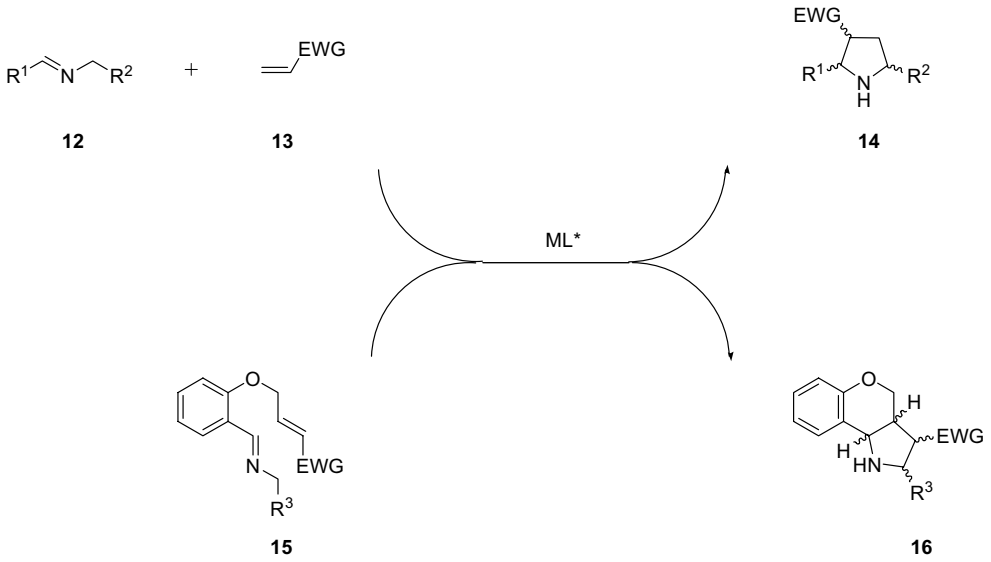
Scheme 1.

The [3+2] cycloaddition of the Scheme above might alternatively be performed by an asymmetric metal-catalyzed 1,3-dipolar cycloaddition reaction. This could then lead directly to the enantioenriched compound without the time consuming resolution step by diastereomeric salt formation.

Chiral pyrrolidines are present in many other biologically active compounds.[16] Therefore, the development of enantioselective catalysts for [3+2] cycloaddition leading to this ring system is highly desirable.

2.2 Objectives

The aim of the thesis was to develop chiral catalysts for enantioselective inter- and intramolecular [3+2] cycloaddition reactions between azomethine ylides precursors **12**, **15** and electron-deficient dipolarophiles **13** (Scheme 2).



Scheme 2.

In initial metal- and ligand screenings Ag(I)-phosphinooxazoline (PHOX) complexes turned out to be the most promising chiral catalysts. Subsequently, the structure of the PHOX ligand **17** (Figure 10) was optimized by systematic variation of the various substituents. The most successful ligand structures were later used to examine the scope of the reaction.

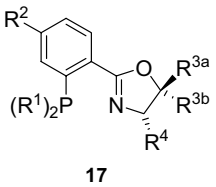
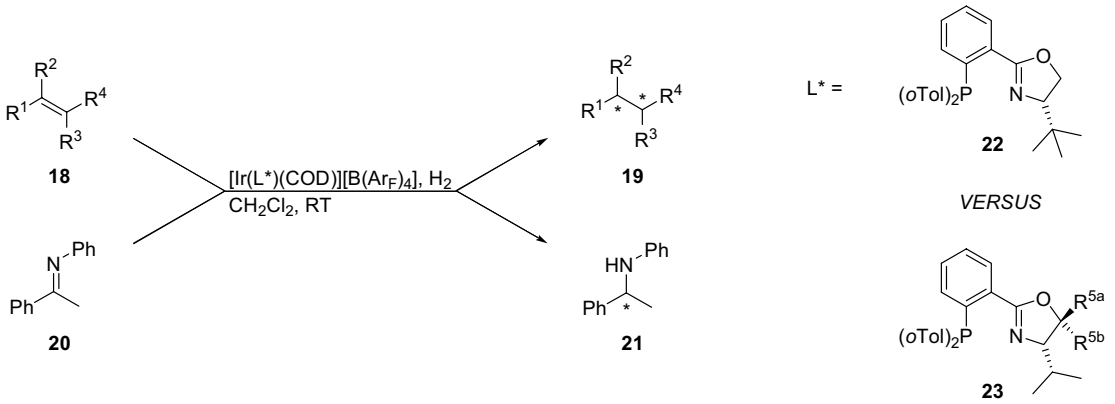


Figure 10.

In connection with the optimization studies we also became interested in applying (*S*)-valine methyl ester derived C5-substituted PHOX ligands **23** to Ir(I)-catalyzed asymmetric hydrogenations of unfunctionalized and functionalized olefins **18** and imines **20.** The aim was to compare them with the successful but expensive (*S*)-*tert*-leucine-derived PHOX ligand **23** (Scheme 3).



Scheme 3.

Chapter 3

[3+2] Cycloadditions

3 [3+2] Cycloadditions

3.1 General Aspects

The [3+2] cycloaddition of a 1,3-dipole to a dipolarophile involves 4π-electrons from the dipole and 2π-electrons from the dipolarophile. The 4π-electron component is of such nature that the stabilized all octet structure can only be represented by zwitterionic forms in which the positive charge is located on the central heteroatomic atom and the negative charge is distributed over the two terminal atoms (Figure 11). There exist two principal types of dipoles. The bent allyl type 1,3-dipoles have their four π-electrons in three parallel atomic p_z-orbitals perpendicular to the plane of the dipole. Dipoles of the propargyl-allenyl type, which have a triple bond in one canonical form, contain an additional π-orbital orthogonal to the allyl-anion type molecular orbital and have a linear structure.

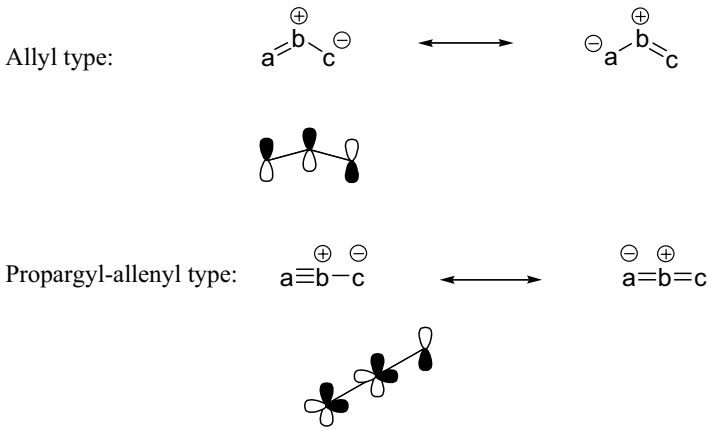
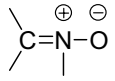
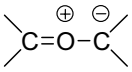
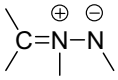
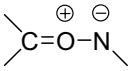
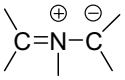
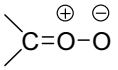
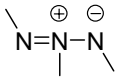
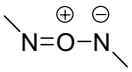
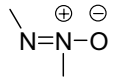
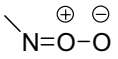
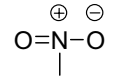
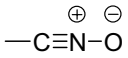
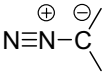
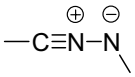
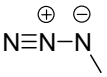
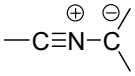


Figure 11.

A considerable number of 1,3-dipoles containing various combinations of carbon and hetero-atoms is theoretically possible. Restricting the permutations to second row elements Huisgen has classified eighteen possibilities of which six are from the propargyl-allenyl type and twelve are from the allyl type (Table 1).[17]

Table 1.

Allyl type[1]			
Nitrogen in the middle		**Oxygen in the middle**	
	Nitrones		Cabonyl Ylides
	Azomethine Imines		Carbonyl Imines
	Azomethine Ylides		Carbonyl Oxides
	Azimines		Nitrosimines
	Azoxy Compounds		Nitrosoxides
	Nitro Compounds		Ozone
Propargyl-allenyl type			
Nitrillium Betaines		**Diazonium Betaines**	
	Nitrile Oxide		Diazoalkanes
	Nitrile Imines		Azides
	Nitrile Ylides		Nitrous Oxide

[1] For facility reasons the bent allyl type 1,3-dipoles are illustrated in a linear from.

The reaction between a 1,3-dipole and a dipolarophile leads to a five-membered heterocycle and proceeds usually via a concerted mechanism. It is thermally allowed with the description [$\pi 4_s$ + $\pi 2_s$] according to the Woodward-Hoffmann rules.[18] This means that the three p_z-orbitals of the 1,3-dipole and the two p_z-orbitals of the alkene both combine suprafacially (Figure 12).

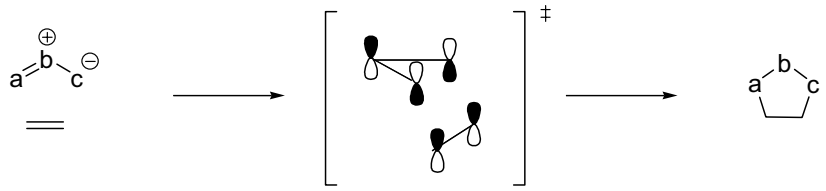


Figure 12.

Depending on the structure of the dipole and the dipolarophile, up to four stereogenic centers can be formed by a 1,3-dipolar cycloaddition reaction in a single step. Three types of selectivities must be considered (Figure 13) - regioselectivity, diastereoselectivity and enantioselectivity which will be discussed on the following pages.

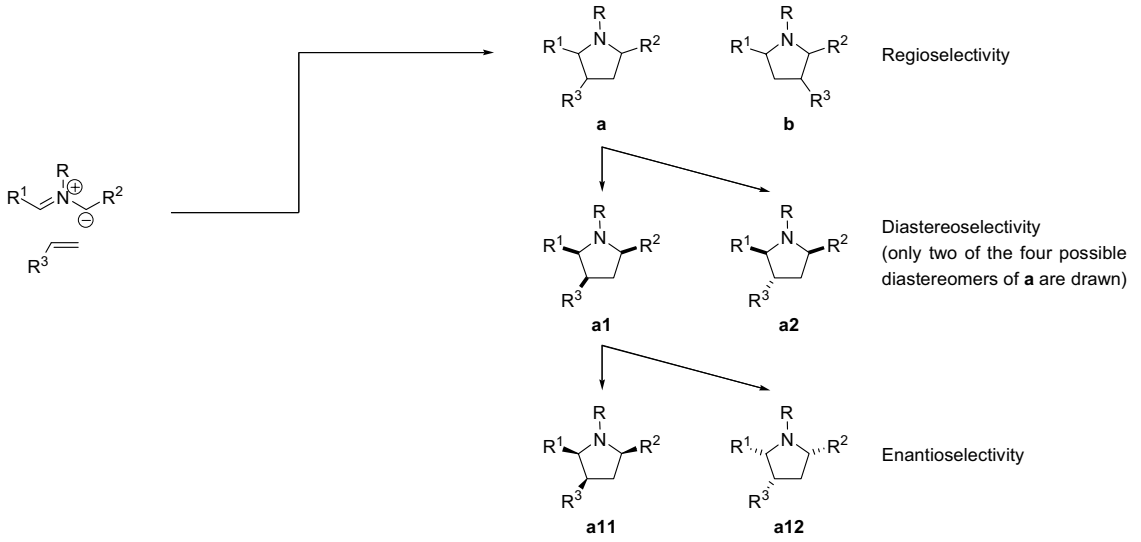


Figure 13.

3.2 Reactivity and Regioselectivity of [3+2] Cycloadditions

Relative activity and regioselectivity of 1,3-dipolar cycloadditon reactions can be explained by means of the FMO-theory. It states that only interactions of filled orbitals with unfilled ones lead to an important energy-lowering effect of the transition-state when two molecules approach each other, particularly the interaction of the HOMO with the LUMO being decisive.

Salem[19] derived a second-order perturbation expression for the energy gained and lost when the orbitals of one reactant overlap with those of another one in a cycloaddition reaction.

$$\Delta E = \underbrace{-\sum_{ab}(q_a + q_b)\beta_{ab}S_{ab}}_{\text{first term}} + \underbrace{\sum_{k<l}(Q_k Q_l)/(\varepsilon R_{kl})}_{\text{second term}} + \underbrace{\sum_{r}^{occ.}\sum_{s}^{unocc.} - \sum_{s}^{occ.}\sum_{r}^{unocc.} 2(\textstyle\sum_{ab} c_{ra} c_{sb} \beta_{ab})^2/(E_r - E_s)}_{\text{third term}}$$

q_a, q_b : Electron populations in the atomic orbitals a and b.

β : Resonance integral.

S : Overlap integral.

Q_k, Q_l : Total charges on atom k and l.

ε : Local dielectric constant.

R_{kl}: Distance between the atoms k and l.

c_{ra}: Coefficient of atomic orbital a in molecular orbital r; r refers to the molecular orbitals on one molecule and s refers to those on the other one.

E_r: Energy of molecular orbital r.

The first term is the closed-shell repulsion term and represents the interaction of the filled orbitals of one molecule with the filled orbitals of the other one. Overall it has an antibonding effect and presents a good deal of the enthalpy of activation for many reactions.

The second term is the Coulombic repulsion or attraction. This term is obviously important when ions or polar molecules are reacting together.

The third term represents the interaction of all filled orbitals with all the unfilled orbitals of correct symmetry. The denominator of this expression indicates that, the closer in energy the orbitals, the more they will interact, while the numerator indicates that, if the orbitals are of the same symmetry and overlap effectively, the interaction will be large. The largest contribution to this term is obtained from the HOMO/LUMO interaction.

Most perturbation treatments of cycloaddition reactivity have focused on the last term of the second-order perturbation expression and have considered only interactions between frontier orbitals on the 1,3-dipole and the dipolarophile. This frontier orbital approximation is remarkably successful in rationalizing reactivity and regioselectivity phenomena, in spite of the fact that interactions of extrafrontier orbitals, closed-shell repulsion, and coulombic terms also contribute to energy changes.

The application of the perturbation theory to the 1,3-dipolar cycloaddition reaction is only possible if the 1,3-dipoles and dipolarophiles frontier orbital energies and coefficients are approximately known. Calculations on specific addends of all types by a variety of methods have been reported,[20] but simple generalizations often suffice for predictive purposes. In the following the qualitative substituent effect on alkene coefficients and energies will be described (Figure 14).

Electron-withdrawing substituents lower the HOMO energy slightly but have a much larger effect on the LUMO energy. The coefficient on the unsubstituted atom is larger than on the substituted atom in both HOMO and LUMO, with the difference in coefficient magnitudes much larger in the LUMO.

Electron-donating groups increase the LUMO energy slightly but have a much larger effect on the HOMO energy. The unsubstituted HOMO coefficient is larger than the substituted HOMO coefficient. The LUMO coefficients are opposite in magnitude, but the difference in coefficient magnitudes is smaller.

Conjugating substituents raise the HOMO energy and lower the LUMO energy, and the coefficients are larger at the unsubstituted centers in both molecular orbitals.

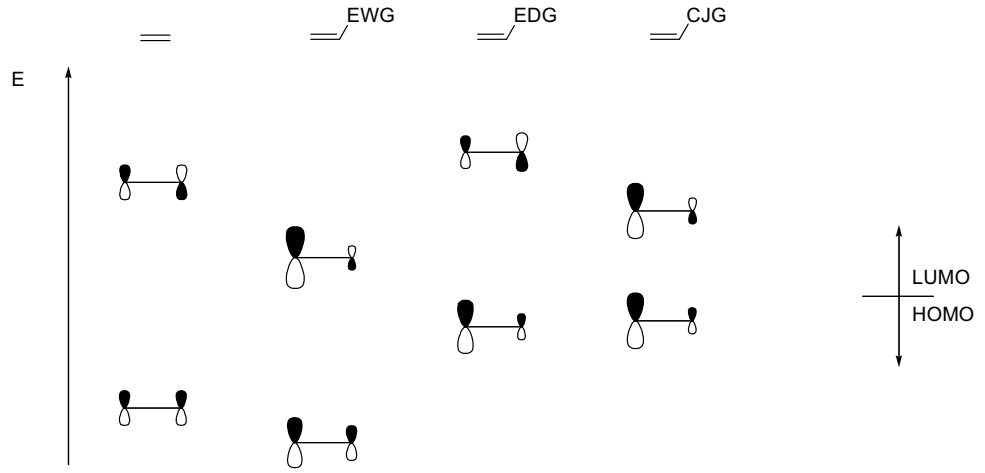


Figure 14.

Due to the limited experimental data which are available to determine the effect of dipole substituents on frontier orbital energies and coefficients, only very qualitative assumptions can be done. All 1,3-dipoles have in common a three atomic orbital π system containing four electrons analoguous to an allyl anion (Figure 15). It can be assumed that the effect of various types of substituents on dipole frontier orbital energies and coefficients will be qualitatively similar to the effect of these substituents on dipolarophile frontier orbital energies and

coefficients. Figure 15 shows the average orbital coefficients of the most common 1,3-dipoles. The effect of a substituent on dipole energies and coefficients is expected to be a function of the magnitude of the coefficient at the site of attachment on the parent dipole (Figure 15).[21] Therefore the substituent effect for the HOMO of the dipole should be in the order anionic terminus > neutral terminus >> central atom. The corresponding order for the LUMO is neutral terminus ~ central atom > anionic terminus.[20b]

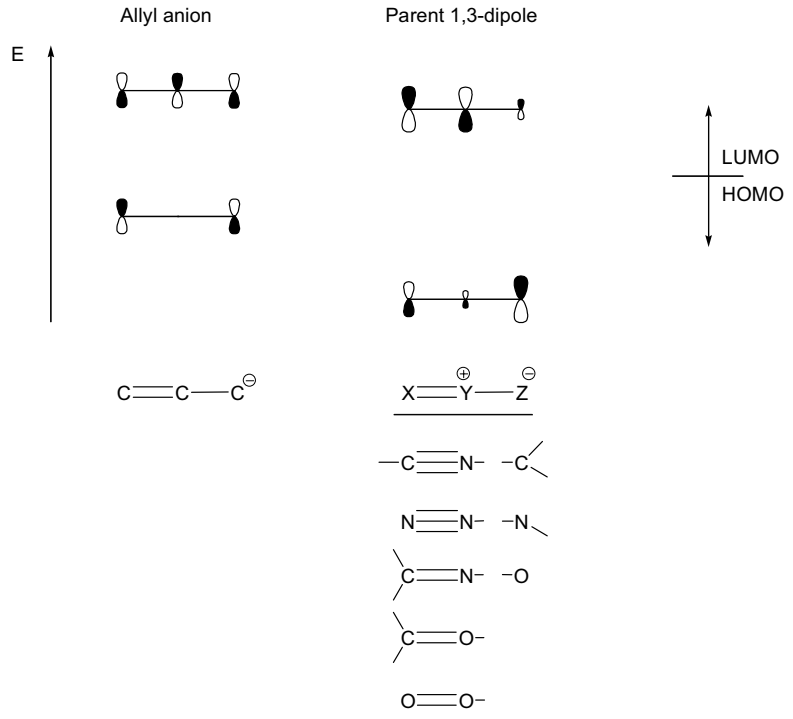


Figure 15.

From these generalizations the regioselectivity of most 1,3-dipolar cycloadditions can be rationalized from Figure 16 assuming that the larger orbital coefficient of one molecule is interacting with the larger orbital coefficient of the other molecule. Control of regioselectivity by the dipole HOMO will lead to five-membered heterocycles with the substituent close to the neutral terminus X for monosubstituted, conjugated, and electron-deficient dipolarophiles and to products with the substituent near the anionic terminus Z for electron rich dipolarophiles. Control of regioselectivity by the dipole LUMO will lead to products with the substituent near the anionic atom Z for all monosubstituted dipolarophiles.

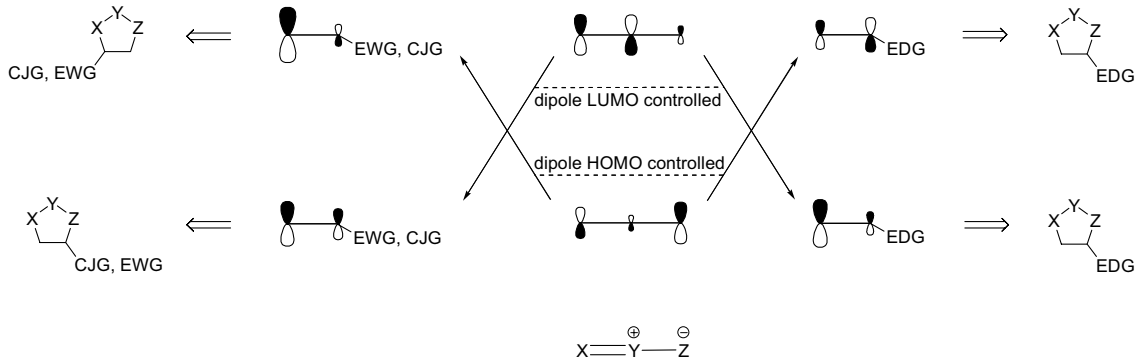


Figure 16.

It will be necessary to identify if a $HOMO_{dipole}$ – $LUMO_{dipolarophile}$ or a $LUMO_{dipole}$ – $HOMO_{dipolarophile}$ interaction is taking place in order to rationalize or predict product regiochemistry. Sustmann has classified the 1,3-dipolar cycloaddition reaction into three types[22], on the basis of the relative FMO energies between the dipole and the dipolarophile indicating which FMO interaction will be favoured (Figure 17). In type I 1,3-dipolar cycloaddition reactions the dominant FMO interaction is that of the dipole HOMO with the dipolarophile LUMO (HOMO-controlled), in type II both FMO interactions are possible (HOMO,LUMO-controlled) and in type III the dipole LUMO interacts with the dipolarophile HOMO (LUMO-controlled). HOMO-controlled reactions will be accelerated by substituents which raise the dipole HOMO energy or lower the dipolarophile LUMO energy but on the other hand these substituents decelerate LUMO-controlled reactions. Conversely, substituents which lower the dipole LUMO energy or raise the dipolarophile HOMO energy will accelerate LUMO-controlled reactions and decelerate HOMO-controlled reactions. HOMO, LUMO-controlled reactions will be accelerated by an increase of either frontier orbital interactions.

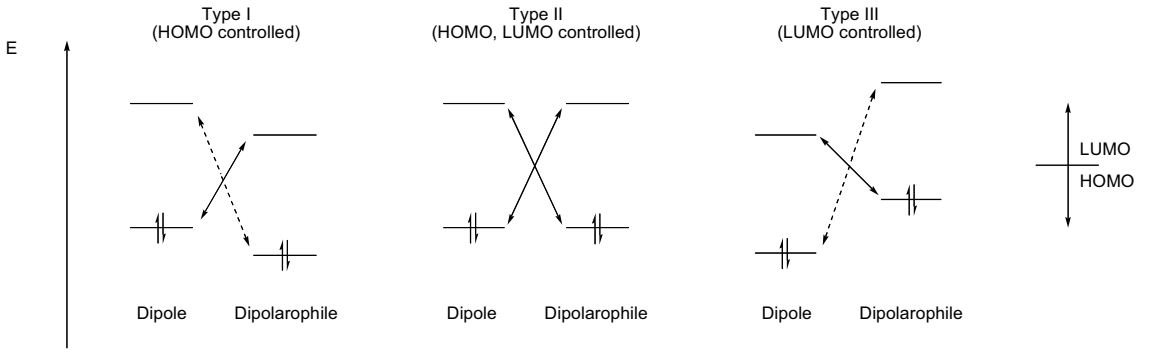
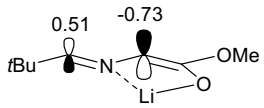


Figure 17.

Considering azomethine ylides, which are the 1,3-dipoles of main interest in this work, it has to be emphasized that the unsubstituted 1,3-dipole has C_{2v} symmetry, thus regioselectivity is not an issue in this case. Unsymmetrically substituted azomethine ylides can form regioisomers with unsymmetrical dipolarophiles, but the regiochemistry will be induced by asymmetry in the dipole frontier orbitals caused by the substituents. Presumably the azomethine ylides will react readily with both electron-deficient and electron-rich dipolarophiles due to the narrow frontier orbital separation.

The presence of metals, such as a lewis acid, can alter both the orbital coefficients of the reacting atoms and the energy of the frontier orbitals of the 1,3-dipole or the alkene. Thus lewis acids may have an influence not only on the reactivity but also on the selectivity of the 1,3-dipolar cycloaddition reaction, since regio-, diastereo-, and enantioselectivity can be controlled by the presence of a metal-ligand complex.

Kanemasa *et al*.[29c] calculated the energy level of the HOMO and the corresponding orbital coefficients of the lithium enolate illustrated in Figure 18. The high-lying HOMO[23] of this 1,3-dipole implies that the 1,3-dipolar cycladdition reaction between a metal-stabilized azomethine ylide and an electron-deficient dipolarophile proceeds by a HOMO-controlled interaction which is confirmed by experimental data.



HOMO: -7.47 kcal/ mol

Figure 18.

The perturbation treatment satisfactorily predicts both the regioselectivity of 1,3-dipolar cycloadditions and the relative reactivities of each individual dipole with a series of dipolarophiles, but it usually fails in the comparison of relative reactivities of widely different 1,3-dipoles. The reasons for these difficulties can be partially found in the crudeness of the frontier orbital energy estimates, as well as the neglect of electrostatic interactions, closed-shell repulsions, and steric effects.[24,27] An additional factor which must be taken into account is the stability of products and reactants.

3.3 Mechanism of [3+2] Cycloadditions

3.3.1 Concerted versus Stepwise Mechanism

The vivid debate of Huisgen[25] and Firestone[26] in the 1970's about the mechanism of the 1,3-dipolar cycloaddition reaction (Figure 19) will be shortly summarized.

Huisgen was proposing a concerted mechanism, which implies stereospecificity with respect to the olefin and the allyl anion configuration. On the other hand Firestone was arguing for a stepwise diradical mechanism, whereas this two step pathway is equally compatible with a stereospecific or nonstereospecific reaction course. The former mechanism emerged as the only mechanism that satisfactorily explains all the experimental observation in particular the stereospecificity that characterizes these reactions. It is now generally accepted that in general the reaction follows a concerted pathway.[27]

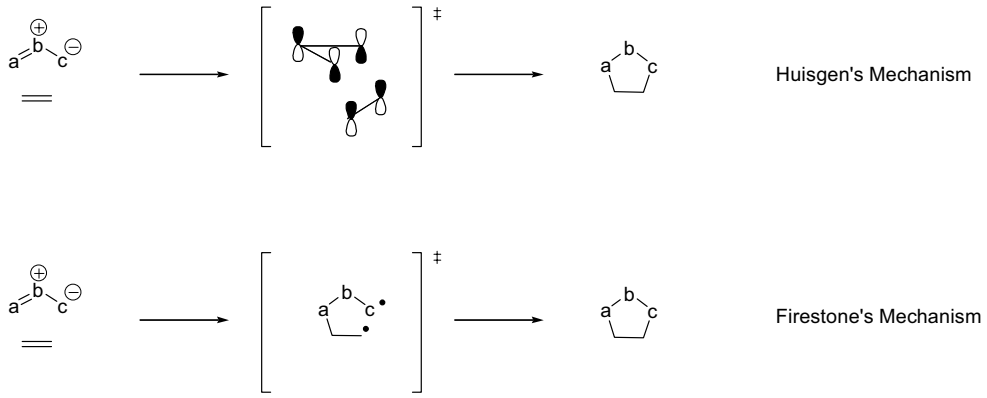
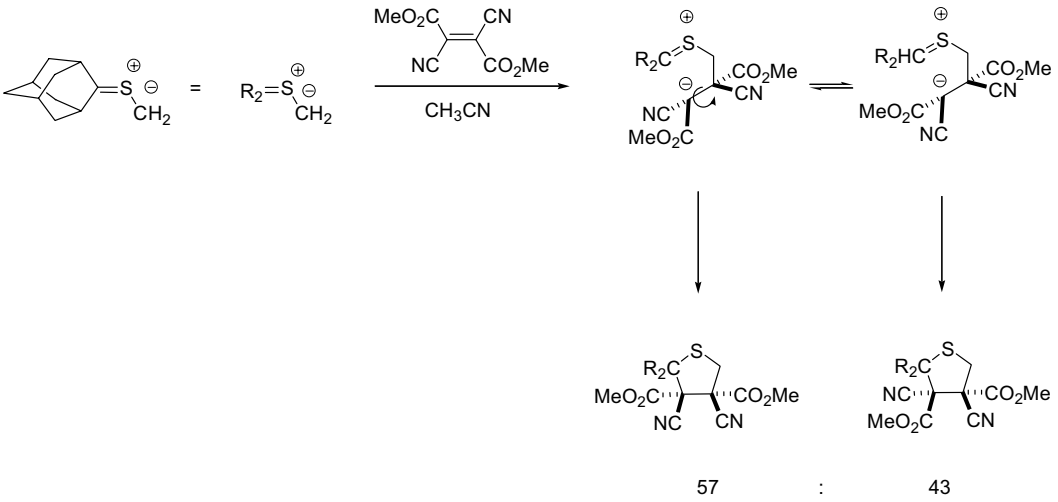


Figure 19.

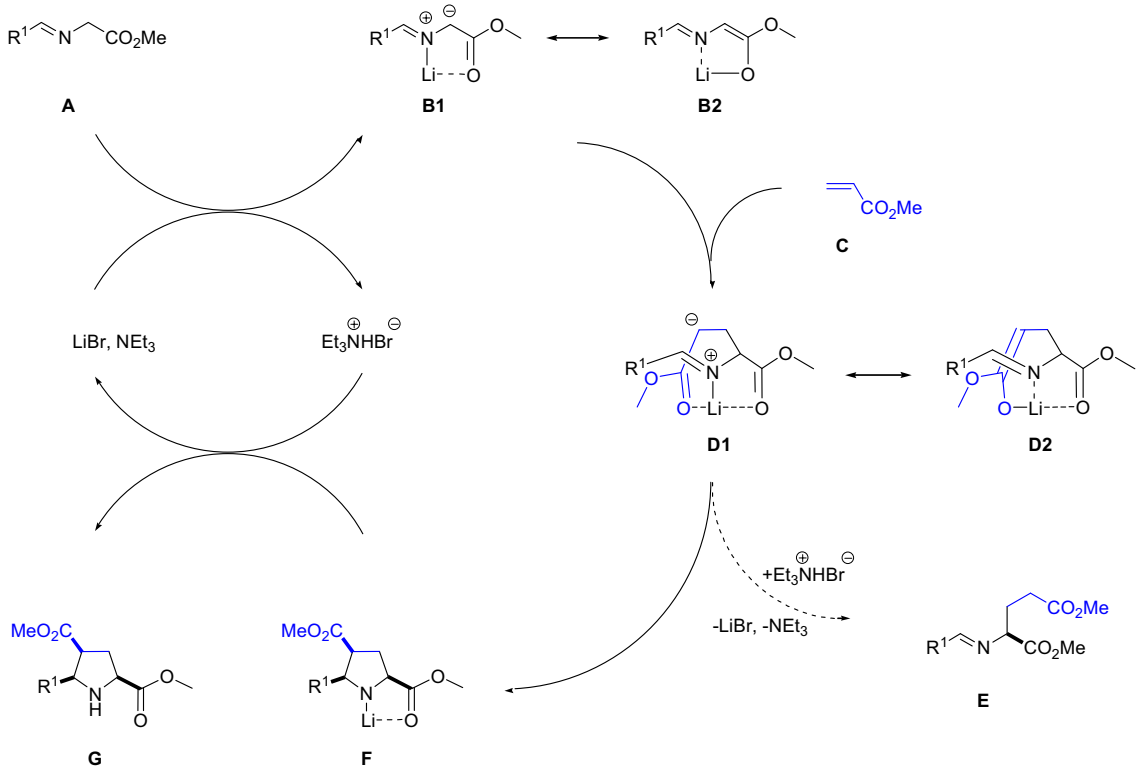
Huisgen *et al*.[28] found later 1,3-dipolar cycloadditions which did not follow a stereospecific course. This was explained by bond-rotations of a postulated zwitterionic intermediate in the course of a two-step non-concerted [3+2] cycloaddition, but not by a diradical mechanism (Scheme 4).



Scheme 4.

3.3.2 Mechanistic Aspects of [3+2] Cycloadditions of Metal-Stabilized Azomethine Ylides

Kanemasa[29] as well as Cossío[30] proposed on the basis of compuntional and experimental studies independently a mechanism for [3+2] cycloadditions between metal stabilized azomethine ylides and electron-deficient dipolarophiles (Scheme 5).



Scheme 5.

According to the mechanistic cycle (Scheme 5) the stabilized lithium azomethines ylide **B** is built in the first step which exist exclusively in the conformation where the lithium is not only coordinated to the nitrogen but also to the carbonyl oxygen of the ester. Electron density and NBO (natural bond orbital) calculations state that the structure is closer to that of an enolate **B2** than to that of an azomethine ylide **B1**. However, bond formation at the β-carbon of the methyl acrylate **C** proceeds at the α-carbon of intermediate **B**. Protonation of intermediate **D** would lead to Michael adduct **E** whose formation competes with the intramolecular cyclization producing the lithiated cycloadduct **F** which upon protonation leads to the desired pyrrolidine moiety **G** and regeneration of the catalyst.

Figure 20 shows the qualitative reaction pathway calculated by Kanemasa *et al.*[13c] by the MNDO- and PM3-methods for the Michael additions between the lithium *Z*-enolates of *N*-alkylidene-glycinates and methyl crotonate (α to χ) and the subsequent cyclization leading to the 1,3-dipolar cycloaddition products (χ to ε).

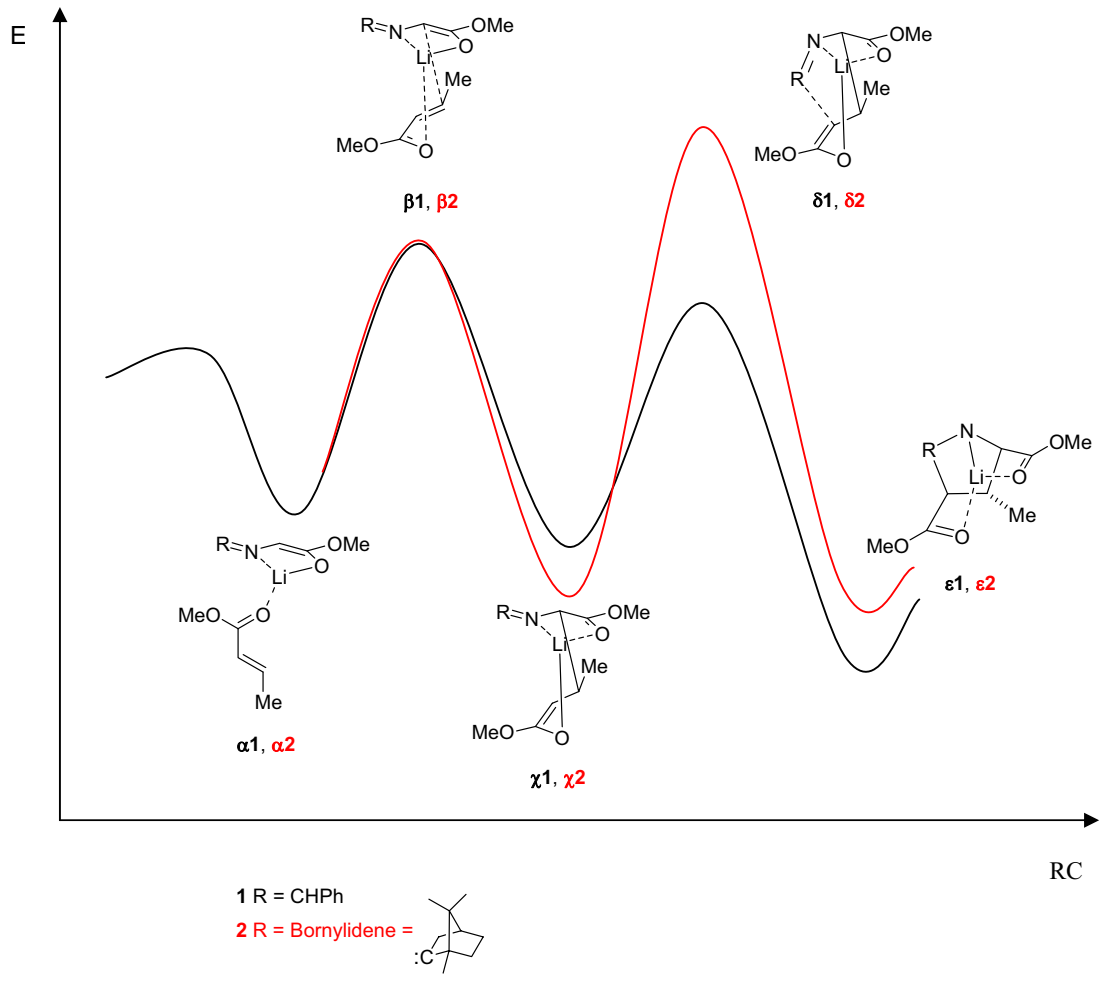


Figure 20.

The reaction pathway which results by employing substrate **1** indicates that the cyclized product **ε1** is thermodynamically more stable than the Michael-adduct **χ1** and the energy barrier for the cyclization step is lower than that for the Michael-addition step. For that reason the reaction of **1** with methyl crotonate leads to the preferred formation of the 1,3-dipolar cycloadduct **ε1** what was also found experimentally.

By contrast, sterically demanding substituents like boronylidene lead to an alternative pathway indicating that the energy barrier for the cycloaddition step is larger than the one for the formation of the Michael-adduct **χ2**. In addition, the cycloadduct **ε2** has nearly the same stability like the Michael-adduct **χ2**. Therefore the Michael-adduct **χ2** is formed preferentially what is likewise found experimentally.

On the basis of these computional data, it can be revealed that the reaction of sterically less hindered substrates like **1** with methyl crotonate lead only to the 1,3-dipolar cycloadduct **ε1**, whereas sterically hindered substrates like **2** preferentially lead to the Michael adduct **χ2**.

To get a complete picture of the thermodynamic stability not only the enthalpic contribution but also the entropic contributions have to be considered. PM3 calculations showed that the entropy change favours the cycloadducts but the contributions to thermodynamic stability were that small (max. 1 kcal/mol) that the above conclusions do not have to be changed.

3.4 Diastereoselectivity of [3+2] Cycloadditions

In the reaction between a disubstituted 1,3-dipole and a disubstituted dipolarophile up to four new chiral centers can theoretically be formed and up to eight different diastereomers may be obtained. The formation of the different diastereomers will be explained by focusing on the reaction between a metal stabilized azomethine ylide **A** and dimethyl maleate as outlined in Figure 21. As formerly mentioned, the metal stabilized azomethine ylide (**B1**, **B2**) exists exclusively in the conformer in which the metal interacts with both the nitrogen and the oxygen atom.[30] Thus, only the conformational change from **B1** to **B2** is possible, whereas **B1** seems to be the reacting intermediate according to experimental data. Taking this into account the number of possible diastereomers is reduced to four (**C**, **C'**, **D**, **D'**).

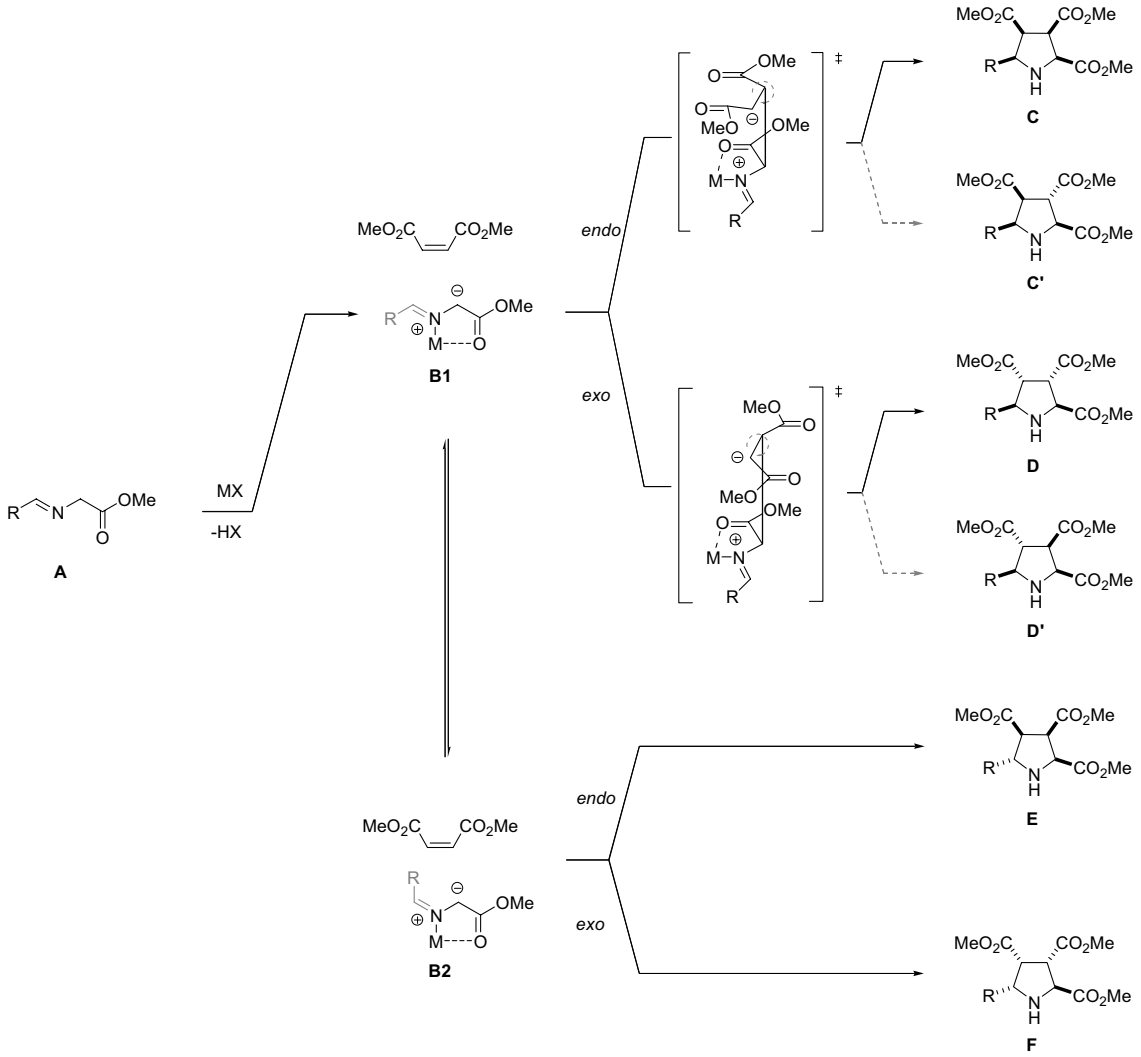


Figure 21.

The number of possible diastereomeric products is reduced to diastereomers **C** and **D** by the fact that the relative orientation of the substituents at the dipolarophile usually correlates with that in the cycloadduct such that *cis*-disubstituted alkenyl dipolarophiles lead to 3,4-*cis*-disubstituted pyrrolidine products and *trans*-disubstituted alkenyl dipolarophiles lead to 3,4-*trans*-disubstituted pyrrolidine products. This result is expected on the basis that the rotation around the former alkene-bond of the dipolarophile is slower than the cyclization step according to the mechanism discussed before. Finally, diastereomer **C** and **D** are formed by the *endo* respectively *exo* orientation of the substituents on the dipolarophile to the newly formed ring. Depending upon the substituents on the dipolarophile, the *endo* transition state may be stabilized by small secondary π-orbital interactions.

3.5 Enantioselectivity of [3+2] Cycloadditions

There exist several methods for inducing asymmetry in [3+2] cycloadditions. They comprise the application of chiral 1,3-dipoles[31], chiral dipolarophiles[32], chiral auxiliaries attached to the 1,3-dipole[33] or the dipolarophile[34], enzymes[35], organocatalysts[36] and chiral metal-complexes. The use of the latter will be discussed in the following chapter.

Chapter 4

Metals and Ligands Employed for [3+2] Cycloadditions of Azomethine Ylides

4 Metals and Ligands Employed for [3+2] Cycloadditions of Azomethine Ylides

4.1 Metals Used to Promote [3+2] Cycloaddition Reactions

A wide range of metals salts have been employed to promote the [3+2] cycloaddition of azomethine ylides with dipolarophiles (Figure 22), including Li(I)[37], Mg(II)[38], Ti(IV)[39], Sn(IV)[40], Mn(II)[41], Co(II) [39a,41], Ni(II)[42], Cu(I), Cu(II), Zn(II), Ag(I) and samarium[43] and a range of rare earth[44] triflates, but only Cu(I)[42,45]-, Cu(II)[46]-, Zn(II)[46b,47]- and Ag(I)[48]-complexes have been used in the catalytic asymmetric variant.

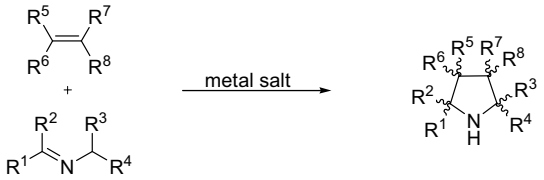


Figure 22.

4.2 Chiral Ligands Used for Cu(I)-Catalyzed [3+2] Cycloadditions

The employment of ferrocene based *P*,*N*-, *P*,*S*- and *P*,*P*-ligands **25**, **26**, **27, 24** and **28** led to date to the most successful induction of asymmetry to Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions between azomethine ylides and electron-deficient dipolarophiles (Figure 23). *P*,*N*-ligands **25**, **26** and **27** were used by the research groups of Zhang[45b], Hou[45d] and Carretero[45a], whereas the latter[45c] also employed *P*,*S*-ligands like **24**. Perchlorate was the counterion of choice and the addition of 10 to 18 mol% of an organic base supported the formation of the metal stabilized azomethine ylide. The employment of 3 to 10 mol% of the catalyst, reaction temperatures of -20 °C to 0 °C and aprotic solvents usually led after reaction times of 6 to 24 h to the formation of the pyrrolidine moieties with good enantioselectivities. Figure 23 shows a selection of the most selective pyrrolidine formations for each ligand type.
Hou claimed that the diastereoselectivity of the reaction is determined by the electronic properties of the substituents at the phosphorous atom. While electron-rich substituents favor the *exo* product, formation of the *endo* product is observed with electron-deficient substituents. This is illustrated in Figure 23 by the results generated by Zhang and Hou.

Grigg[42] successfully employed the Josiphos-ligand **28** to the Cu(I)-catalyzed [3+2] cyclo-addition. In contrast to the other research groups iodide was used as a counterion but no detailed reaction conditions were described.

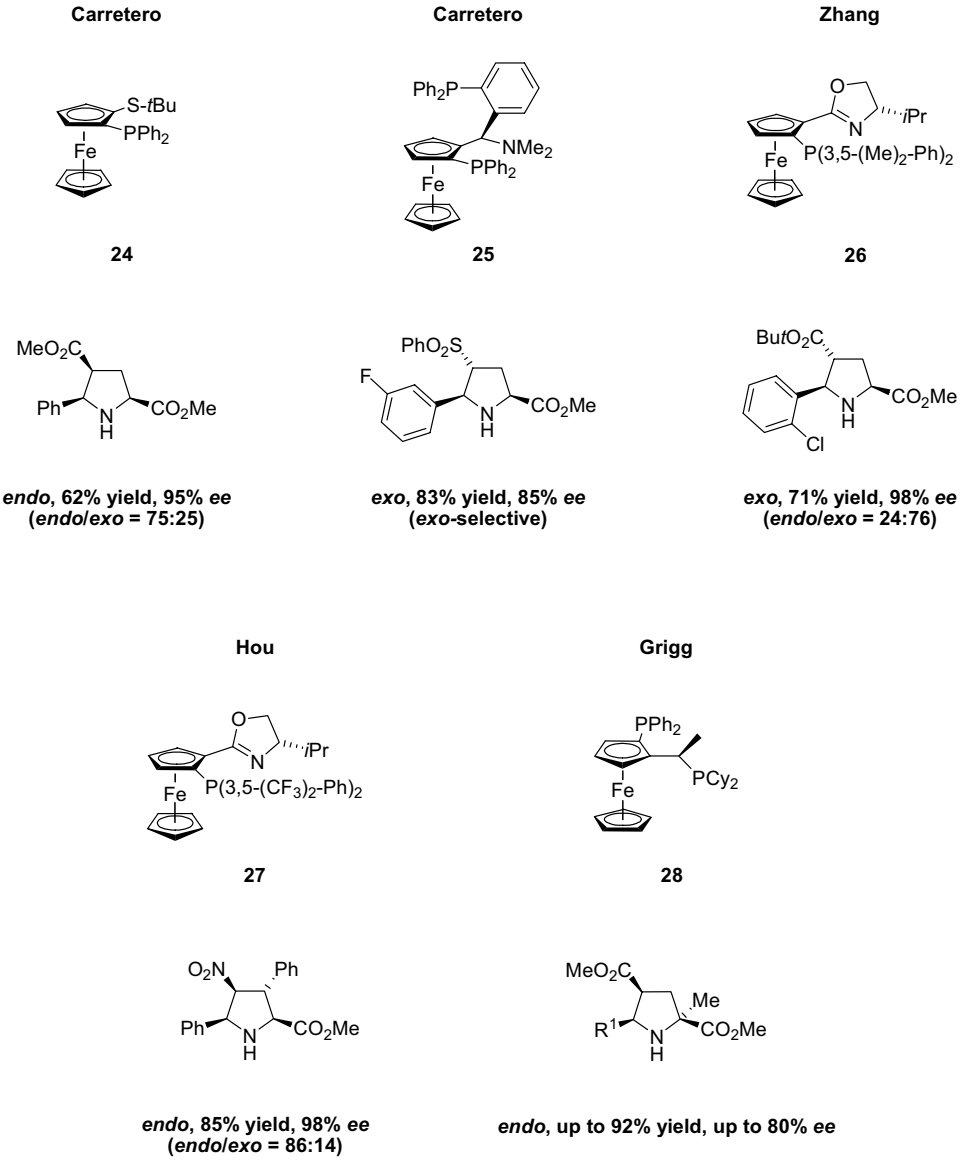


Figure 23.

4.3 Chiral Ligands Used for Cu(II)-Catalyzed [3+2] Cycloadditions

The research group of Komatsu[46a] achieved enantiocontrol in Cu(II)-catalyzed 1,3-dipolar cycloadditions between azomethine ylides and electron-deficient dipolarophiles by using the (*R*)-BINAP- **29** and the (*R*)-SEGPHOS- ligand **30** (Figure 24). Triflate was the counterion of choice and 4 mol% of triethylamine was used to support the formation of the metal stabilized azomethine ylide. The employment of 2 mol% of catalyst, a reaction temperature of -40 °C and dichloromethane as a solvent led after a reaction time of 24 h to the formation of the desired five-membered heterocycles. Figure 24 shows a selection of the most selective heterocyclic ring-formations for the two ligand-types. Jørgensen[46b] and his co-workers applied a Cu(II)-complex derived from $CuOTf_2$ and the (*S*)-*t*Bu-BOX-ligand **31** to [3+2] cycloadditions of azomethine ylides. The desired *endo* products where isolated with high yields but as a racemate.

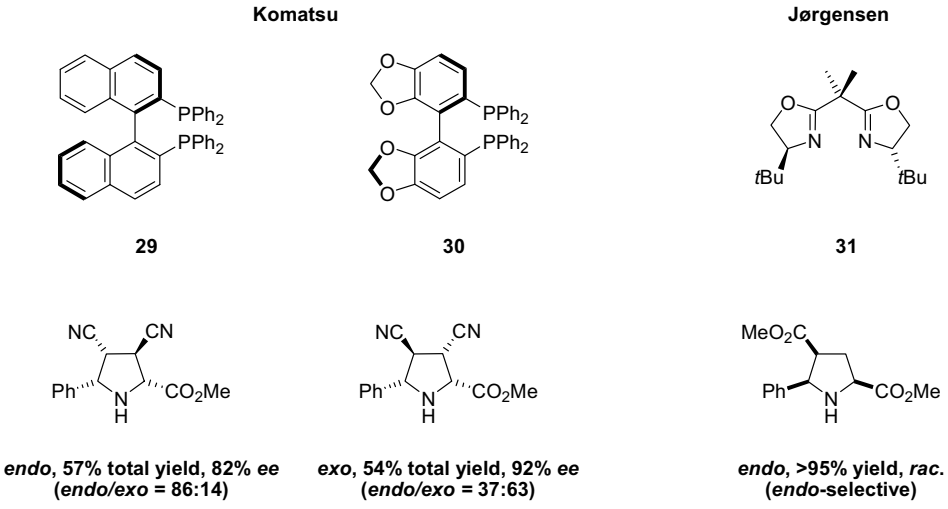


Figure 24.

4.4 Chiral Ligands Used for Zn(II)-Catalyzed [3+2] Cycloadditions

The research groups of Jørgensen[46b] and Dogan[47] applied complexes obtained from zinc triflate and the (*S*)-*t*Bu-BOX- **31** respectively a ferrocenyl-substituted aziridino alcohol ligand **32** to the 1,3-dipolar cycloaddition reaction between azomethine ylides and electron-deficient dipolarophiles (Figure 25).

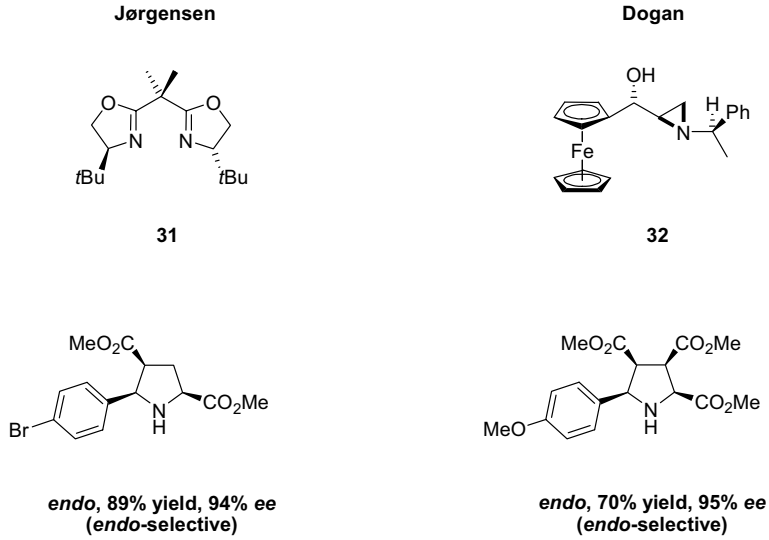


Figure 25.

The performance of the reaction using 10 mol% of the catalyst in combination with 10 mol% of triethylamine in aprotic polar solvents at -20 °C led after a reaction time of 6 to 12 h to the exclusive formation of the *endo* products with high enantioselectvities as shown from the selected examples in Figure 25.

4.5 Chiral Ligands Used for Ag(I)-Catalyzed [3+2] Cycloadditions

The employment of ferrocene based *P*,*P*- and *P*,*N*-ligands **33** and **34** by the research groups of Zhang[48a] and Zhou[48d] as well as the use of the *P*,*N*-ligands QUINAP **36** and PINAP **35** by Schreiber[48b] respectively Carreira[48c] led to successful induction of asymmetry to the Ag(I)-catalyzed 1,3-dipolar cycloaddition between azomethine ylides and electron-deficient dipolarophiles (Figures 26 and 27). Acetate was the counterion of choice and 10 mol% of Hünig base was used to support the azomethine ylide formation. Zhou did not use base claiming that the addition of extra base is not necessary for the acetate probably facilitates the deprotonation of the iminoester to generate the metal stabilized azomethine ylide. The employment of 3 mol% of catalyst, reaction temperatures from -45 °C to 0 °C and aprotic solvents led after reaction times of 3 to 96 h to the formation of the cycloaddition products with high selectivities as shown in Figures 26 and 27.

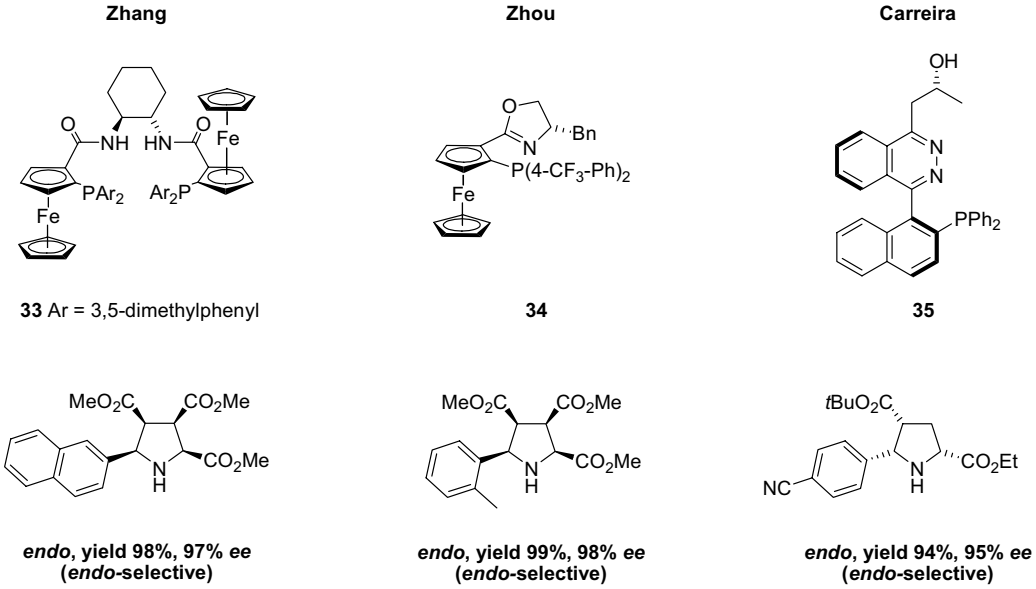


Figure 26.

Schreiber *et al*. additionally investigated the 1,3-dipolar cycloaddition reaction between acyclic electron deficient dipolarophiles and iminoesters derived from amino esters other than glycinate or alaninate. Albeit 10 mol% of the catalyst were used the resulting pyrrolidines with a quaternary center at the 2-position were isolated with good selectivities (Figure 27).

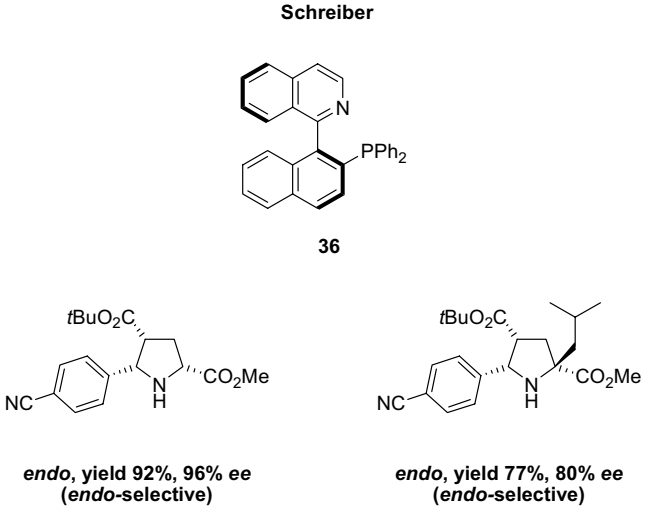


Figure 27.

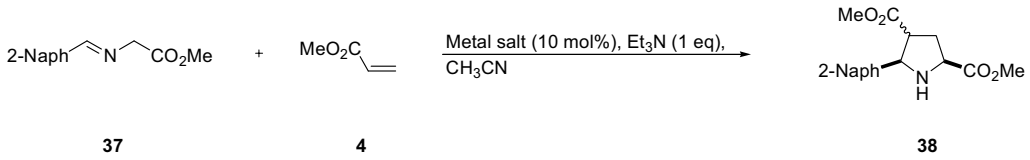
Chapter 5

Initial Metal and Ligand Screening for the [3+2] Cycloaddition of Azomethine Ylides

5 Initial Metal and Ligand Screening for the [3+2] Cycloaddition of Azomethine Ylides

5.1 Metal Screening

The initial screening of metal salts ($Cu(OAc)_2$, AgOAc, $AgSbF_6$, $ZnCl_2$, $MgCl_2$, $Sn(SO_3CF_3)_2$, $AuCl_3$) for the 1,3-dipolar cycloaddition reaction between (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate **37** and methyl acrylate **4** (Scheme 6) performed by *Mark Enzler* in his diploma thesis[49] was supplemented with further metal salts including CuCl, $(Cu(SO_3CF_3))_2 \cdot C_6H_5CH_3$, $CoCl_2$, CoOAc, $NiCl_2$, $Pd(OAc)_2$, AuCl and SmI_2. Apart from the Cu(I) salts none of the other metal salts catalyzed the reaction satisfyingly.



Scheme 6.

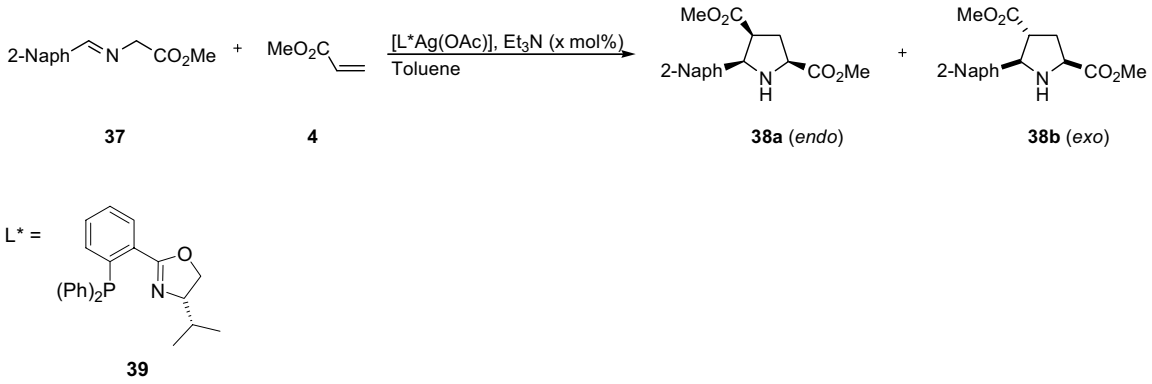
As a result of both screenings only Ag(I) and Cu(I) salts were applied to the asymmetric variant of this reaction.

5.2 Ligand Screening for the Ag(I)-Catalyzed [3+2] Cycloaddition

In addition to the ligands *Mark Enzler* screened during his diploma thesis[1] further ligands were applied to the reaction outlined in Scheme 7. They were chosen from the Pfaltzs' group ligand library with the intention to cover the widest possible range of ligand classes, comprising various *P*,*N*-, *P*,*P*-, *N*,*N*- and monodentate *P*-ligands. The reaction was performed following a general procedure using the *in-situ* preparation of the catalyst. ^{31}P-NMR studies concerning the complexation of AgOAc with the PHOX ligand **39** showed that a complexation time of at least 4 h is required.[49] Due to the fact that different ligand types had to be complexed with AgOAc, the complexation time was increased to 12 h to avoid a background reaction with uncomplexed AgOAc. After preparation of the catalyst a solution of the imine[50] was added, followed by the base and the dipolarophile. Prior to the ligand screening the reaction conditions were optimized in terms of solvent, reaction temperature and base.

5.2.1 Optimization of the Reaction Conditions

Influence of the base on reactivity and selectivity



Scheme 7.

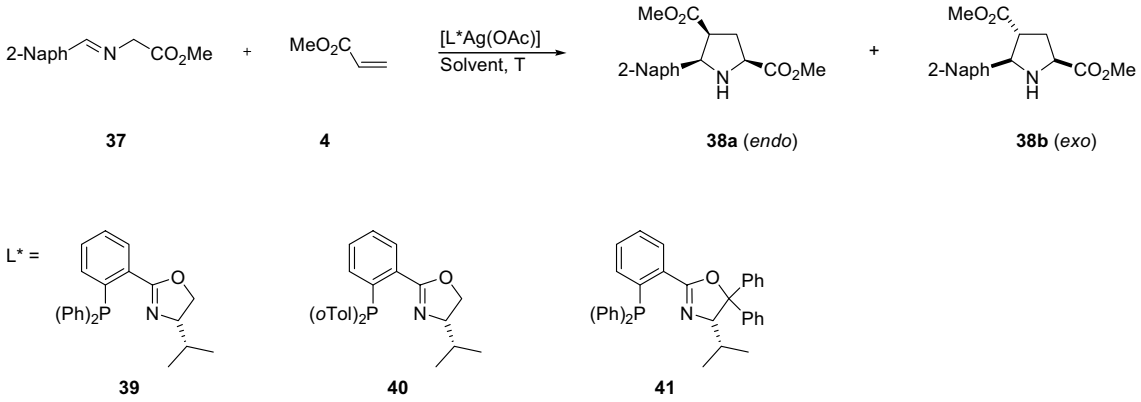
The results illustrated in Table 2 demonstrate that the addition of base affected neither the reactivity nor the selectivity of the reaction (Scheme 7). The basicity of the acetate seems to be sufficient to deprotonate the imine **37** for forming the metal stabilized azomethine ylide (see chapter 4.5). This result was also confirmed by Zhou and co-workers.[48d]

Table 7.

Entry	**L***	**Et_3N** (mol%)	**t** (h)	**Yield** (%)[a]	**38a : 38b**[b]	***ee*** (%)[c] (**38a**)
1	**39**	10	5	95	>40 : 1	22 (+)
2	**39**	0	5	92	>40 : 1	22 (+)

[a] After column chromatography.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligand **39** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), Et_3N (x mol%), toluene, rt.

Influence of the reaction temperature on reactivity and selectivity



Scheme 8.

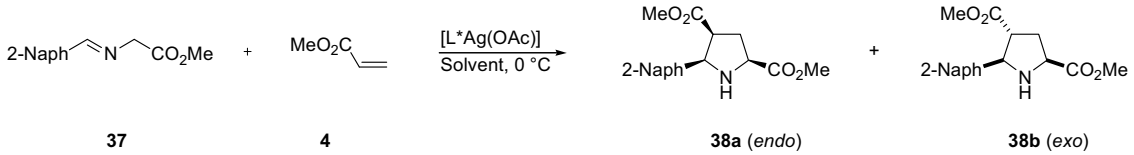
The decrease of the reaction temperature from room temperature to 0 °C did not have an effect on reactivity but on selectivity, which was slightly improved (Table 3, compare entries 1 and 2). Further lowering of the temperature using toluene as solvent was impossible because the substrates precipitated at a temperature of about -6 °C. Therefore the solvent was changed to chlorobenzene or to tetrahydrofuran, to carry out the reaction at -40 °C (Table 3, entry 4 and 5). Neither chlorobenzene nor tetrahydrofuran had a beneficial effect on selectivity and reactivity. Thus subsequent reactions were conducted at 0 °C.

Table 3.

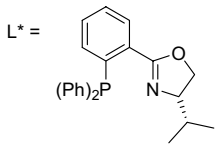
Entry	L*	Solvent	T (°C)	t (h)	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (38a)
1	**39**	Toluene	rt	4	> 95	>40 : 1	22 (+)
2	**39**	Toluene	0	4	> 95	>40 : 1	29 (+)
3	**40**	Toluene	0	8	93[c]	>40 : 1	45 (+)
4	**40**	Chlorobenzene	-40	28	40[c]	11 : 1	30 (+)
5	**41**	Toluene	0	7	89	>40 : 1	49 (+)
6	**41**	Tetrahydrofuran	-40	16	90	>40 : 1	37 (+)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
[c] Yield after column chromatography.
Reaction conditions: AgOAc (3 mol%), ligands **39**-**41** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), solvent, T.

Influence of solvents on reactivity and selectivity



37 **4** **38a** (*endo*) **38b** (*exo*)



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Scheme 9.

The results illustrated in Table 4 for the reaction in Scheme 9 showed that the application of apolar solvents like benzene and toluene had a beneficial effect on reactivity and selectivity compared to the use of aprotic polar solvents (Table 4, compare entries 6 and 7 with entries 1-5). Only tetrahydrofuran could compete with the apolar solvents, but just in terms of reactivity. Therefore toluene was the solvent of choice for the following reactions.

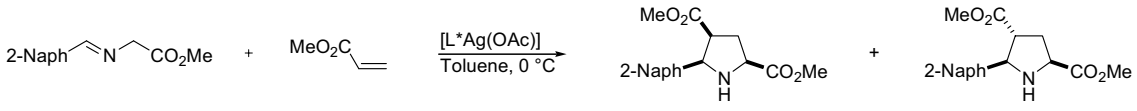
Table 4.

Entry	L*	Solvent	t (h)	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (38a)
1[c]	**39**	Dichloromethane	7	82	10 : 1	13 (+)
2[c]	**39**	1,2-Dichloroethane	12	7	9 : 1	18 (+)
3[c]	**39**	Acetonitrile	4	68	11 : 1	13 (+)
4[d]	**39**	Dioxane	24	38	n.d.	5 (+)
5	**39**	Tetrahydrofuran	6	> 95	>40 : 1	21 (+)
6	**39**	Benzene	6	> 95	>40 : 1	25 (+)
7	**39**	Toluene	5	> 95	>40 : 1	29 (+)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
[c] 10 mol% of Et_3N were used.
[d] Reaction temperature 15 °C.
Reaction conditions: AgOAc (3 mol%), ligands **39** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), solvent, 0 °C.

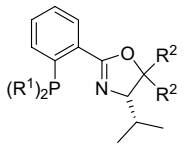
5.2.2 Application of Different *P*,*N*-Ligands to the Ag(I)-Catalyzed [3+2] Cycloaddition

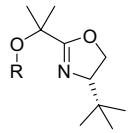
Various *P*,*N*-ligands were applied to the [3+2] cycloaddition outlined in Scheme 10, including PHOX ligands **39**-**41**, phosphate- and bis(*N*-tosylamino)phosphine-oxazoline ligands **42**, **43**, a phosphine-imidazoline ligand **44** and phosphinite-oxazoline ligands **45**-**47**.

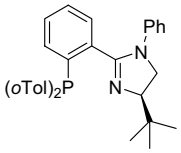


37 **4** **38a** (*endo*) **38b** (*exo*)

L* =

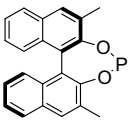




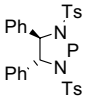


39 R^1 = Ph, R^2 = H
40 R^1 = *o*Tol, R^2 = H
41 R^1 = Ph, R^2 = Ph

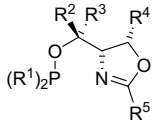
42 R =



43 R =



44



45 R^1 = *o*Tol, R^2 = R^3 = H, R^4 = R^5 = Ph
46 R^1 = *o*Tol, R^2 = H, R^3 = 4-(methylsulfonyl)benzene, R^4 = H, R^5 = Ph
47 R^1 = Ph, R^2 = R^3 = CH_2Ph, R^4 = Ph, R^5 = ferrocene

Scheme 10.

With exception of the phosphite and the bis(*N*-tosylamino)phosphine-oxazoline ligands **42** and **43** all ligand types induced acceptable reactivity and *endo*:*exo* selectivity (Table 5). Promising enantioselectivities were obtained with the phosphite-ligand **42**, the phosphinite-oxazoline ligand **46** and the PHOX ligands **39**-**41** (Table 5, entries 2, 3, 5 and 7). The bis(*N*-tosylamino)phosphine-oxazoline ligand **43** decomposed during complexation and, therefore, no conversion was observed (Table 5, entry 8).

The results generated by the three PHOX ligands allowed a first interpretation of the influence of different substituents at the ligand on asymmetric induction. The introduction of substituents at the C5 position of the oxazoline moiety seemed to have a beneficial effect on

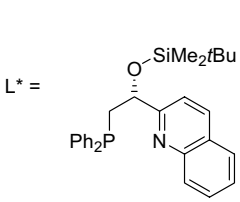
enantioselectivity (Table 5, compare entries 1 and 4). Also the introduction of sterically more demanding substituents at the phosphorous atom led to an enhancement of the enantiomeric excess (Table 5, compare entries 1 and 2).

Table 5.

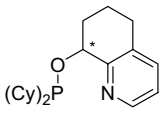
Entry	L*	t (h)	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (38a)
1	**39**	5	95	>40 : 1	29 (+)
2	**40**	8	93	>40 : 1	45 (+)
3	**41**	7	86	>40 : 1	49 (+)
4	**45**	6	>95	>40 : 1	3 (+)
5	**46**	7	>95	>40 : 1	29 (+)
6	**47**	5	81	>40 : 1	17 (+)
7	**42**	14	29	n.d.	41 (–)
8	**43**	20	-	-	-
9	**44**	5	67	33 : 1	*rac*.

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligands **39**-**47** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

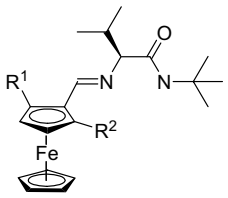
In addition some pyridine derived phosphine- and phosphinite ligands **48** and **49** as well as phosphine imine ligands **50** and **51** (Figure 28) were applied to the reaction of Scheme 10.



48



49



50 R^1 = H, R^2 = PPh_2
51 R^1 = PPh_2, R^2 = H

Figure 28.

The application of these ligands led to silver complexes with medium to good reactivity forming the desired pyrrolidine products **38a** and **38b** with excellent *endo*:*exo* selectivities but poor enantioselectivities (Table 6).

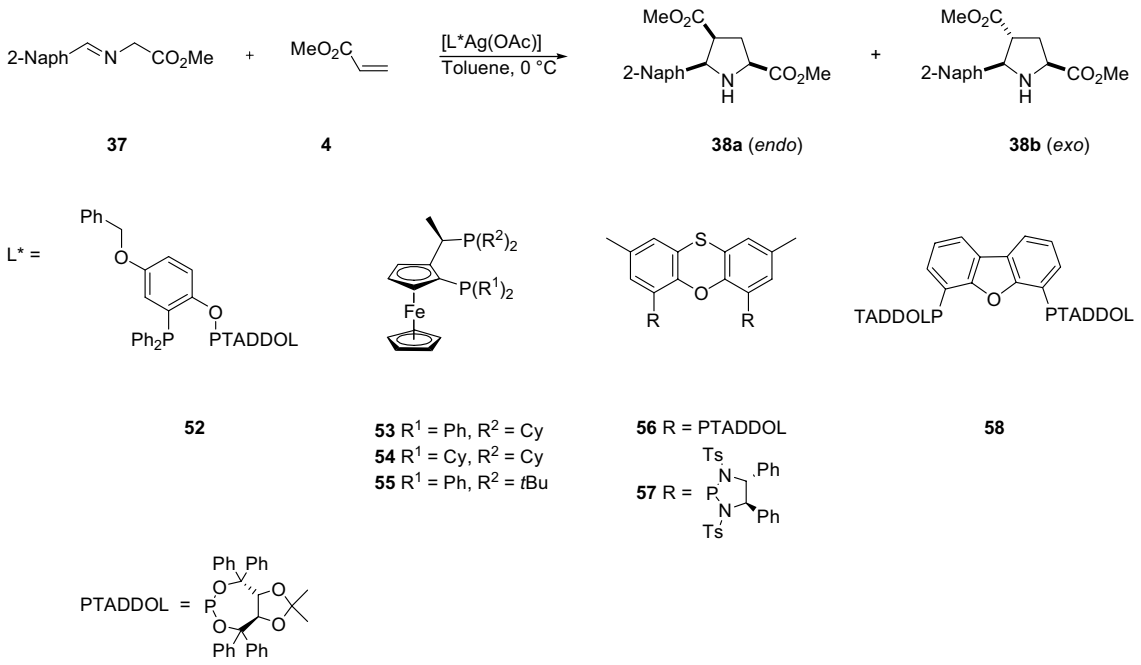
Table 6.

Entry	**L***	**t** (h)	**Conversion** (%)[a]	**38a : 38b**[a]	***ee*** (%)[b] (**38a**)
1	**48**	6.5	95	>40 : 1	*rac.*
2	**49**	8	58	40 : 1	*rac.*
3	**50**	5	71	>40 : 1	20 (+)
4	**51**	6	80	>40 : 1	*rac.*

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligands **48**-**51**(3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

5.2.3 Application of Different *P*,*P*-Ligands to the Ag(I)-Catalyzed [3+2] Cycloaddition

Several *P*,*P*-ligands were employed in the [3+2] cycloaddition reaction of Scheme 11. These comprise a TADDOL-phosphite ligand **52**, the Josiphos ligands **53**-**55**, two dimeric TADDOL derived phosphonite ligands **56** and **58** linked by phenoxathiin or dibenzofuran and a dimeric bis(*N*-tosylamino)phosphine ligand **57** linked by phenoxathiin.



Scheme 11.

Silver complexes of these ligands usually showed low reactivity and low asymmetric induction with exception of the TADDOL derived phosphonite ligand **58** (Table 7). Using this ligand the pyrrolidines **38a** and **38b** were formed with moderate *endo*:*exo* selectivity but promising enantioselectivity of 59%. As already observed for the bis(*N*-tosyl-amino)phosphine-oxazoline ligand **43** also the dimeric bis(*N*-tosylamino)phosphine ligand **57** decomposed during complexation and, therefore, no product could be isolated (Table 7, entry 6).

Table 7.

Entry	L*	t (h)	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (38a)
1	**52**	12	57	>40 : 1	3 (+)
2	**53**	12	35	2 : 1	*rac.*
3	**54**	12	24	1 : 2	20 (–)
4	**55**	12	16	2 : 1	10 (–)
5	**56**	8	15	>40 : 1	*rac.*
6	**57**	24	-	-	-
7	**58**	7	34	24 : 1	59 (–)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligands **52-58** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino) acetate (**37**) (1.0 eq), toluene, 0 °C.

5.2.4 Application of an *N,N*-Ligand to the Ag(I)-Catalyzed [3+2] Cycloaddition

The application of the BOX ligand **31** (Figure 29) to the reaction of Scheme 11 following the general procedure did not lead to any formation of product.

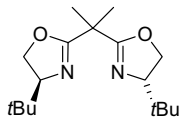


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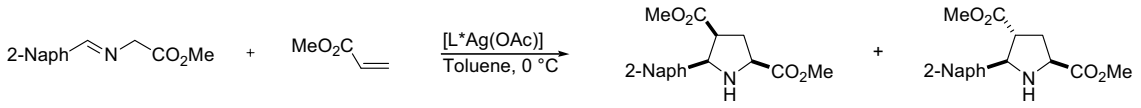
Figure 29.

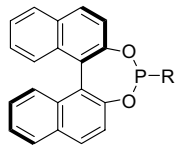
5.2.5 Application of Different Monodentate *P*-Ligands to the Ag(I)-Catalyzed [3+2] Cycloaddition

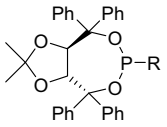
Monodentate BINOL and TADDOL derived phosphoramidite **59**, **61** and **62** and phosphite ligands **60** and **63** were applied to the reaction in Scheme 12.



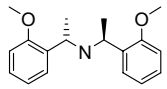
37 **4** **38a** (*endo*) **38b** (*exo*)

L* =





59 R = NMe_2
60 R = OCH_2tBu
61 R =



62 R = NMe_2
63 R = OCH_2tBu

Scheme 12.

Each reaction was carried out using either one or two equivalents of ligand with respect to AgOAc. The corresponding complexes showed different ^{31}P-NMR shifts in the two cases. This is probably due to the fact that a monomeric or a dimeric complex is formed. However, the metal/ligand ratio did not have an effect on the reactivity of the complexes or its asymmetric induction.

The silver complex of the BINOL derived phosphite ligand **60** was not reactive at all (Table 8, entry 2) whereas the analogous phosphoramidite ligands **59** and **61** led to complexes with good reactivity (Table 8, entries 1 and 3). An enantioselectivity of 70% was obtained when this ligand type contained a chiral amine building block (**61**).

The catalysts of both TADDOL derived ligands **62** and **63** showed good reactivity and *endo*:*exo* selectivity whereas only the phosphoramidite ligand **62** could induce good enantioselectivtiy (Table 8, entry 4 and 5).

Table 8.

Entry	L*	t (h)	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (38a)
1	**59**	5.5	>95	>40 : 1	3 (+)
2	**60**	72.0	-	-	-
3	**61**	5.5	86	>40 : 1	70 (+)
4	**62**	6.0	>95	>40 : 1	61 (–)
5	**63**	9.0	>95	>40 : 1	12 (+)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligands **59**-**63** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

5.2.6 Conclusion

The results of the ligand screening focused the interest on *P*,*N*- and on monodentate *P*-ligands.

Based on the results obtained with monodentate *P*-ligands, the variation of the structure of TADDOL derived phosphoramidites appeared most promising. Unfortunately, the synthesis of this ligand type derived from sterically more demanding amines is not trivial and the yields are usually low as demonstrated by Alexakis *et al*.[51]

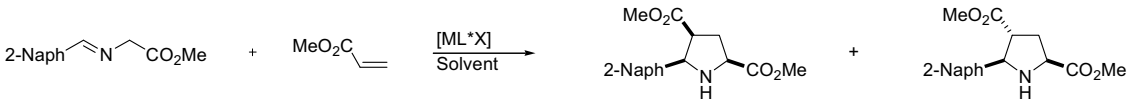
Therefore the efforts were directed to *P*,*N*-ligands. The first results generated by the three PHOX ligands **39**-**41** already indicated a strong influence of its substitution pattern on asymmetric induction. Motivated by these results and the fact that this ligand type is highly variable and easily accessible, it was chosen to be optimized for the [3+2] cycloaddition reaction between azomethine ylides and electron-deficient dipolarophiles.

5.3 Ligand Screening for the Cu(I)-Catalyzed [3+2] Cycloaddition

Several Cu(I) sources were tested in the asymmetric [3+2] cycloaddition including CuOAc, CuO*t*Bu and $Cu(CH_3CN)_4PF_6$. Since the initially used CuOAc required a laborious complexation method[52] to obtain the desired catalyst, CuO*t*Bu[53] was synthesized and used as catalyst precursor. This metal salt is soluble in organic solvents including apolar solvents like cyclohexane and benzene and allowed complexation with the PHOX ligand under the same conditions used for Ag(I) complexes. Commercially available $Cu(CH_3CN)_4PF_6$ could be used in the same way as CuO*t*Bu with the difference that Et_3N had to be added to the reaction mixture to assure the formation of the azomethine ylide.[45a,45c]

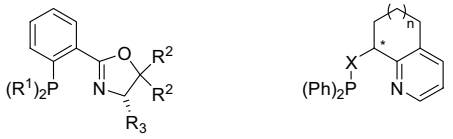
The ligand screening comprised a limited number of *P*,*N*-, *P*,*P*- and *N*,*N*-ligands and was performed following the general procedure used for the Ag(I)-catalyzed 1,3-dipolar cycloaddition reaction.

5.3.1 Application of Different *P*,*N*-Ligands to the Cu(I)-Catalyzed [3+2] Cycloaddition



37 **4** **38a** (*endo*) **38b** (*exo*)

L* =



39 R^1 = Ph, R^2 = H, R^3 = *i*Pr
63 R^1 = Ph, R^2 = H, R^3 = *t*Bu
41 R^1 = Ph, R^2 = Ph, R^3 = *i*Pr
64 R^1 = *o*Tol, R^2 = Ph, R^3 = *i*Pr

65 X = CH_2, n = 1
66 X = O, n = 2

Scheme 13.

Cu(I)-PHOX complexes showed good activities in the reaction illustrated in Scheme 13 and formed the products with up to 76% enantiomeric excess but with low *endo*:*exo* selectivity (Table 9). Decreasing the temperature from room temperature to 0 °C improved the *ee*-values and the *endo*:*exo* selectivity slightly whereas the conversion dropped (Table 9, compare entries 1 and 2). Increasing the steric bulk at the C4 position of the oxazoline moiety or the

introduction of two phenyl groups at the C5 position favoured the generation of the *exo* product and lowered the enantiomeric excess of the *endo* product dramatically while the *ee*-value of the *exo* product raised (Table 9, compare entry 2 with entries 3 and 4). The use of CuO*t*Bu and cyclohexane/benzene instead of CuOAc and toluene led to a higher *endo* selectivity and slightly higher enantioselectivity for the *endo* product (Table 9, compare entries 1 and 5). The application of pure benzene instead of the cyclohexane/benzene mixture led to a decrease of the *endo*:*exo* selectivity. Complexation of $Cu(CH_3CN)_4PF_6$ with the PHOX ligand **64** led to a highly reactive catalyst which afforded preferentially the *exo* product whereas the enantioselectivities were rather low.

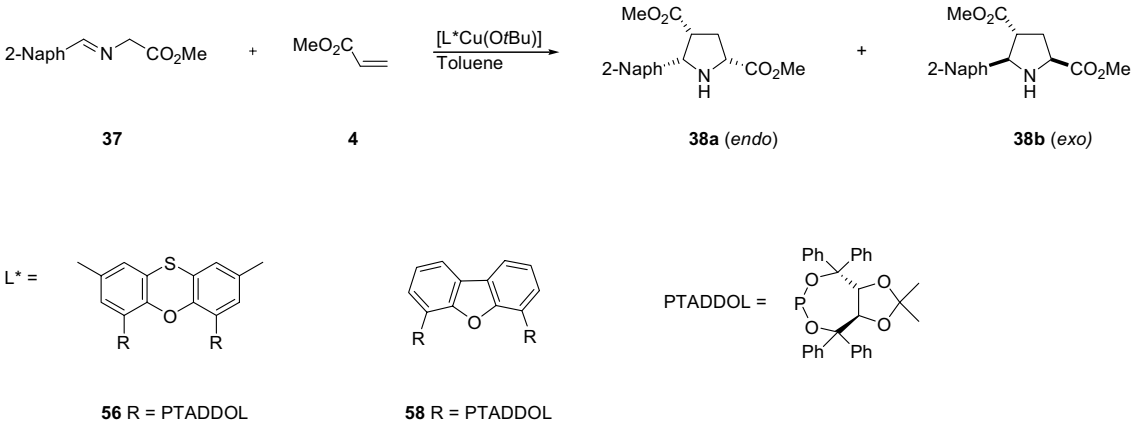
Table 9.

Entry	Metal salt	L*	Cat. (mol%)	T (°C)	Solvent	t (h)	Conv.[a] (%)	38a : 38b[a]	*ee* (%)[b] (**38a**) / *ee* (%)[b] (**38b**)
1	CuOAc	**39**	5	rt	toluene	12	85	1.5 : 1.0	70 (–) / 23[d]
2	CuOAc	**39**	5	0	toluene	12	71	2.5 : 1.0	76 (–) / 24[d]
3	CuOAc	**63**	5	0	toluene	12	80	1.0 : 1.9	3 (+) / 43[d]
4	CuOAc	**41**	5	0	toluene	12	70	1.0 : 3.5	28 (+) / 62[d]
5	CuO*t*Bu	**39**	3	rt	cyclohexane /benzene (4:1)	4	84	5.4 : 1.0	74 (–) / 23[d]
6	CuO*t*Bu	**63**	3	rt	benzene	3.5	65	1.5 : 1.0	10 (+) / 39[d]
7	CuO*t*Bu	**63**	3	rt	cyclohexane /benzene (4:1)	4	61	4.9 : 1.0	4 (+) / 34[d]
8[c]	$Cu(CH_3CN)_4PF_6$	**64**	5	0	toluene	5	90	1 : 3	56 (+) / 30[d]
9	CuO*t*Bu	**65**	3	0	cyclohexane /benzene (2:1)	5	>95	4 : 1	*rac.* / 10[d]
10	CuO*t*Bu	**66**	3	0	cyclohexane /benzene (2:1)	7	>95	38 : 1	10 (–) / n.d.

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC.
[c] Addition of 10 mol% Et_3N to the reaction solution.
[d] Optical rotation not determined.
Reaction conditions: Metal salt (x mol%), ligands **39**, **41**, **63**-**66** (x.x mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), solvent, T.

The Cu(I) complexes of the pyridine derived phosphine- **65** and phosphinite-ligands **66** showed excellent reactivity but formed the products with low enantioselectivites. The use of the phosphinite ligand **66** led to the highest *endo* selectivity in the course of this screening.

5.3.2 Application of Different *P*,*P*-Ligands to the Cu(I)-Catalyzed [3+2] Cycloaddition



Scheme 14.

The Cu(I)-catalyzed [3+2] cycloaddition using the two dimeric TADDOL derived phosphonite ligands **56** and **58** linked by phenoxathiin or dibenzofuran proceeded with extremely low yield even after a reaction time of 24 h (Table 10). Interestingly the ligand with the phenoxathiin linker gave the *endo* product with a medium enantioselectivity of 60% whereas the ligand with the dibenzofuran linker gave the *exo* product with an enantioselectivity of 59%.

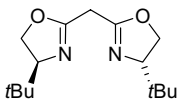
Table 10.

Entry	L*	t (h)	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (**38a**) *ee* (%)[b] (**38b**)
1	**56**	24	<5	n.d.	14 (–) 59[c]
2	**58**	24	<10	n.d.	60 (–) n.d.

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
[c] Optical rotation not determined.
Reaction conditions: AgOAc (3 mol%), ligands **56** and **58** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

5.3.3 Application of an *N,N*-Ligand to the Cu(I)-Catalyzed [3+2] Cycloaddition

The Cu(I)-BOX complex derived from CuOAc and ligand **67** showed no reactivity in the [3+2] cycloaddition reaction illustrated in Scheme 14.



67

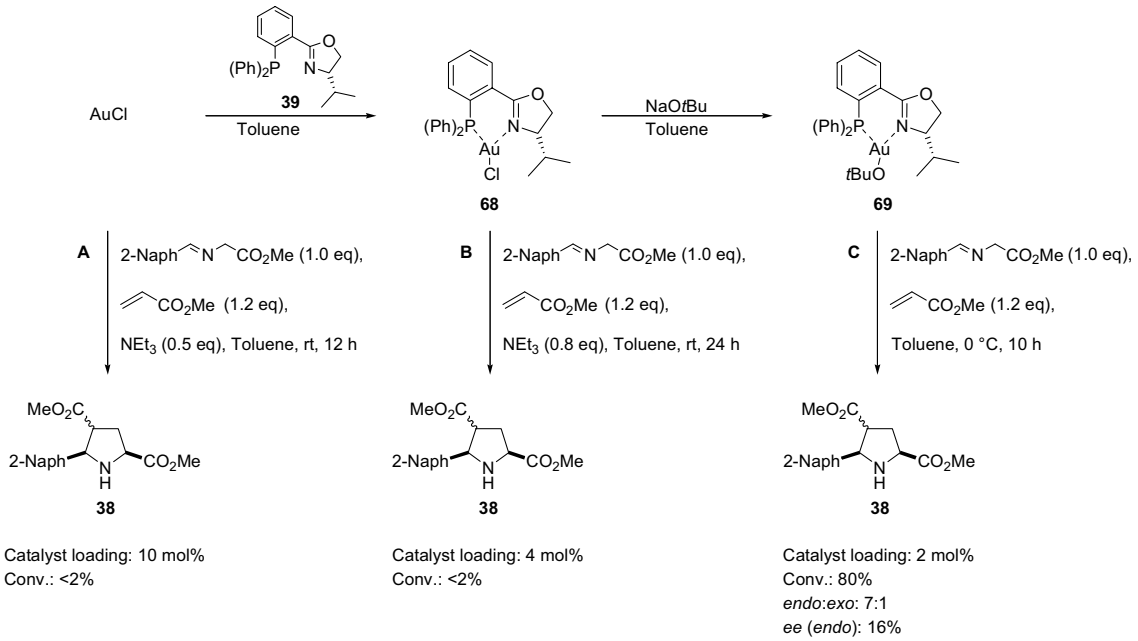
Figure 30.

5.3.4 Conclusion

With regard to the results generated during the narrow ligand screening for the Cu(I)-catalyzed [3+2] cycloaddition, the PHOX ligand represents the most promising ligand type. Cu(I) catalysts derived from this ligand type were usually quite active and produced the cycloaddition products with moderate to good enantioselectivities. On the other hand the low *endo*:*exo* selectivity and the lack of conclusive models explaining the influence of the substituents at the ligand on asymmetric induction demand further ligand screening.
In addition further Cu(I) sources should be tested to make the complexation and the reaction more practicable.

5.4 Au(I)-Catalyzed [3+2] Cycloaddition

After the successful application of Cu(I) and Ag(I) complexes to the [3+2] cycloaddition reaction between (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) and methyl acrylate (**4**) the focus was laid on Au(I), the remaining d^{10}-transition metal representative of this group. The initial metal screening demonstrated that the use of 10 mol% of AuCl in combination with 0.5 equivalents of triethylamine did not lead to the formation of pyrrolidine **38** (Scheme 15, method A).



Scheme 15.

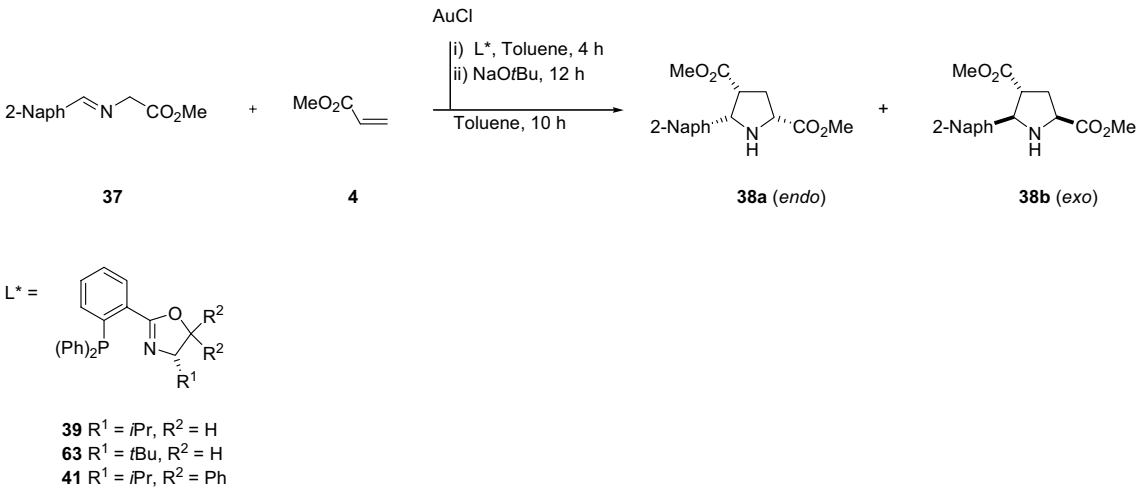
Despite these results a Au(I)-PHOX complex similar to the effective PHOX-Ag(I) acetate or PHOX-Cu(I) *tert*-butoxide was generated. As neither AuOAc nor Au*O*t*Bu are commercially available the desired complex was prepared by initial formation of the corresponding PHOX-Au(I) chloride complex and subsequent anion exchange with sodium *tert*-butoxide to create **69**. A suspension of AuCl and the PHOX ligand **39** in toluene was stirred for 4 h. ^{31}P-NMR studies of the resulting solution showed that the desired complex must have been formed since the signal of the free ligand disappeared (-8.5 ppm ($CDCl_3$)) whereas a new signal appeared at 30.6 ppm. After addition of sodium *tert*-butoxide, the reaction solution was stirred for an additional 12 h and analyzed by ^{31}P-NMR spectroscopy. As the obtained signal did not shift significantly from the signal of the starting material ($\Delta\delta$ = 0.4 ppm) no statement can be made if the anion exchange took place. A complexation trial using sodium

tert-butoxide with the PHOX ligand **39** excluded the formation of a sodium PHOX complex, as proved by ^{31}P-NMR studies of the reaction solution which showed only the signal of the free ligand.

The application of the PHOX-Au(I) chloride complex **68** to the [3+2] cycloaddition shown in Scheme 15 (Method B) did not lead to the formation of the desired product **38**. Even after a reaction time of 24 h and the addition of 0.8 equivalents of base, which should assure the formation of the azomethine ylide, none of the pyrrolidine product **38** could be isolated. On the other hand excellent reactivity was obtained if the reaction was performed in a filtered solution of a PHOX-Au(I) complex, prepared from the PHOX-Au(I) chloride complex **68** by treatment with sodium *tert*-butoxide at 0 °C (Scheme 15, method C). The desired five-membered heterocycle **38** was obtained with a *endo*:*exo* selectivity of 7:1 and an enantioselectivity of 16%.

A control experiment demonstrated that the 1,3-dipolar cycloaddition reaction is also catalyzed by 10 mol% of sodium *tert*-butoxide suspended in toluene. After a reaction time of 12 h almost full conversion was obtained. However, filtration of a suspension of sodium *tert*-butoxide in toluene prior to the addition of the substrates did not show catalytic activity, excluding the possibility of a background reaction caused by the alkali salt.

5.4.1 Application of Different PHOX-Ligands to the Au(I)-Catalyzed [3+2] Cycloaddition



Scheme 16.

The Au(I)-PHOX complexes derived from ligands **39**, **41** and **63** and AgOAc showed good reactivity towards the [3+2] cycloaddition illustrated in Scheme 16. The pyrrolidines **38a** and

38b were isolated with an acceptable *endo*:*exo* selectivity of 7:1 but low enantioselectivities (Table 11).

Table 11.

Entry	L*	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (38a)
1	**39**	80	7 : 1	16 (–)
2	**63**	87	7 : 1	19 (–)
3	**41**	91	7 : 1	7 (–)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
Reaction conditions: AuCl (5 mol%), ligands **39**, **41** and **63** (5.5 mol%), NaO*t*Bu (0.3 eq), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, rt, 10 h.

5.4.2 Conclusion

The experiments with Au(I)-PHOX complexes demonstrate that the Au(I) species presumably catalyzes the reaction shown in Scheme 16 if it is complexed with a PHOX ligand and disposes of the adequate counterion. However, low asymmetric induction, the small choice of different commercially available Au(I) salts, the high prize of the AuCl and the impractical complexation method speak against further investigations of this catalytic system.

5.5 Final Conclusion

Although one of the Cu(I)-PHOX catalysts tested led to the formation of the desired cycloaddition product with higher enantiomeric excess than analogous Ag(I) and Au(I) complexes (Table 9, entry 2 and Table 3, entry 2) the attention was directed to the Ag(I)-PHOX system. Firstly, because only the results obtained with Ag(I)-PHOX complexes indicated a strong influence of the ligand substitution pattern on asymmetric induction. This suggested the possibility of substantial improvement of the enantioselectivity by optimizing the substitution pattern of the ligand. Secondly, high *endo* selectivity was observed in comparison to the Cu(I) and Au(I) system. Thirdly, the practical realization of the Ag(I)-catalyzed 1,3-dipolar cycloaddition reaction is easier than in the Cu(I) or Au(I) series.
It was decided to optimize the substitution pattern of the PHOX ligand at the phosphorous atom and the C5 position of the oxazoline moiety, as these structural elements seemed to have the highest influence on asymmetric induction (Table 5, entries 1-3).

Chapter 6

Phosphinooxazolines

6 Phosphinooxazolines

6.1 General Aspects

The research groups of Pfaltz[54], Helmchen[54] and Williams[55] independently developed the so called PHOX-ligand **39** which contains a "soft" π-accepting phosphorous atom and a "hard" σ-donating nitrogen atom. The electronic properties of this nonsymmetrical ligand type having two coordinating electronically different heteroatoms can aid the control of the stereochemical outcome of a catalyzed reaction. This was demonstrated by the palladium-catalyzed allylic alkylation. In this reaction the nucleophile preferentially attacks the allylic carbon atom *trans* to the phosphorus atom due to strong electronic differentiation of the allylic termini caused by the ligand (Figure 31, **A**).[54]

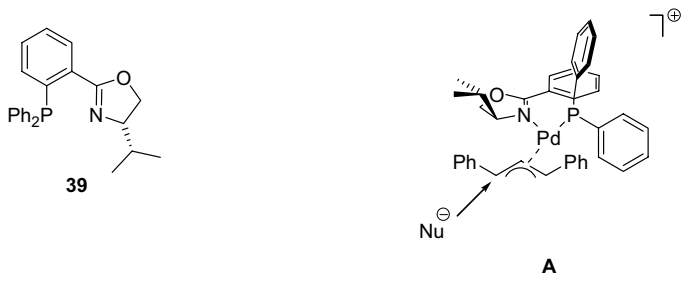
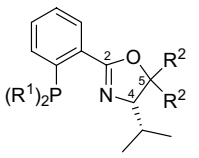


Figure 31.

The PHOX ligand possesses a highly modular structure allowing variations at the oxazoline ring, the backbone and the phosphine moiety. This property often enables the creation of a ligand tailored to the requirements of its application. Heck-reactions[56], Diels-Alder reactions[57] and hydrogenations[58] are only some examples of reactions to which PHOX ligands were applied to.

6.2 Synthesis of C5-Disubstituted Phosphinooxazoline Ligands

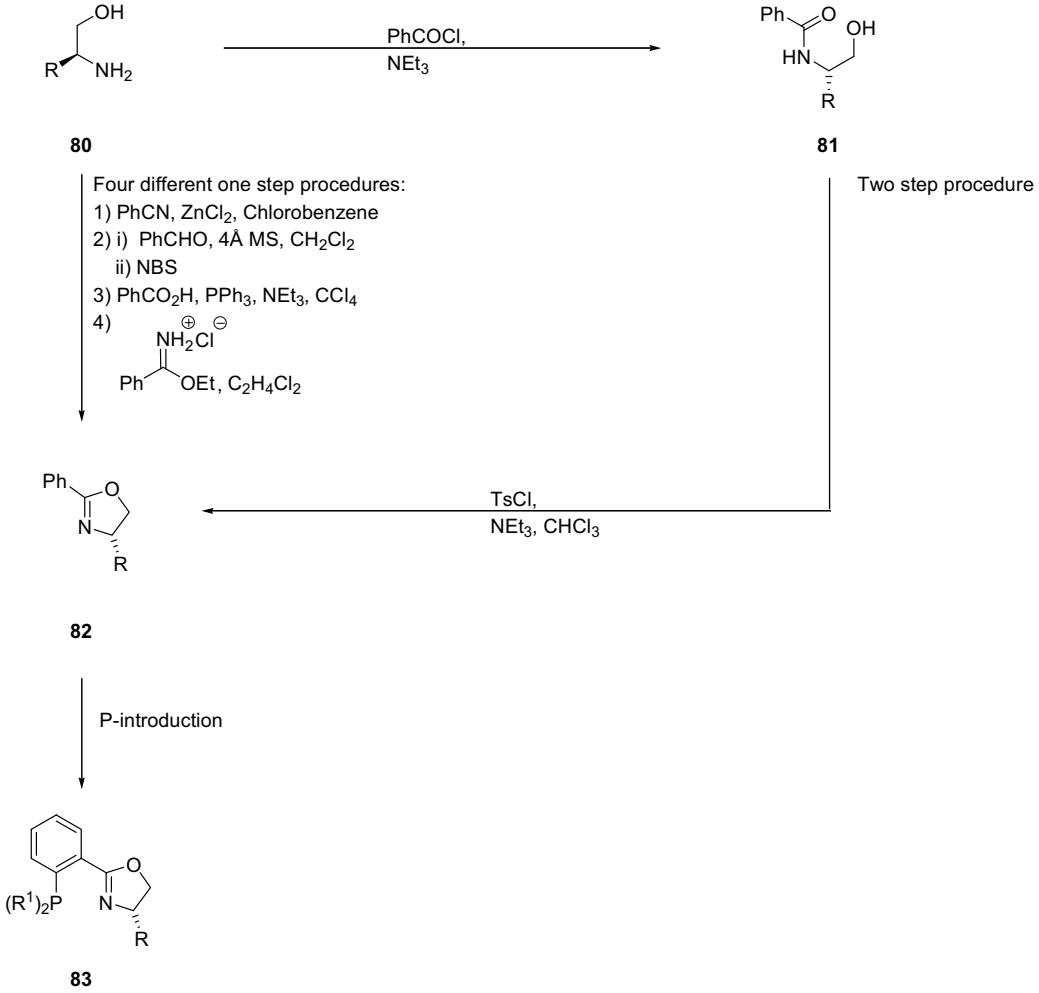
A preliminary ligand screening for the Ag(I)-catalyzed [3+2] cycloaddition reaction showed promising results by applying C5-disubstituted PHOX ligands (Table 5, entry 3) to this reaction. On the basis of these initial experiments a small library of this ligand type was synthesized (Figure 32).



70 R^1 = Ph, R^2 = Et
71 R^1 = *o*Tol, R^2 = Et
72 R^1 = *o*Tol, R^2 = Cy
41 R^1 = Ph, R^2 = Ph
64 R^1 = *o*Tol, R^2 = Ph
73 R^1 = Ph, R^2 = 2-Naph
74 R^1 = *o*Tol, R^2 = 2-Naph
75 R^1 = 3,5-dimethylphenyl, R^2 = 2-Naph
76 R^1 = *o*Tol, R^2 = *o*Tol
77 R^1 = *o*Tol, R^2 = 3,5-dimethylphenyl
78 R^1 = *o*Tol, R^2 = 3,5-dimethoxyphenyl
79 R^1 = *o*Tol, R^2 = 3,5-di-*tert*-butylphenyl

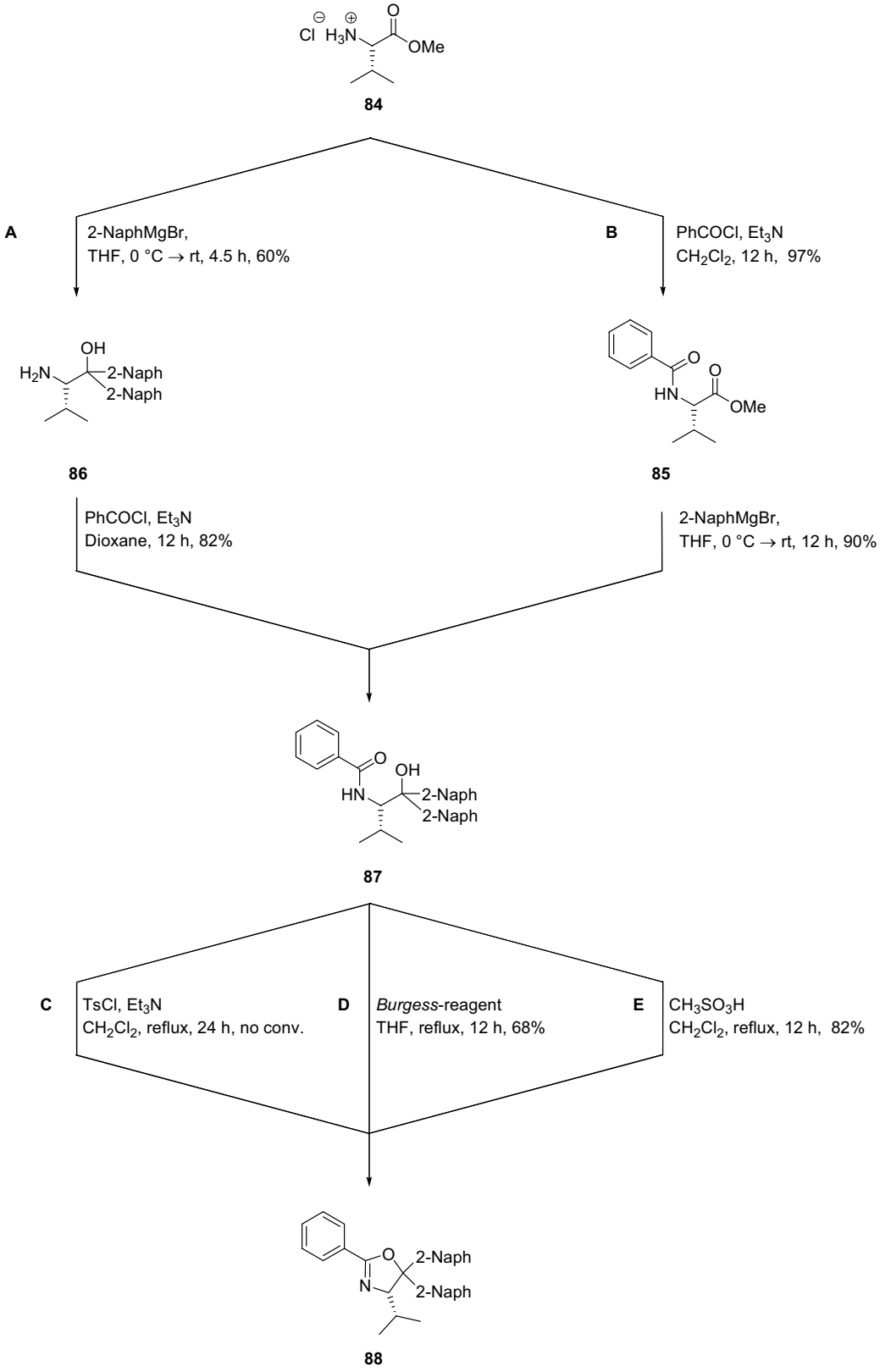
Figure 32.

The synthesis of PHOX ligands is usually achieved by the formation of an aryl-oxazoline **82** and subsequent preparation of the corresponding phosphorous derivative **83** by substitution. There exist several methods for preparing oxazoline rings[59] and the chiral variants are usually synthesized from the chiral pool of natural amino acids. The most common methods involve four one step procedures[60] and a two step procedure[61] (Scheme 17).



Scheme 17.

The first step of the synthesis of chiral C5-disubstituted oxazolines requires the formation of the amide **87**. This can be achieved by following either pathway **A** or **B** which differ only in

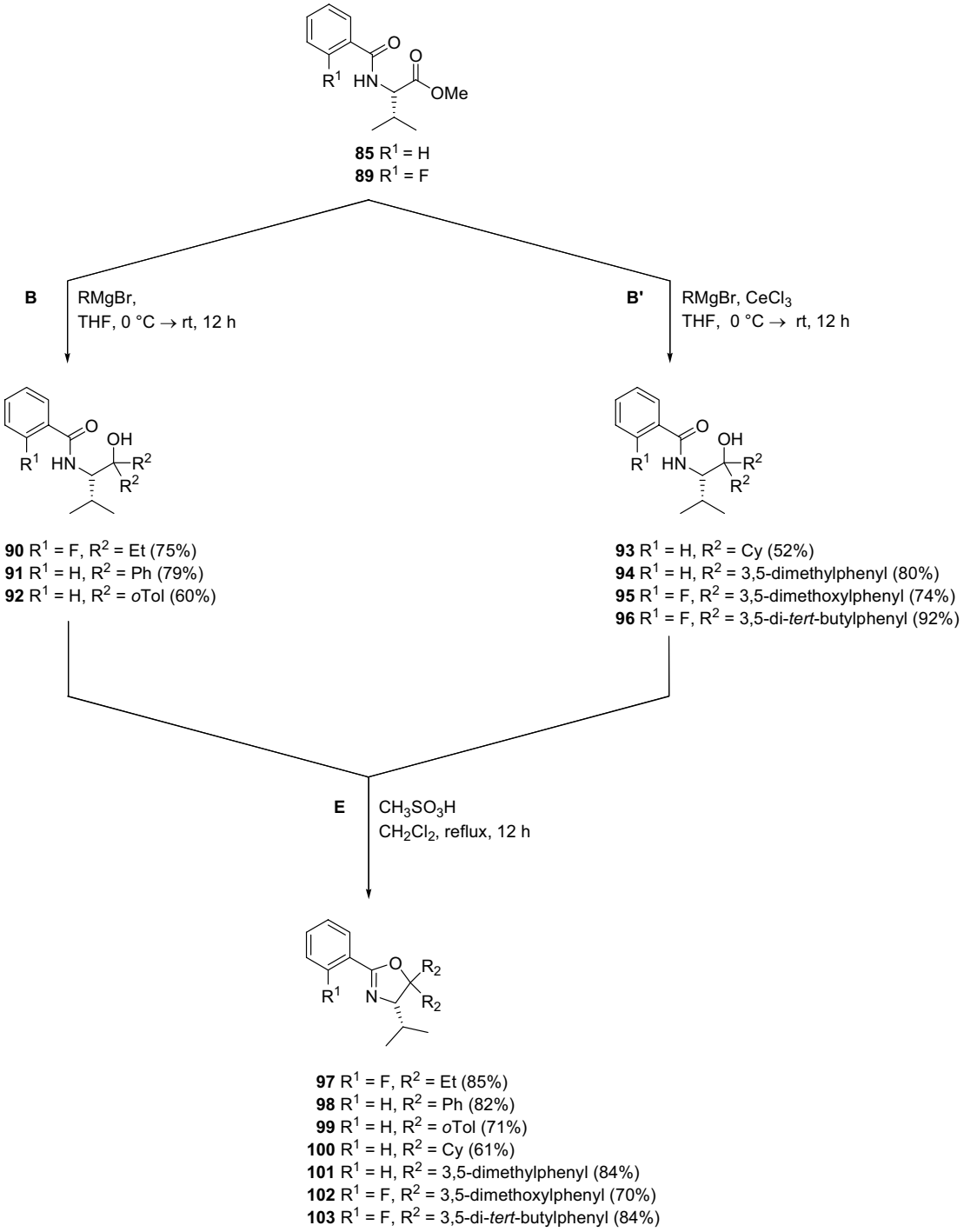


Scheme 18.

the sequence of the steps. While pathway **A** converts L-valin methyl ester **84** to the corresponding tertiary alcohol **86** by the appropriate *Grignard* reagent and subsequently forms the amide **87**, in pathway **B** the reactions are performed in the opposite order. Reaction sequence **B** is more convenient since the isolation and handling of amide **85** is easier in contrast to the alternative amino alcohol **86**. In addition, the remarkable difference between the overall yields of 49% and 87% for pathway **A** and **B**, respectively, also favours the latter synthetic sequence.

Subsequent formation of the oxazoline **88** by use of tosylchloride[62] failed presumably due to the difficulty in transforming a sterically hindered tertiary alcohol into the sulfonate (Scheme 18, method **C**). The application of the *Burgess* reagent[63] led to the desired product **88** (Scheme 18, method **D**) but the most efficient ring closing reaction was achieved by intramolecular condensation using methanesulfonic acid[64] under azeotropic removal of water (Scheme 18, method **E**). This was confirmed by the cyclization reaction of the amides bearing two phenyl- or cyclohexyl groups at the tertiary alcohol carbon. The phenyl substituted oxazoline was formed with a yield of 65% using the *Burgess* reagent but with a yield of 82% if methanesulfonic acid was used. In the case of the cyclohexyl substituted oxazoline no product could be isolated by employing method **D** whereas a yield of 61% was obtained following method **E**.

The efficient synthesis of 2-phenyloxazoline **88** following pathway **B** and method **E** resulted in an overall yield of 72% and did not require further optimization.[65] Based on this synthetic sequence methyl-[65], ethyl-, propyl-[65], phenyl-, and *ortho*-tolyl-substituents were introduced to amide **85** or **89** with yields ranging from 60% to 79% (Scheme 19). The preparation of tertiary alcohols by the use of sterically more demanding *Grignard* reagents like cyclohexyl- or isopropylmagnesiumbromide[65] was only possible in the presence of cerium chloride (Scheme 19, pathway **B'**).[66] The products were isolated with yields of 52% respectively 68%. Imamoto[67] stated that cerium chloride activates the carbonyl group by coordination whereas Colon[68] claimed that transmetalation generates a more nucleophilic species. In the absence of an activating reagent only the corresponding ketone could be isolated. 3,5-dimethylphenyl-, 3,5-dimethoxyphenyl- and 3,5-di-*tert*-butoxyphenyl-substituents were also introduced by the "activation process" expecting higher yields than if the reaction would have been done in the conventional way. Cyclization of the tertiary alcohols **90**-**96** to the 2-phenyloxazolines **97**-**103** proceeded with yields ranging from 61% to 85%.



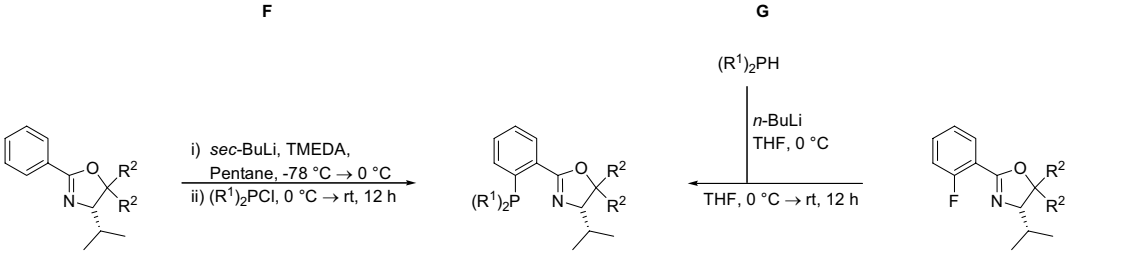
Scheme 19.

The final PHOX ligands **41, 64,** and **70-79** were obtained by either *ortho*-lithiation of the corresponding 2-phenyloxazolines **88** and **98-101** with *sec*-butyllithium/TMEDA in pentane and subsequent treatment with chlorodiarylphosphines[60b](method **F**, Scheme 20) or nucleophilic substitution by the treatment of the 2-(2-fluorophenyl)oxazolines **97, 102** and **103** with a diarylphosphide[61](method **G**, Scheme 20).

The 2-phenyloxazolines **88** and **98-101** were easily transformed to 2-(2-phosphinoaryl)oxazolines **41, 64 and 72-77** by the appropriate commercially available chlorodiarylphosphines using method **F** (Scheme 20). However, the purification of the crude product by column chromatography was usually quite demanding since unreacted phenyloxazolines, phosphino-oxazolines and side-products have very similar R_f values.

The introduction of the phosphino group by the reaction of the oxazolines **97, 102** and **103** with lithium diarylphosphide was very clean, allowing easy purification of the crude product. However, the use of method **G** required the preparation of the phosphane moiety[69] which is not commercially available.

A selective introduction of the phosphane group is not possible by pathway **F** if the 2-phenyloxazoline bears two 3,5-dimethoxyphenyl groups at the C5 position of the oxazoline moiety. The *ortho*- and especially the *para*-position of the 3,5-dimethoxyphenyl group are prone to lithiation and subsequent reaction with the electrophilic phosphorous reagent. Presumably also a simple electrophilic aromatic substitution can take place at the formerly mentioned positions. On this account the introduction of the phosphane moiety was realized by pathway **G**.



100 R^2 = Cy
98 R^2 = Ph
88 R^2 = 2-Naph
99 R^2 = *o*Tol
101 R^2 = 3,5-dimethylphenyl

70 R^1 = Ph, R^2 = Et 68% (42%)[1]
71 R^1 = *o*Tol, R^2 = Et 55% (34%)[1]
72 R^1 = *o*Tol, R^2 = Cy 52% (16%)[1]
41 R^1 = Ph, R^2 = Ph 80% (50%)[1]
64 R^1 = *o*Tol, R^2 = Ph 73% (46%)[1]
73 R^1 = Ph, R^2 = 2-Naph 71% (51%)[1]
74 R^1 = *o*Tol, R^2 = 2-Naph 70% (50%)[1]
75 R^1 = 3,5-dimethylphenyl, R^2 = 2-Naph 58% (42%)[1]
76 R^1 = *o*Tol, R^2 = *o*Tol 69% (23%)[1]
77 R^1 = *o*Tol, R^2 = 3,5-dimethylphenyl 84% (55%)[1]
78 R^1 = *o*Tol, R^2 = 3,5-dimethoxyphenyl 53% (27%)[1]
79 R^1 = *o*Tol, R^2 = 3,5-di-*tert*-butylphenyl 54% (40%)[1]

[1] total yield over 4 steps

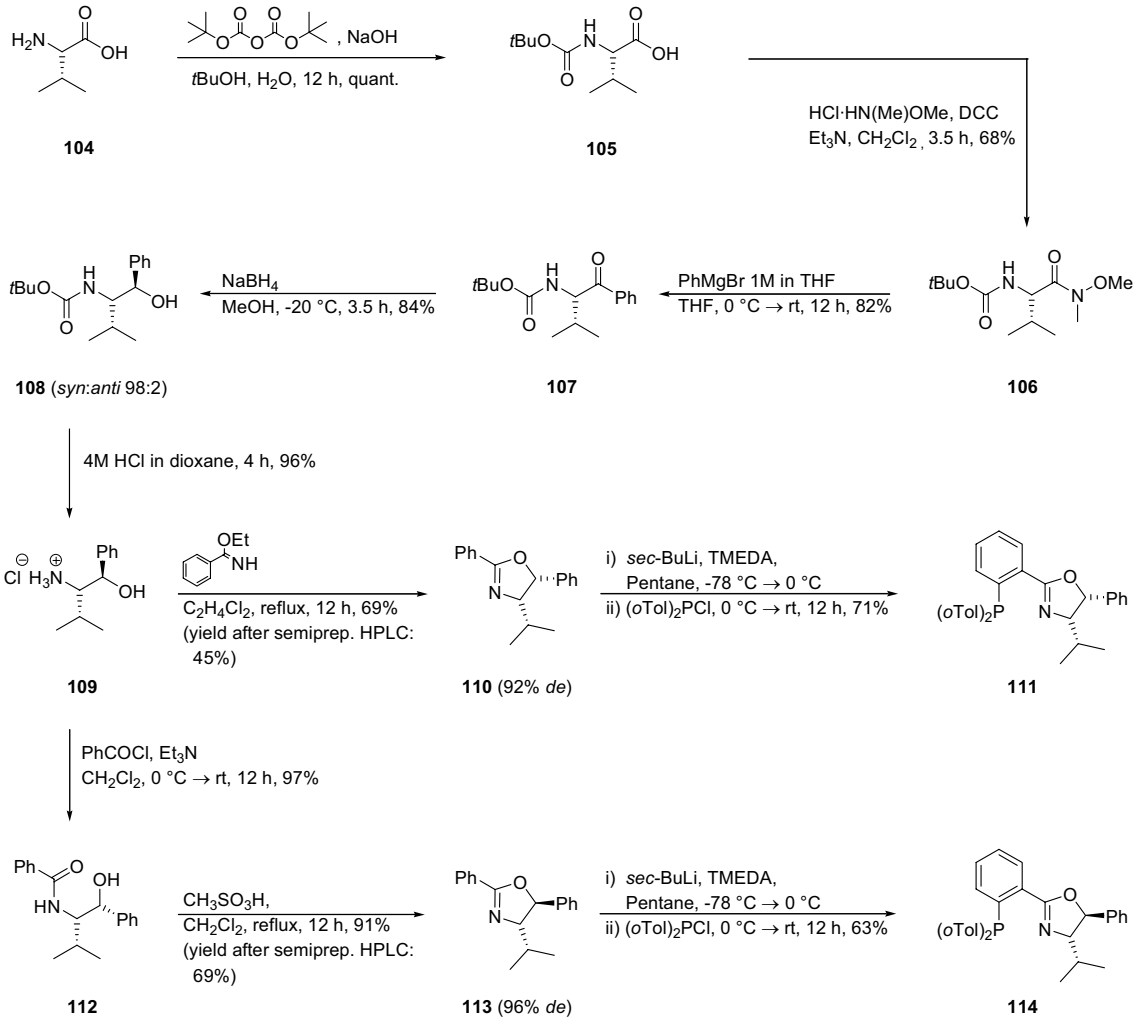
97 R^2 = Et
102 R^2 = 3,5-dimethoxyphenyl
103 R^2 = 3,5-di-*tert*-butylphenyl

Scheme 20.

The C5-disubstituted PHOX ligands **41, 64** and **70-79** can be efficiently synthesized following pathway **B**, method **E** and method **F** or **G**. The yield over the four step synthetic pathway reaches from 16% to 55% as illustrated in Scheme 20.

6.3 Synthesis of Phosphinooxazoline Ligands Bearing Two Chirality Centers at the Oxazoline Unit

The (4*S*,5*R*)- **111** and (4*S*,5*S*)-PHOX **114** ligands, prepared by the synthetic pathway illustrated in Scheme 21, were designed to examine the influence of a second stereocenter at the oxazoline unit on asymmetric induction in comparison to the analogous C5-disubstituted PHOX ligand **64**.



Scheme 21.

Boc-protection[70] of L-valine **104** and subsequent reaction with *O*,*N*-dimethylhydroxylamine led to the formation of the *Weinreb* amide[71] **106**. The *N*-methoxy-*N*-methylamide **106** has the beneficial property to react cleanly with phenylmagnesium bromide to ketone **107** without producing a tertiary alcohol even if 2.5 equivalents of the *Grignard* reagent were used. The reduction of the aminoketone **107** with sodium borohydride led to formation of the

boc-protected amino alcohol **108** with a *syn*:*anti* ratio of 98:2. This result was in accordance to the data reported by Zhou *et al*.[72] With regard to the following reaction steps, which could further shift the diastereomeric ratio, it was planned to separate the diastereomers at the latest possible step before the introduction of the phosphorous group, namely at the stage of the 2-phenyloxazolines **110** and **113**. Deprotection of the amino group was achieved with a 4M HCl-solution in dioxane whereas reagents like trifluoroacetic acid or a 1% HF-solution failed to react.

Conversion of the amino alcohol **109** with ethyl iminobenzoate yielded the (4*S*,5*R*)-4-isopropyl-2,5-diphenyl-4,5-dihydrooxazole **110.**[60a] Although the reaction proceeded with retention of configuration, the product could be isolated with a diastereoselectivity of only 92%. Separation of the diastereomers by semipreparative HPLC provided the pure compound **110**.

The C5-diastereomeric (4*S*,5*S*)-4-isopropyl-2,5-diphenyl-4,5-dihydrooxazole **113** was obtained by a two step procedure. Upon formation of the amide **112** the cyclization to the oxazoline **113** was achieved with methanesulfonic acid.[64a] The reaction took place under inversion of the configuration. The product could be isolated with a diastereoselectivity of 96% and was likewise purified by semipreparative HPLC.

The final PHOX ligands **111** and **114** were obtained by *ortho*-lithiation of the 2-phenyloxazolines **110** and **113** with *sec*-butyllithium/TMEDA in pentane and subsequent treatment with chloro-di-*ortho*-tolylphosphines.[60b]

The synthesis of the (4S,5R)-4-isopropyl-2,5-diphenyl-4,5-dihydrooxazole **111** and the C5-diastereomeric (4S,5S)-4-isopropyl-2,5-diphenyl-4,5-dihydrooxazole **114** is straightforward and provides the products with overall yields of 13% over 7 steps (**111**) and 19% over 8 steps (**114**), respectively. The replacement of the disadvantageous HPLC separation of the diastereomers **110** and **113** by crystallization would improve the synthetic ease of the pathway. Upon this optimization it would represent a versatile method to synthesize PHOX ligands with a second stereocenter at the oxazoline unit.

Chapter 7

Optimization of the Ligand Structure for Ag(I)-Catalyzed [3+2] Cycloadditions

7 Optimization of the Ligand Structure for Ag(I)-Catalyzed [3+2] Cycloadditions

7.1 Introduction

Preliminary results of the ligand screening for the Ag(I)-catalyzed [3+2] cycloaddition reaction showed especially for the PHOX ligand a strong influence of its substitution pattern on asymmetric induction. Thus, it was intended to investigate this issue in greater detail. For this purpose the influence of different substituents at the phosphorous atom, the phenyl backbone and the oxazoline moiety on stereoselectivity of the reaction were examined (Figure 33). The ligands used for these investigations were derived from the Pfaltzs' group ligand library or were synthesized as previously described (Chapter 6).

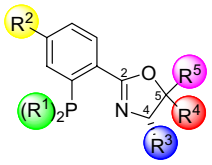
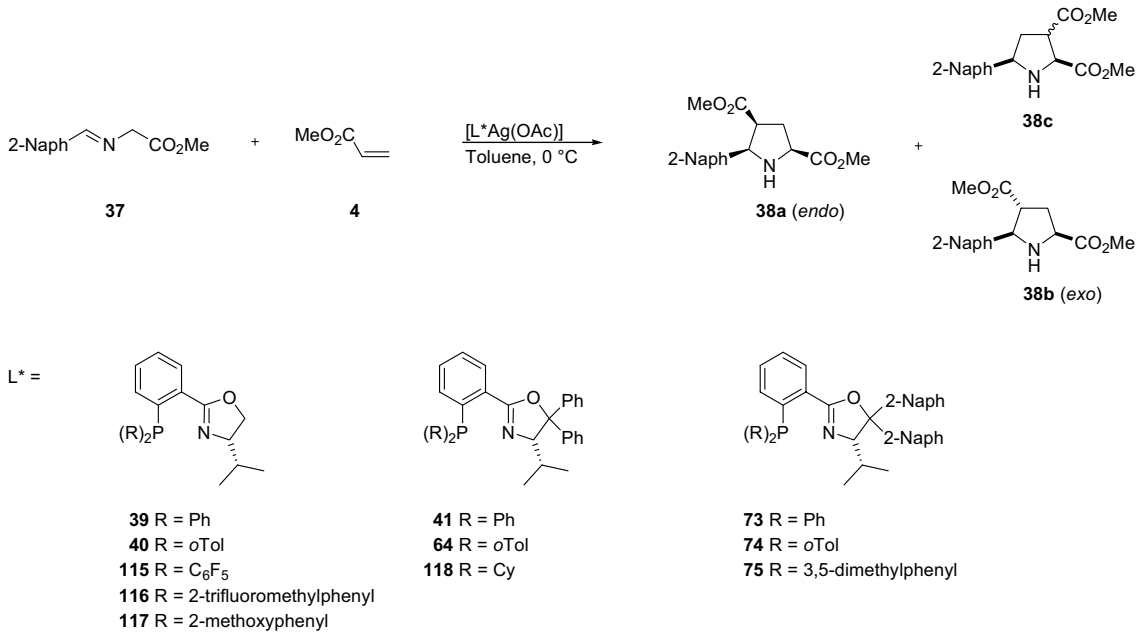


Figure 33.

7.2 Influence of Different Substituents at the Phosphorous Atom of the PHOX Ligand

PHOX ligands **39**-**41**, **64**, **73**-**75**, **115**-**118** with different substituents at the phosphorous atom were applied to the reaction illustrated in Scheme 22. The results in Table 12 display a remarkable influence of these groups on the stereoselectivity of this reaction and the reactivity of the catalysts.



Scheme 22.

The introduction of sterically more demanding and electron-rich 2-methoxyphenyl groups (**117**) at the phosphorous atom of the ligand was not advantageous, as it led to a lower reaction rate, *endo*:*exo* selectivity and enantioselectivity than if the reaction was performed with the reference PHOX ligand **39** (Scheme 22 and Table 12, entry 5). Pentafluorophenyl and 2-trifluoromethylphenyl substituents prevented complexation with AgOAc (Table 12, entries 3 and 4) and a silver mirror could be observed on the reaction flask after a reaction time of 12 h.

The replacement of the phenyl groups of **39** by sterically more demanding *ortho*-tolyl substituents improved the enantioselectivity regardless if the ligand was carrying substituents at the C5 position of the oxazoline ring or not (Table 12, compare entries 1, 7 and 10 with 2, 8 and 11). On the other hand the *endo*:*exo* selectivity and the regioselectivity decreased whereas the activity of the catalyst stayed the same. Exchange of the *ortho*-tolyl groups by 3,5-dimethylphenyl-substituents improved the reactivity, regioselectivity and

endo:*exo* selectivity (Table 12, compare entries 11 and 12) but the enantioselectivity was lower than with the *ortho*-tolyl substituted PHOX ligand **74**.

The aliphatic cyclohexyl groups had a comparable effect on enantioselectivity to *ortho*-tolyl groups but a disadvantageous effect on *endo*:*exo* selectivity, regioselectivity and reactivity of the catalyst (Table 12, compare entries 7, 8 and 9).

Table 12.

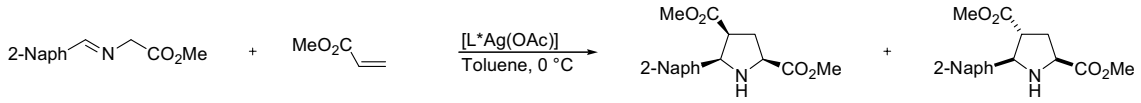
Entry	**L***	**t** (h)	**Yield** (%)[a]	**38a : 38b**[b]	**38a : 38c**[b]	***ee*** (%)[c] (**38a**)
1	**39**	5	95	>40 : 1	>40 : 1	29 (+)
2	**40**	8	93	>40 : 1	>40 : 1	45 (+)
3	**115**	12	-	-	-	-
4	**116**	12	-	-	-	-
5	**117**	8	24[d]	9 : 1	>40 : 1	10 (+)
7	**41**	7	86	>40 : 1	>40 : 1	49 (+)
8	**64**	7	90	40 : 1	35 : 1	65 (+)
9	**118**	7	80	24 : 1	30 : 1	62 (+)
10	**73**	7	78	>40 : 1	>40 : 1	17 (+)
11	**74**	6	81	26 : 1	15 : 1	60 (+)
12	**75**	6	87	>40 : 1	39 : 1	49 (+)

[a] After column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
[d] Conversion: Determined by ^{1}H NMR.
Reaction conditions: AgOAc (3 mol%), ligands **39**-**41**, **64**, **73**-**75**, **115**-**118** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

It was clear that *ortho*-tolyl substitutents had the most beneficial effect on the reaction. The enantioselectivity reached the highest value of this serie and was accompanied by an acceptable loss of reactivity, *endo*:*exo* selectivity and regioselectivity in comparison to the reference ligand **39**.

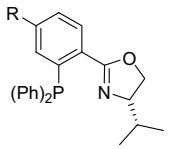
7.3 Influence of Different Substituents at the Phenyl Backbone of the PHOX Ligand

The influence of different substituents at the phenyl backbone of the PHOX ligand on the reaction of Scheme 23 was briefly investigated. Structural variation was limited to the introduction of a hydroxy- and a silyloxy-group at the *para* position of the phenyl backbone (Scheme 23, structures **119** and **120)**.



37 **4** **38a** (*endo*) **38b** (*exo*)

L* =



39 R = H
119 R = OH
120 R = OTBDMS

Scheme 23.

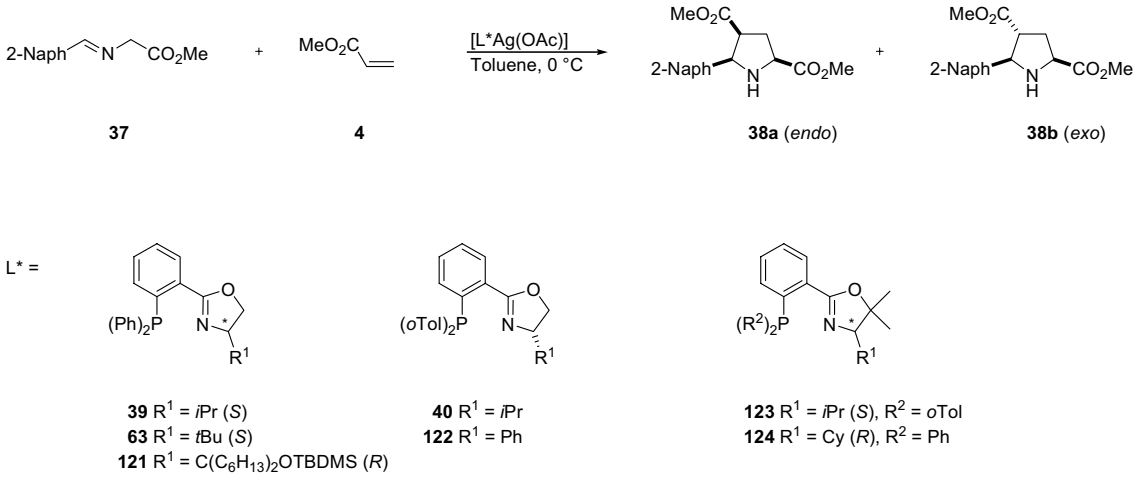
The results in Table 13 show that electron donating groups at the phenyl backbone slow down the reaction similar to the situation previously discussed for 2-methoxyphenyl substituents at the phosphorous atom. In addition, ligands **119** and **120** induced lower enantioselectivities than the unsubstituted ligand **39**.

Table 13.

Entry	L*	t (h)	Conversion (%)[a]	38a : 38a[a]	*ee* (%)[b] (38a)
1	**39**	5	>95	>40 : 1	29 (+)
2	**119**	24	traces	n.d.	12 (+)
3	**120**	8	65	>40 : 1	20 (+)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligand **39**, **119**, **120** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

7.4 Influence of Different Substituents at the C4 Position of the Oxazoline Ring



Scheme 24.

PHOX ligands carrying an isopropyl substituent at the C4 position of the oxazoline ring **39**, **40** and **123** were compared with the corresponding ligands bearing a *tert*-butyl- **63**, a cyclohexyl- **124** or a phenyl-substituent **122** at this position. Furthermore the L-serine derived PHOX ligand **121** was applied to the reaction illustrated in Scheme 24.

Table 14.

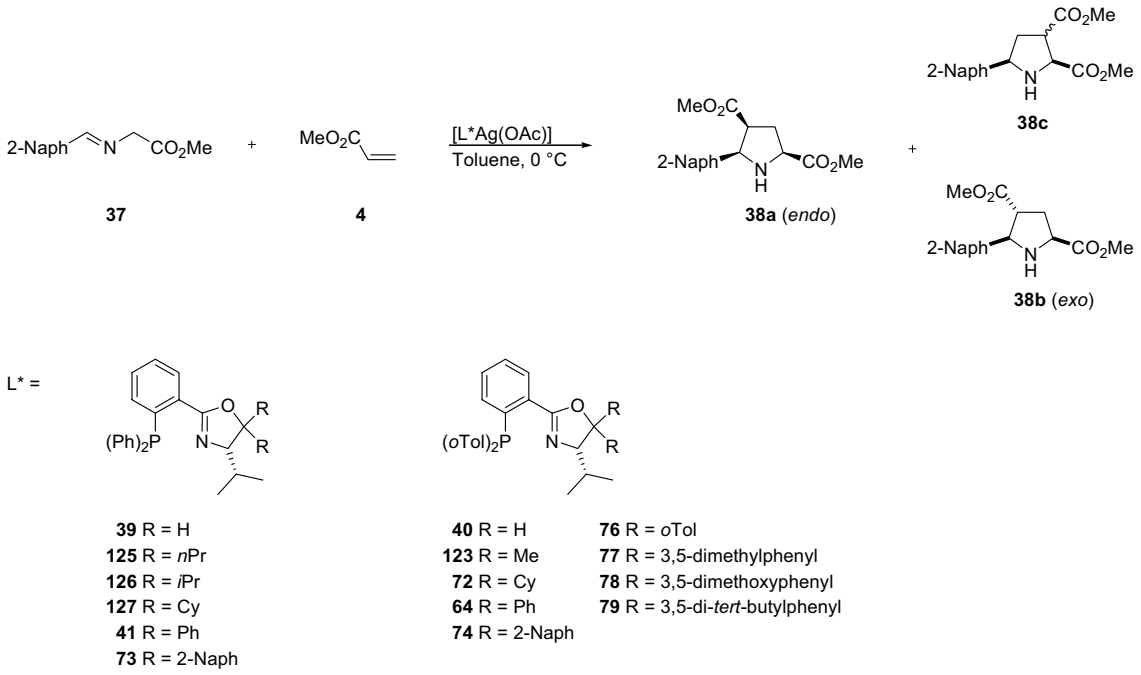
Entry	L*	t (h)	Conversion (%)[a]	38a : 38b[a]	*ee* (%)[b] (**38a**)
1	**39**	5	>95	>40 : 1	29 (+)
2	**63**	6	>95	>40 : 1	27 (+)
3	**121**	7	>95	>40 : 1	48 (–)
4	**40**	8	>95	>40 : 1	45 (+)
5	**122**	7	>95	>40 : 1	15 (+)
6	**123**	8	49	>40 : 1	62 (+)
7	**124**	7	81	>40 : 1	23 (–)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligands **39**, **40**, **121**-**124** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

The *tert*-butyl group had almost no effect on the enantioselectivity of the reaction (Table 14, compare entries 1 and 2) whereas the cyclohexyl and the phenyl substituted ligands **124** and **122** reduced the enantioselectivity strongly (Table 14, compare entries 4 with 5 and 6 with 7). The sterically demanding L-serine-derived ligand **121** had a positive influence on the asymmetric induction with regard to the reference ligand **39** (Table 14, compare entries 1 and 3). A comparable positive effect on asymmetric induction was obtained if the phenyl group at the phosphorous atom was replaced by an *ortho*-tolyl group (Table 14, compare entries 1 with 3 and 1 with 4).

7.5 Influence of Different Substituents at the C5 Position of the Oxazoline Ring

PHOX ligands bearing various aliphatic or aryl substituents at the C5 position of the oxazoline ring were applied to the [3+2] cycloaddition reaction outlined in Scheme 25.



39 R = H
125 R = *n*Pr
126 R = *i*Pr
127 R = Cy
41 R = Ph
73 R = 2-Naph

40 R = H
123 R = Me
72 R = Cy
64 R = Ph
74 R = 2-Naph

76 R = *o*Tol
77 R = 3,5-dimethylphenyl
78 R = 3,5-dimethoxyphenyl
79 R = 3,5-di-*tert*-butylphenyl

Scheme 25.

In general the enantioselectivity is positively influenced by substituents at the C5 position of the oxazoline ring whereas the reactivity decreases. For ligands bearing *ortho*-tolyl substituents at the phosphorous atom, the increase of the steric bulk at the C5 position of the oxazoline moiety usually led to a decrease of the *endo*:*exo* selectivity and the formation of the opposite regioisomer **38c**.

The results obtained with ligands possessing aliphathic substituents at the C5 position of the oxazoline ring did not follow a clear trend. Cyclohexyl, methyl and *n*-propyl groups had a more positive effect on the enantioselectivity than if the ligand incorporated isopropyl substituents (Table 15, compare entries 2 and 3 with 4 and 8). Ligand **125** stood out since it gave the product with low *endo*:*exo* selectivity whereas comparable ligands **39**, **41**, **73**, **126** and **127** also bearing phenyl substitutents at the phosphorous atom typically induced almost perfect *endo* selectivity.

Table 15.

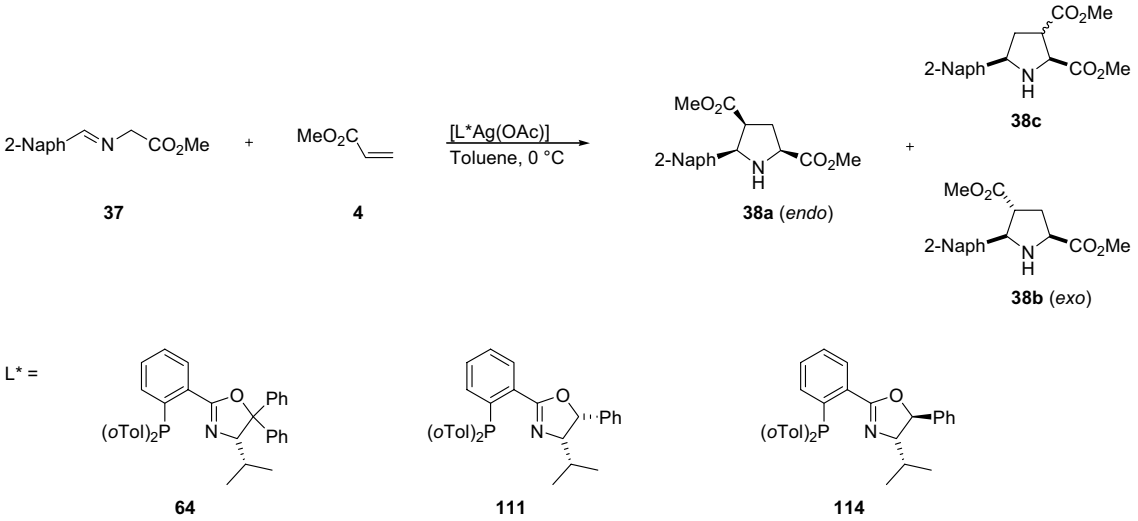
Entry	L*	t (h)	Yield (%)[a]	38a : 38b[b]	38a : 38c[b]	*ee* (%)[c] (38a)
1	**39**	5	95	>40 : 1	>40 : 1	29 (+)
2	**125**	8	57	>24 : 1	n.d.	43 (+)
3	**126**	7	86	>40 : 1	>40 : 1	32 (+)
4	**127**	7	88	>40 : 1	>40 : 1	53 (+)
5	**41**	7	86	>40 : 1	>40 : 1	49 (+)
6	**73**	7	78[d]	>40 : 1	>40 : 1	17 (+)
7	**40**	8	93	>40 : 1	>40 : 1	45 (+)
8	**123**	8	49	24 : 1	24 : 1	62 (+)
9	**72**	9	40	9 : 1	9 : 1	62 (+)
10	**64**	7	90	40 : 1	>40 : 1	65 (+)
11	**74**	6	81	26 : 1	15 : 1	60 (+)
12	**76**	6	56	12 : 1	12 : 1	67 (+)
13	**77**	6.5	73	14 : 1	14 : 1	81 (+)
14	**78**	6	91	18 : 1	16 : 1	74 (+)
15	**79**	7	80	>40 : 1	>40 : 1	84 (+)

[a] After column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
[d] Conversion: Determined by ^{1}H NMR.
Reaction conditions: AgOAc (3 mol%), ligands of Scheme 25 (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

Aryl substituents tend to have a more positive effect on asymmetric induction than their aliphatic counterparts. Since phenyl groups had a promising effect on the enantioselectivity of the reaction, this substitution pattern was somewhat varied. The introduction of an *ortho*-tolyl substituent at the C5 position of the oxazoline ring increased the enantioselectivity while the regio- and the *endo*:*exo* selectivity as well as the yield dropped (Table 15, compare entry 10 with 12). The 3,5-dimethylphenyl-substituted ligand **77** formed a quite active Ag(I) complex which induced even higher enantioselectivity and a comparatively improved *endo*:*exo*- and regioselectivity (Table 15, compare entry 12 with 13). The Ag(I) complex of ligand **78** incorporating 3,5-dimethoxyphenyl substituents was even more reactive and formed the product with higher *endo*- and regioselectivity but with lower enantiomeric excess (Table 15, compare entry 13 with 14). Introduction of 3,5-di-*tert*-butylphenyl groups at the C5 position of the oxazoline ring led to the most efficient PHOX ligand **79** to date. The cycloaddition product **38a** was formed with an enantioselectivity of 84%, high *endo*:*exo* selectivity and a yield of 80% after a reaction time of 7 hours.

7.5.1 Influence of an Additional Chirality Center at the C5 Position of the PHOX Ligand

The PHOX ligands **111** and **114** were synthesized to investigate the influence of a second stereocenter on the asymmetric induction of the reaction illustrated in Scheme 26. Additionally the steric influence of the substituents *cis* respectively *trans* to the isopropyl group at the oxazoline ring on the outcome of the reaction was examined.



Scheme 26.

A comparison of the results generated by the C5-disubstituted ligand **64** and the ligands bearing a second stereocenter at the oxazoline ring **111** and **114** showed that the additional stereocenter did not have a beneficial effect on enantioselectivity (Table 16, compare entries 1 with 2 and 3).

Table 16.

Entry	L*	t (h)	Yield (%)[a]	38a : 38b[b]	38a : 38c[b]	*ee* (%)[c] (38a)
1	**64**	7.0	90	40 : 1	>40 : 1	65 (+)
2	**111**	4.5	85	>40 : 1	>40 : 1	52 (+)
3	**114**	4.5	84	30 : 1	26 : 1	45 (+)

[a] After column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligand **64**, **111**, **114** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (**37**) (1.0 eq), toluene, 0 °C.

7.6 Conclusion

Studies of the influence of different substitution patterns at the PHOX ligand on the reaction rate and asymmetric induction of the [3+2] cycloaddition demonstrated several trends. Sterically more demanding alkyl-substituted aryl groups at the phosphorous atom of the ligand had the most beneficial effect on the reaction. The application of ligands with an unsubstituted phenyl backbone led in contrast to the substituted phenyl analog to superior results. An L-serine-derived and functionalized PHOX ligand gave higher enantioselectivity than its isopropyl-substituted analog. Despite this fact the focus was laid on the L-valine derived PHOX ligand since C5-substituted ligands are easily accessible from this amino acid. Studies concerning the substituents at the C5 position demonstrated that *meta* substituted phenyl groups had a very positive effect on reaction rate and asymmetric induction.

Chapter 8

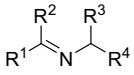
Scope of the Asymmetric Ag(I)-Catalyzed Intermolecular [3+2] Cycloaddition

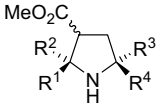
8 Scope of the Asymmetric Ag(I)-Catalyzed Intermolecular [3+2] Cycloaddition

In the course of the optimization of the PHOX ligands' substitution pattern differently substituted azomethine ylides and dipolarophiles were applied to the [3+2] cycloaddition. The variations should provide an indication of the limitation of the reaction.

8.1 Application of Differently Substituted Azomethine Ylides

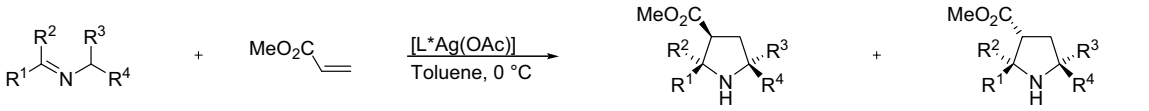
The substituents introduced to the imine system illustrated in Scheme 27 allowed the investigation of different features in comparison to the reference imine **37**. Imines **128**-**131** should demonstrate the effect of electron withdrawing and electron donating substituents on the outcome of the reaction. The influence of sterically more demanding 1,3-dipoles was examined by replacing the methyl ester (**37**) with a tertiary butyl ester (**134**), the incorporation of a substituent alpha to the imine (**133**) or the formation of a ketimine (**132**). The substitution of the ester group of substrates **37** and **131** by a pyridine (**135**) or a phenyl (**136**) group was chosen to study the importance of the coordination of this group to the silver ion.





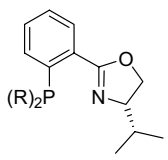
128 R^1 = *p*FPh, R^2 = R^3 = H, R^4 = CO_2Me
129 R^1 = *p*BrPh, R^2 = R^3 = H, R^4 = CO_2Me
130 R^1 = *p*MeOPh, R^2 = R^3 = H, R^4 = CO_2Me
37 R^1 = 2-Naph, R^2 = R^3 = H, R^4 = CO_2Me
131 R^1 = Benzo[1,3]dioxol, R^2 = R^3 = H, R^4 = CO_2Me
132 R^1 = Ph, R^2 = Ph, R^3 = H, R^4 = CO_2Me
133 R^1 = Ph, R^2 = H, R^3 = *i*Pr, R^4 = CO_2Me
134 R^1 = 2-Naph, R^2 = R^3 = H, R^4 = CO_2*t*Bu
135 R^1 = 2-Naph, R^2 = R^3 = H, R^4 = Py
136 R^1 = Benzo[1,3]dioxol, R^2 = R^3 = H, R^4 = Ph

137 R^1 = *p*FPh, R^2 = R^3 = H, R^4 = CO_2Me
138 R^1 = *p*BrPh, R^2 = R^3 = H, R^4 = CO_2Me
139 R^1 = *p*MeOPh, R^2 = R^3 = H, R^4 = CO_2Me
38 R^1 = 2-Naph, R^2 = R^3 = H, R^4 = CO_2Me
140 R^1 = Benzo[1,3]dioxol, R^2 = R^3 = H, R^4 = CO_2Me
141 R^1 = Ph, R^2 = Ph, R^3 = H, R^4 = CO_2Me
142 R^1 = Ph, R^2 = H, R^3 = *i*Pr, R^4 = CO_2Me
143 R^1 = 2-Naph, R^2 = R^3 = H, R^4 = CO_2*t*Bu
144 R^1 = 2-Naph, R^2 = R^3 = H, R^4 = Py
145 R^1 = Benzo[1,3]dioxol, R^2 = R^3 = H, R^4 = Ph

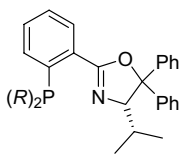


37, 128-136 + **4** → **38a, 137a-145a** (*endo*) + **38b, 137b-145b** (*exo*)

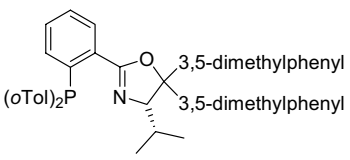
L* =



39 R = Ph
40 R = *o*Tol



41 R = Ph
64 R = *o*Tol



77

Scheme 27.

Table 17.

Entry	L*	1,3-Dipole	t (h)	Yield (%)[a]	*endo* : *exo*[b]	*ee* (%)(*endo*)[c]	*ee* (%)(*exo*)[c]
1[d]	**77**	**128**	6	69	9 : 1	65 (+)	n.d.
2	**39**	**129**	8	>95[e]	30 : 1	30 (+)	n.d.
3	**64**	**129**	7	82	7 : 1	50 (+)	n.d.
4	**77**	**129**	7	87	4 : 1	57 (+)	n.d.
5	**77**	**130**	12	43	n.d.	85[f]	n.d.
6	**39**	**37**	5	95	>40 : 1	29 (+)	n.d.
7	**40**	**37**	8	93	>40 : 1	45 (+)	n.d.
8	**64**	**37**	7	90	40 : 1	65 (+)	n.d.
9	**77**	**37**	6.5	73	14 : 1	81 (+)	n.d.
10	**39**	**131**	7	91[e]	>40 : 1	17 (+)	n.d.
11	**40**	**131**	7	85[e]	>40 : 1	17 (+)	n.d.
12	**64**	**131**	7	60	>40 : 1	47 (+)	n.d.
13[i]	**-**	**132**	12	-	-	-	-
14[i]	**-**	**133**	12	-	-	-	-
15	**40**	**134**	6.5	92[e]	>40 : 1	20 (+)	n.d.
16	**64**	**134**	6	68	13 : 1	41 (+)	n.d.
17	**39**	**135**	9	>95[e]	3 : 1	41[f]	16[f,g]
18	**40**	**135**	5.5	80[e]	1 : 1	7[f,h]	8[f]
19	**41**	**135**	4	96[e]	3 : 1	73[f]	25[f]
20	**64**	**135**	7	88[e]	1 : 2	52[f]	74[f]
21	**39**	**136**	7	-	-	-	-

[a] After column chromatography. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] 5 mol% of the catalyst was used. [e] Conversion: Determined by ^{1}H NMR. [f] Optical rotation not determined. [g] The opposite enantiomer was detected by chiral HPLC, with respect to the enantioselectivity found for the *exo* products under entry 18-20. [h] The opposite enantiomer was detected by chiral HPLC, with respect to the enantioselectivity found for the *endo* products under entry 17, 19 and 20.

[i] Reaction conditions: AgOAc (3 mol%), Et_3N (1.1 eq), methyl acrylate (**4**) (2.4 eq), 1,3-dipoles **132**, **133** (1.0 eq), CH_3CN, rt.

Reaction conditions: AgOAc (3 mol%), ligands **39**-**41**, **64**, **77** (3.3 mol%), methyl acrylate (**4**) (1.2 eq), 1,3-dipoles **37**, **128**-**131**, **134**-**136** (1.0 eq), toluene, 0 °C.

Electron-withdrawing substituents at the imine **128** and **129** did not affect the reactivity of the system in comparison to the reference imine **37** (Table 17, compare entries 1, 4 and 9), but the corresponding pyrrolidine products were formed with lower *endo*- and enantioselectivity.

Imines **130** and **131** bearing electron-donating groups usually reacted slower with the dipolarophile, with no effect on the *endo*:*exo* selectivity of the reaction (Table 17, compare entries 5 with 9 and 8 with 12). Depending on the particular substituent, higher or lower enantioselectivities were obtained in comparison to the reference imine **37**.

Starting from ketimine **132** and methyl acrylate (**4**) no reaction was observed applying 10 mol% of AgOAc (Table 17, entry 13). Although formation of the Michael-adduct might be expected, only starting material was recovered after 12 h reaction time.[29,30] Later Carretero *et al.* performed the reaction between the identical ketimine **132** and *N*-phenylmaleimide in the presence of 3 mol% of a Cu(I)-Fesulphos catalyst and isolated the desired product with good yields and enantioselectivity.[45c]

The incorporation of an isopropyl group at the α-position of the imine (**133**) was unfavourable (Table 17, entry 14). The reaction with methyl acrylate (**4**) did not proceed following the Lewis acid protocol (Table 17, footnote f). Schreiber *et al.* likewise applied the sterically less hindered iminoesters derived from leucine, phenylalanine and tryptophan to the [3+2] cycloaddition with *tert*-butyl acrylate. The corresponding pyrrolidine bearing a quaternary center at the C2 position could be isolated with moderate to excellent yields and good enantioselectivities.[48b]

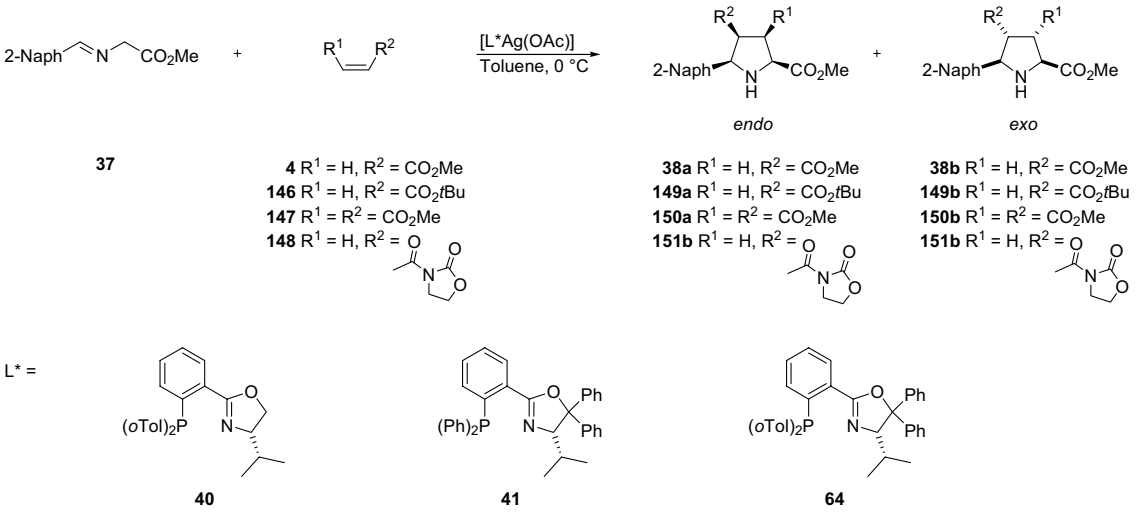
Increasing the steric bulk at the ester group of imine **37** by implementing a *tert*-butyl ester group in compound **134** decreased reactivity as well as selectivity (Table 17, compare entry 8 with 16).

The replacement of the ester group in imine **131** by a phenyl group led to a completely inactive 1,3-dipole **136** (Table 17, entry 21). This indicates that the coordination of the carbonyl oxygen of the ester group to the silver is crucial for the activation of the azomethine ylide since the phenyl group can not coordinate to the metal ion. The introduction of a pyridine moiety linked over the C2 atom should provide the possibility of coordination thus leading to an activated 1,3-dipole, and indeed conversion to the desired pyrrolidine product **144** was quite high (Table 17, entries 17-20). The 1,3-dipolar cycloaddition reaction using substrate **135** showed a somewhat unusual influence of the ligand substitution pattern on asymmetric induction. The exchange of the phenyl groups at the phosphorous atom by *ortho*-tolyl groups slowed down the reaction, increased the enantiomeric excess of the *exo* products and lowered the *endo* selectivity as well as the enantioselectivity of the

endo products (Table 17, compare entries 17 with 18 and 19 with 20). The decrease of the enantioselectivity of the *endo* product corresponds to an effect which is opposite to previous findings. However, the implementation of phenyl substituents at the C5 position of the oxazoline moiety had the expected effect on the outcome of the reaction (Table 17, compare entries 17 with 19 and 18 with 20). The pyrrolidine products were formed with higher enantiomeric excesses but slightly lower *endo*:*exo* selectivities and lower conversions.

8.2 Application of Differently Substituted Dipolarophiles

In order to study how steric and electronic factors influence the reaction the dipolarophiles **4, 146-148** illustrated in Scheme 28 were used as reactants.



Scheme 28.

The influence of different steric demands of the dipolarophile on the outcome of the cycloaddition (Scheme 28) could be easily examined by applying methyl acrylate **4** and *tert*-butyl acrylate **146** to the reaction since their electronic properties are similar. The larger steric bulk of the tertiary ester had a disadvantageous effect on asymmetric induction as well as on reaction rate (Table 18, compare entries 1 with 3 and 2 with 4). The use of the oxazolidinone dipolarophile **148** resulted in a similar effect (Table 18, compare entries 7 and 8).

Dimethyl maleate (**147**) representing the most electron poor dipolarophile of Scheme 28 was expected to react fastest with the azomethine ylide. Surprisingly, the formation of the corresponding pyrrolidine **150** was slower than if methyl acrylate (**4**) was used as the dipolarophile (Table 18, compare entries 1 with 5 and 2 with 6). However, the negative

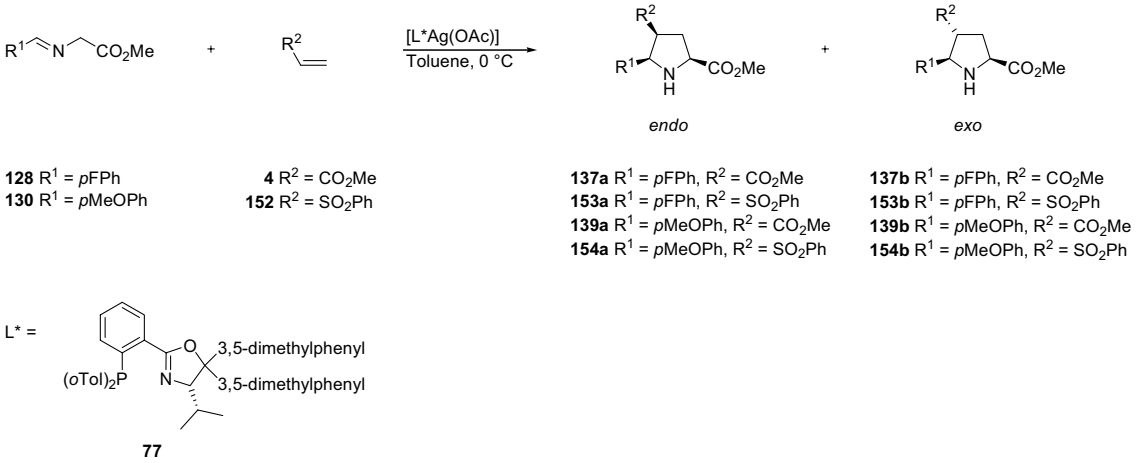
influence on asymmetric induction and reaction rate was not as strong as observed with *tert*-butyl acrylate **146** (Table 18, compare entries 3 with 5 and 4 with 6).

Table 18.

Entry	L*	Dipolarophile	t (h)	Yield (%)[a]	*endo* : *exo*[b]	*ee* (%)(*endo*)[c]
1	**41**	**4**	7	86	>40 : 1	49 (+)
2	**64**	**4**	7	90	40 : 1	65 (+)
3	**41**	**146**	12	84[d]	8 : 1	9 (+)
4	**64**	**146**	9	60	3 : 1	43 (+)
5	**41**	**147**	12	83	35 : 1	39 (+)
6	**64**	**147**	7	73	7 : 1	60 (+)
7	**40**	**4**	8	93	>40 : 1	45[e]
8	**40**	**148**	6	65[d]	n.d.	14[e]

[a] After column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
[d] Conversion: Determined by ^{1}H NMR.
[e] Optical rotation not determined.
Reaction conditions: AgOAc (3 mol%), ligands **40**, **41**, **64** (3.3 mol%), dipolarophiles **4, 146-148** (1.2 eq), (*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)-acetate (**37**) (1.0 eq), toluene, 0 °C.

Carretero and co-workers investigated the 1,3-dipolar cycloaddition of azomethine ylides with aryl vinyl sulfones.[45c] The desired pyrrolidine products were formed with complete *exo* selectivity and enantioselectivities of up to 85% by employing a Cu(I)-Taniaphos catalyst system. Brief studies using AgOAc instead of $Cu(CH_3CN)_4ClO_4$ in combination with various Fesulphos, Walphos and Taniaphos ligands showed that the silver catalyst system led to lower asymmetric induction. Interested by these results it was intended to apply phenyl vinyl sulfone **152** to our catalyst system.



Scheme 29.

The conversion of phenyl vinyl sulfone **152** with the electron poor as well as the electron rich phenyl imines **128** and **130** was realized with a catalyst derived from AgOAc and the PHOX ligand **77.** The results generated by these reactions were compared with the one of the corresponding reaction using methyl acrylate (**4)** instead of phenyl vinyl sulfone **152**.

The higher electron deficiency of the CC-double bond of the α,β-unsaturated sulfone **152** (Table 19, compare entries 1 and 2) presumably accelerated the cycloaddition with the electron-poor phenyl imine **128** since compound **153** was isolated with a higher yield than cycloproduct **137**. While the use of the vinyl ester **4** led to the preferential formation of the *endo* product with an enantioselectivity of 65%, the reaction with phenyl vinyl sulfone **152** preferentially led to the *exo* product with an enantiomeric excess of 88%. The latter result is superior to that of Carretero and co-workers obtained with their catalyst system (82% *ee*) for this reaction. Reduction of the catalyst loading from 5 to 3 mol% lowered the reaction rate and the enantioselectivity slightly, but the results were still superior to those of Carreteros' study (Table 19, compare entries 2 and 3).

Initial studies with the electron rich phenyl imine **130** showed that the cycloaddition with phenyl vinyl sulfone **152** is much faster than with the unsaturated ester **4** (Table 19, compare entries 4 with 5). In contrast to methyl acrylate (**4**), phenyl vinyl sulfone **152** reacted preferentially to the *exo* product but both products were formed with similar enantioselectivities. Carretero *et al*. isolated the pyrrolidine **154** with slightly higher enantiomeric excess (84% *ee*) but they used a higher catalyst loading (5 mol%).

Table 19.

Entry	1,3-Dipole	Dipolarophile	t (h)	Yield (%)[a]	*endo* : *exo*[b]	*ee* (%)[c] (*endo*)
1[d]	**128**	**4**	6	69	9 : 1	65 (+)
2[d]	**128**	**152**	6	90	1 : 10	88 (+)
3	**128**	**152**	6	80	1 : 10	86 (+)
4	**130**	**4**	12	43	n.d.	85[e]
5	**130**	**152**	6	83	1 : 14	82 (+)

[a] After column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
[d] 5 mol% of catalyst were used.
[e] Optical rotation not determined.
Reaction conditions: AgOAc (3 mol%), ligand **77** (3.3 mol%), dipolarophile **4**, **152** (1.2 eq), 1,3-dipoles **128**, **130** (1.0 eq), toluene, 0 °C.

8.3 Conclusion

The differently substituted azomethine ylides and dipolarophiles, which were applied to the [3+2] cycloaddition, provided an indication of the limits of the reaction.

Sterically more demanding 1,3-dipoles either could not be converted to the desired products or slowed down the reaction and the corresponding products were formed with lower *endo*:*exo* selelctivity and enantioselectivity. Variations of the substituents in the β-position of the imine demonstrated that, in addition to the coordination of the silver ion to the imine nitrogen, coordination to a second atom is also necessary to create an active 1,3-dipole. In the absence of such a second coordination site no reaction could be observed. Electron-deficient phenyl substituents at the imine did not affect the reaction rate but the substrates were transformed to pyrrolidines with lower selectivity. The electron-rich analogs reacted more slowly, but depending on their substituents they were converted to five-membered heterocycles with high enantioselectivities.

Dipolarophiles containing sterically more demanding groups were less reactive and gave lower selectivity. Phenyl vinyl sulfones, in contrast to vinyl esters, preferentially formed the *exo* products with high yields and enantioselectivity.

Chapter 9

Asymmetric Ag(I)-Catalyzed Intramolecular [3+2] Cycloadditions of Azomethine Ylides

9 Asymmetric Ag(I)-Catalyzed Intramolecular [3+2] Cycloadditions of Azomethine Ylides

9.1 Introduction

In the course of the investigations of intermolecular [3+2] cycloadditions the idea arose to apply the Ag(I)-PHOX system to the intramolecular variant of this reaction. This project was started by *Florentine Wahl*[73] in her diploma thesis.

The substrate of the intramolecular cycloaddition incorporates both the dipole and the dipolarophile what makes the reaction entropically more favourable. The dipolarophile can be connected to either the nitrogen or to one of the two carbon atoms of the azomethine ylide (Figure 34, **Type A** and **Type B**). Attachment to the carbon atom is more common and could basically lead to two regioisomeric products (Figure 34, **Type A**). Conformational constraints usually limit effective orbital overlap to such an extent that one regioisomer is much preferred over the other. Experimental data support this conclusion since almost all examples in which the dipolarophile is connected to a carbon atom of the azomethine ylide give the fused bicyclic amine product.[74] Cyclization of a substrate in which the dipolarophile is connected to the nitrogen atom gives necessarily a bridged bicyclic product (Figure 34, **Type B**).

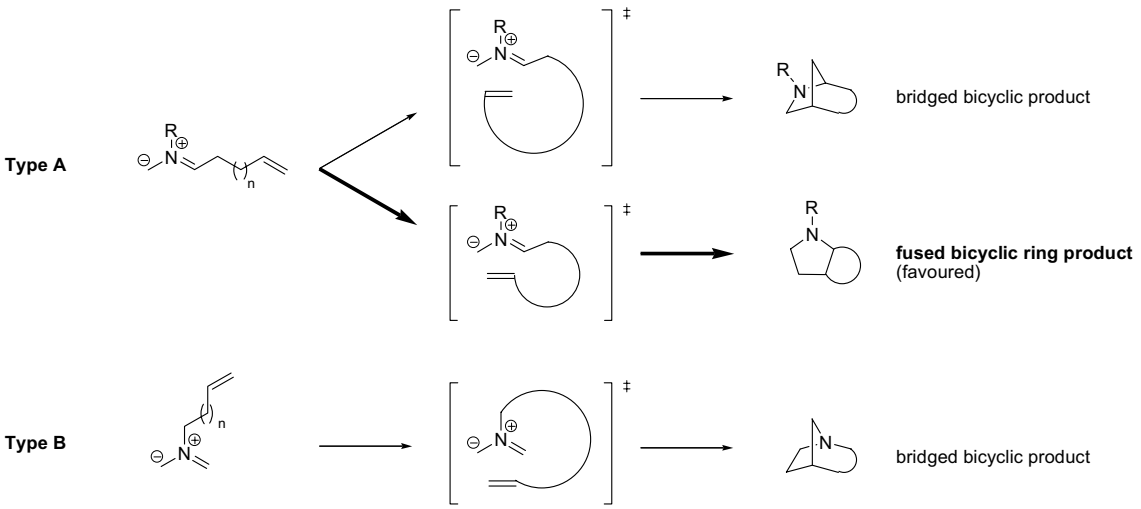
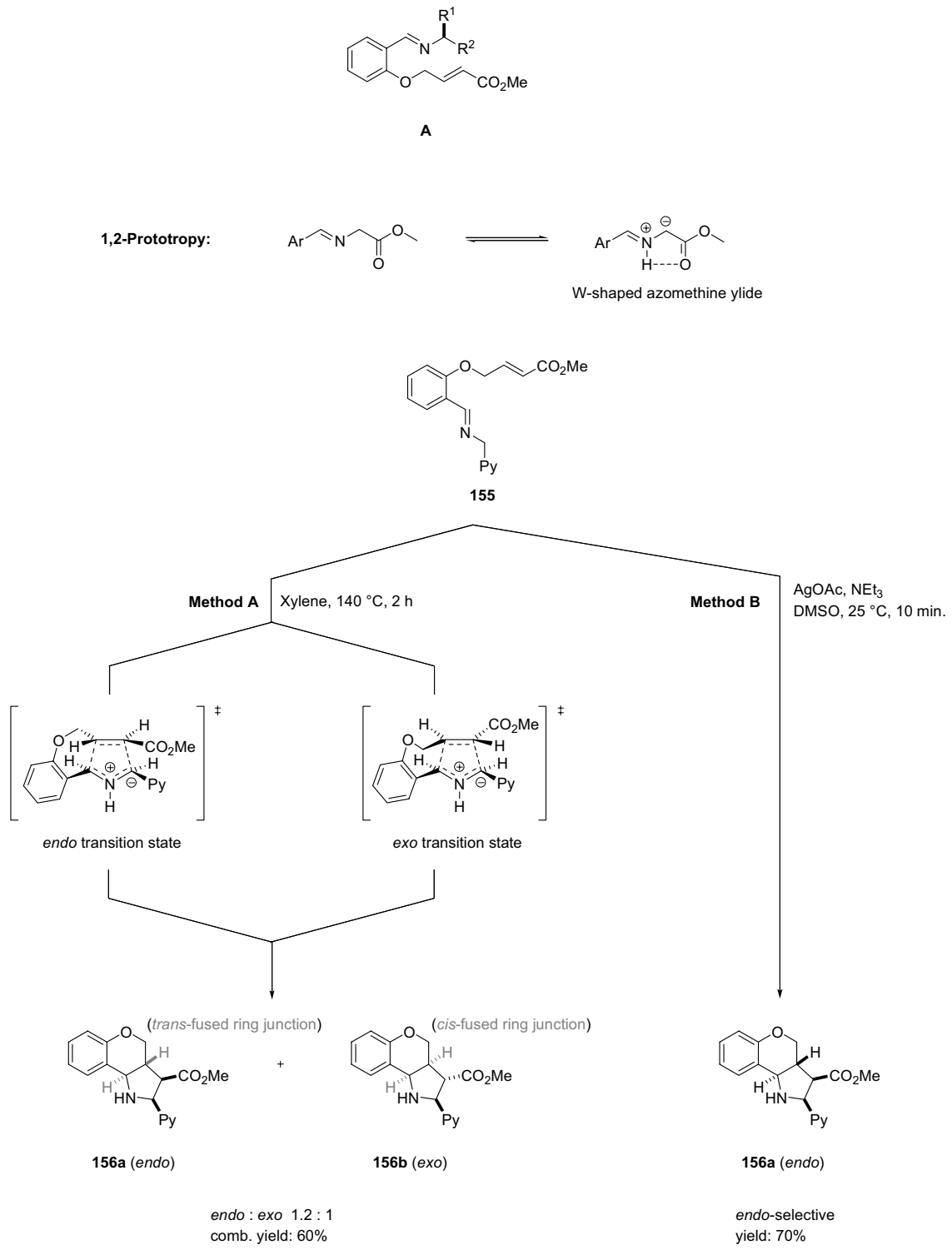


Figure 34.

It was planned to investigate substrates of **Type A**. Their structure was designed to be as close as possible to the 1,3-dipole and the dipolarophile of the intermolecular cycloaddition, resulting in structure **A** (Scheme 30).


A
1,2-Prototropy:
W-shaped azomethine ylide
155
Method A
Xylene, 140 °C, 2 h
Method B
AgOAc, NEt3
DMSO, 25 °C, 10 min.
endo transition state
exo transition state
(trans-fused ring junction)
(cis-fused ring junction)
156a (endo)
156b (exo)
156a (endo)
endo : exo 1.2 : 1
comb. yield: 60%
endo-selective
yield: 70%

Scheme 30.

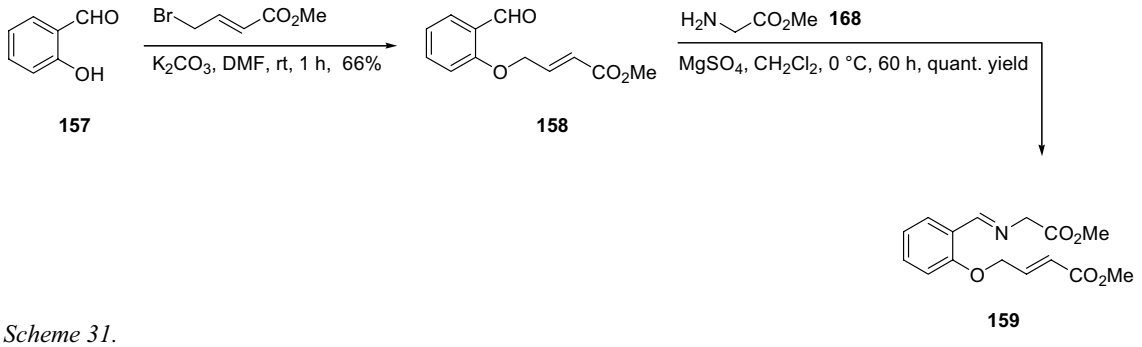
Grigg and co-workers were the first to cyclize these kind of substrates.[75] Initial studies showed that a 1,2-prototropic shift (Scheme 30) could be promoted on heating imines derived from aromatic aldehydes and α-amino esters or 2-picolylamine.[76] The derived azomethine ylide is preferentially formed in its W-shaped form. The concept of 1,2-prototropy was subsequently applied to the intramolecular cycloaddition of imine **155** (Scheme 30, **Method A**). Upon heating of this substrate in xylene, the tricyclic compounds **156a** and **156b** were isolated with a ratio of 1.2 : 1. The major product had the *trans* fused ring junction and resulted from the energetically more favoured *endo* transition state. The fraction of the thermodynamically more favoured *exo* product incorporating the *cis* fused ring junction usually increases if secondary orbital interactions are less important, if sterical reasons gain importance or the reaction conditions are severe enough to permit equilibration.

Later Grigg and his co-workers induced the intramolecular cycloaddition reaction of imine **155** with metal salts like AgOAc (Scheme 30, **method B**).[77] Similar to the azomethine ylides formed by prototropy also the *N*-metalated azomethine ylides predominantly exist in the W-shaped form.[30] The cycloaddition of substrate **155** proceeded at ambient temperature and the product was generated with complete *endo* selectivity.[75d]

The often high regio- and stereoselectivity of the reaction, the enhanced reactivity and the ability to generate complex bicyclic or polycyclic ring systems in only a few steps makes the intramolecular [3+2] cycloaddition an interesting reaction. The development of an asymmetric version of this reaction was therefore strived for.

9.2 Substrate Synthesis

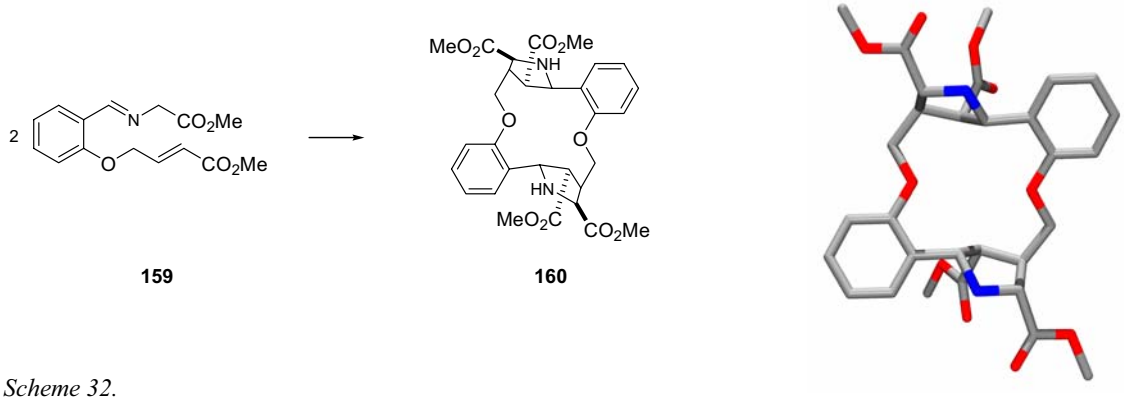
Substrate **159** was prepared according to the reaction pathway illustrated in Scheme 31 by formation of the ether species **158**[78] and its subsequent conversion with glycine methyl ester to the imine **159**.[50] It was used without further purification in the subsequent cycloaddition reaction, since the crude product contained only 6 mol% of the starting aldehyde **158** as an impurity and none of the common purification methods could reduce the amount of compound **158**.



157 **158** **159**

Scheme 31.

Surprisingly, substantial amounts of a macrocyclic species **160** (>30 mol% by ^{1}H NMR) (Scheme 32) were observed as a side product when aldehyde **158** reacted with glycine methyl ester and anhydrous magnesium sulfate in dichloromethane at ambient temperature to form the imine **159**. The structure of this macrocyclic compound **160** resulted from dimerization of imine **159** by a double cycloaddition (Scheme 32) and was unambiguously determined by X-ray analysis. Dimerization could be easily suppressed by performing the reaction at 0 °C in a diluted reaction solution.

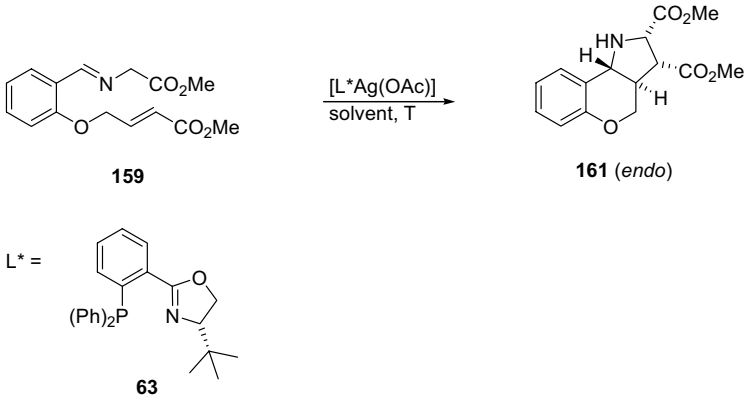


159 **160**

Scheme 32.

9.3 Influence of Solvent and Reaction Temperature

The silver(I) catalyst derived from the standard PHOX ligand **63** and AgOAc was successfully applied to the intramolecular cyclization reaction illustrated in Scheme 33. The initial reaction was performed in toluene at 0 °C and led to full conversion after a reaction time of 6 h. The formation of a single diastereomer with low enantioselectivity was observed (Table 20, entry 1). In the following the influence of solvents and reaction temperatures on the reaction was investigated.



Scheme 33.

The results in Table 20 demonstrate that the intramolecular [3+2] cycloaddition (Scheme 33) proceeded with full conversion and generated the tricyclic product **161** as a single diastereomer, irrespective in which solvent the reaction was performed. The employment of acetonitrile or dichloromethane led to a substantial decrease of the enantioselectivity whereas all other solvents did not influence asymmetric induction significantly. Since the substrates precipitated in toluene at temperatures below 0 °C, the influence of lower reaction temperatures was investigated using THF as a solvent. The increase of enantiomeric excess was however negligible.

The results of the solvent screening did not ask for a change of the reaction conditions already applied to the intermolecular cycloaddition reaction and therefore all subsequent reactions were performed at 0 °C in toluene.

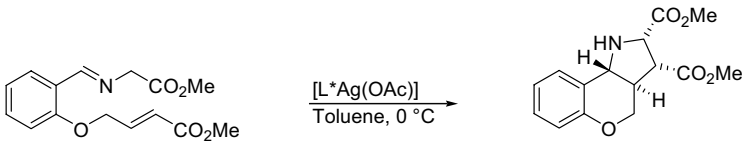
Table 20.

Entry	Solvent	T (°C)	Conversion (%)[a]	*endo* : *exo*[a]	*ee* (%)[b] (**161**)
1	Toluene	0	>95	>40 : 1	18 (+)
2	THF	0	>95	>40 : 1	17 (+)
3	THF	-40	>95	>40 : 1	20 (+)
4	Cyclohexane/ Benzene[c]	0	>95	>40 : 1	21 (+)
5	Acetonitrile	0	>95	>40 : 1	6 (+)
6	Dichloromethane	0	>95	>40 : 1	11 (+)

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
[c] ratio: 3 : 2.
Reaction conditions: AgOAc (3 mol%), ligand **63** (3.3 mol%), substrate **159** (1.0 eq), solvent, 6 h, T.

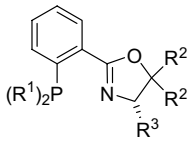
9.4 Ligand Screening for the Ag(I)-Catalyzed Intramolecular [3+2] Cycloaddition

A ligand screening comprising several differently substituted PHOX ligands was performed for the reaction illustrated in Scheme 34.



159 **161** (*endo*)

L* =



63 R^1 = Ph, R^2 = H, R^3 = *t*Bu
39 R^1 = Ph, R^2 = H, R^3 = *i*Pr
126 R^1 = Ph, R^2 = *i*Pr, R^3 = *i*Pr
124 R^1 = Ph, R^2 = Me, R^3 = Cy
127 R^1 = Ph, R^2 = Cy, R^3 = *i*Pr
41 R^1 = Ph, R^2 =Ph, R^3 = *i*Pr
118 R^1 = Cy, R^2 = Ph, R^3 = *i*Pr

40 R^1 = *o*Tol, R^2 = H, R^3 = *i*Pr
123 R^1 = *o*Tol, R^2 = Me, R^3 = *i*Pr
72 R^1 = *o*Tol, R^2 = Cy, R^3 = *i*Pr
64 R^1 = *o*Tol, R^2 = Ph, R^3 = *i*Pr
77 R^1 = *o*Tol, R^2 = 3,5-dimethylphenyl, R^3 = *i*Pr
78 R^1 = *o*Tol, R^2 = 3,5-dimethoxyphenyl, R^3 = *i*Pr

Scheme 34.

When imine **159** was treated with Ag(I)-PHOX complexes full conversion was obtained after a reaction time of 6 h and the tricyclic product **161** was formed as a single diastereomer; no traces of other diastereomers could be detected in the ^{1}H and ^{13}C NMR spectra. The enantioselectivities induced by the different ligands illustrated in Scheme 34 showed the same trends as in the intermolecular cycloaddition. The isopropyl substituent at the C4 position of the oxazoline ring had a more positive effect on enantioselectivity than tertiary butyl respectively cyclohexyl groups (Table 21, compare entries 1A, 1B and 1D). Furthermore the introduction of *ortho*-tolyl instead of phenyl groups at the phosphorous atom (Table 21, compare entries 1B and 1H) as well as the incorporation of substituted phenyl groups at the C5 position of the oxazoline (Table 21, compare entries 1H with 1M) improved the asymmetric induction. The highest enantioselectivity was achieved with ligand **77** (Table 21, entry 1M). While the screening experiments were carried out using 3 mol% of PHOX complex, the catalyst loading could be reduced to 1 mol% without loss of enantioselectivity or yield. Studies of the reaction time indicated that full conversion was achieved after 1.5 h using 3 mol% of the catalyst.

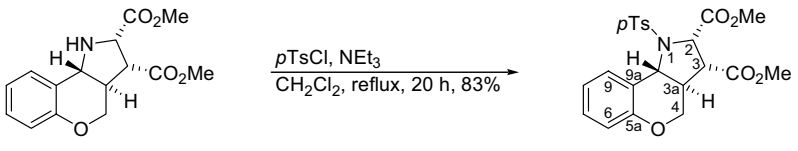
Table 21.

Ligand	**63**	**39**	**126**	**124**	**127**	**41**	**118**	**40**	**123**	**72**	**64**	**77**	**78**
Product	A	B	C	D	E	F	G	H	I	K	L	M	N
161 *ee* (%)[a] 1	18 (+)	26 (+)	54 (+)	18 (+)	82 (+)	65 (+)	67 (+)	66 (+)	75 (+)	88 (+)	96 (+)	98 (+)	96 (+)

[a] Determined by chiral HPLC.
Reaction conditions: AgOAc (3 mol%), ligands illustrated in Scheme 34 (3.3 mol%), substrate **159** (1.0 eq), toluene, 0 °C, 6 h.

9.5 Absolute Configuration of a Tricyclic Product

Tosylation of the tricyclic product **161** was performed to determine its absolute configuration. The reaction product **162** could be isolated with good yield and an enantiomeric excess of 97%.



161 (*endo*) (96% *ee*) **162** (*endo*) (97% *ee*)

Scheme 35.

Recrystallization of the tosylated compound **162** from ethylacetate/pentane gave crystals suitable for single crystal X-ray structure determination. The analysis revealed a (2*S*, 3*R*, 3a*R*, 9b*R*)-configuration for **162** and therefore also for **161** (Figure 35).

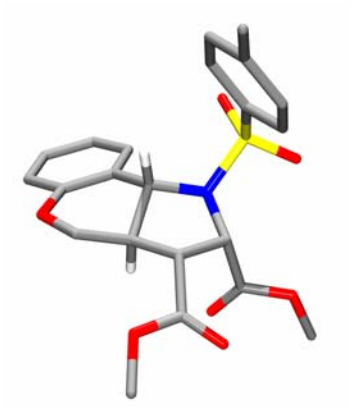
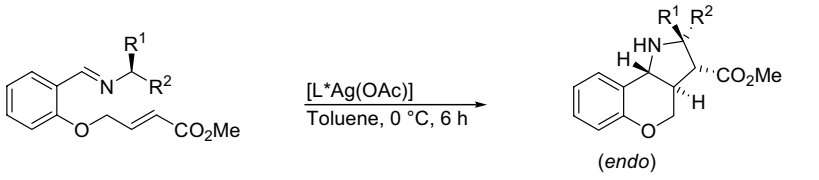


Figure 35.

9.6 Scope of the Ag(I)-Catalyzed Intramolecular [3+2] Cycloaddition

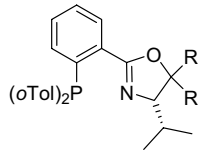
The most successful ligands **64** and **77** of the preliminary ligand screening were applied to three other substrates (Scheme 36). The variation of the substrate concerned the α-position of the imine. The methyl ester of imine **159** was replaced by a sterically more demanding tertiary butyl ester (**163**) and by a pyridine moiety (**155**). Additionally, a sterically more demanding alanine derived substrate **164** was synthesized. In contrast to the glycine derivatives **159** and **163**, imines **164** and **155** did not show any tendency to dimerize at room temperature and were therefore synthesized without cooling the reaction mixture (compare chapter 9.2).



159 R^1 = H, R^2 = CO_2Me
163 R^1 = H, R^2 = CO_2tBu
164 R^1 = Me, R^2 = CO_2Me
155 R^1 = H, R^2 = Py

161 R^1 = H, R^2 = CO_2Me
165 R^1 = H, R^2 = CO_2tBu
166 R^1 = Me, R^2 = CO_2Me
156 R^1 = H, R^2 = Py

L* =



64 R = Ph
77 R = 3,5-dimethylphenyl

Scheme 36.

The replacement of the methyl ester of imine **159** by a tertiary butyl ester in **163** increased the asymmetric induction. The tricyclic product **165** was isolated with slightly lower yield but higher enantioselectivity (Table 22, entries 1 and 2). Substrate **155**, with a pyridine ring instead of an ester group, reacted with lower enantioselectivity but comparable yield (Table 22, entries 1 and 4). The cyclization product of the alanine-derived substrate **164** was isolated with the comparatively lowest yield but high enantioselectivity (Table 22, entry 3).

The ligands applied to the cycloaddition illustrated in Scheme 36 differed only in their substituents at the C5 position of the oxazoline ring. The 3,5-dimethylphenyl substituted ligand **77** gave the tricyclic product with higher enantioselectivity but lower yield than its phenyl substituted counterpart **64**.

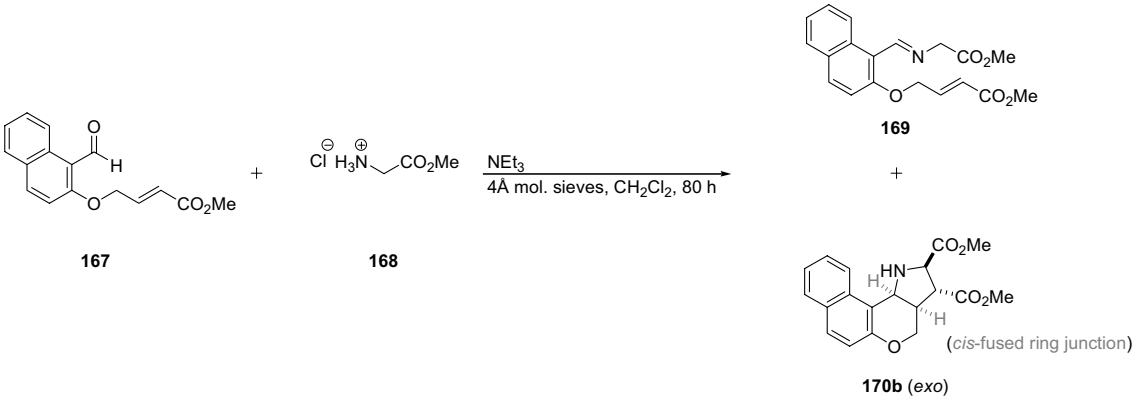
Table 22.

Entry	Product	Yield (%)[a]	*ee* (%)[b]
1	**161**	68 (74)[c]	98 (+) (96 (+))[c]
2	**165**	62 (66)[c]	99 (+) (99 (+))[c]
3	**166**	60 (61)[c]	96 (+) (96 (+))[c]
4	**156**	67 (70)[c]	85 (–) (83 (–))[c]

[a] After column chromatography.
[b] Determined by chiral HPLC.
[c] The free standing values were generated by using ligand **77**, the values in brackets were generated by using ligand **64**.
Reaction conditions: AgOAc (3 mol%), ligands **77**, **64** (3.3 mol%), substrates **155**, **159**, **163**, **164** (1.0 eq), toluene, 0 °C.

Application of the conditions used for the preparation of the non-glycine derived imines **159** and **163** to the synthesis of substrate **169** failed, since the tricyclic product **170b** was isolated as the major product (Scheme 37). X-ray analysis of compound **170b** indicated that it possesses the *cis*-fused ring junction of the thermodynamically more stable *exo* product (Figure 36).[79] Its formation occurs presumably via the *exo* transition state of the W-shaped 1,3-dipole which is probably generated by prototropy.[75a] The replacement of $MgSO_4$ by molecular sieves increased the fraction of the imine **169** only slightly excluding the possibility that 1,3-dipole generation could have proceeded via the *N*-metalated azomethine ylide route by complexation of the magnesium to the imine **169**.[38] However, decreased reaction temperature suppressed the formation of the tricyclic product **170b** almost completely and imine **169** was isolated as the major product. According to ^{1}H NMR studies the crude product

mixture contained after a reaction time of 80 h 67 mol% of imine **169**, 25 mol% of the aldehyde **167** and 8 mol% of the cycloproduct **170b**.



167 **168** **169** **170b** (*exo*)

Scheme 37.

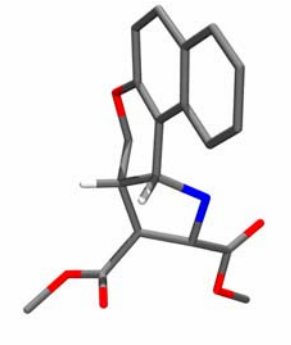
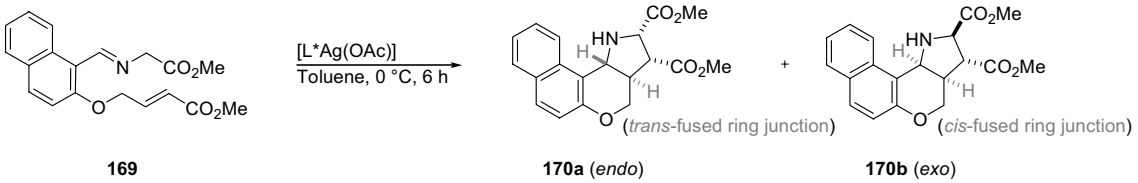


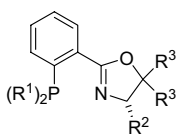
Figure 36.

For reasons already discussed for substrate **159** the crude product was applied without further purification to the cycloaddition reaction catalyzed by Ag(I)-PHOX complexes derived from ligands **63** and **64** and AgOAc (Scheme 38).



169 **170a** (*endo*) **170b** (*exo*)

L* =



63 R^1 = Ph, R^2 = *t*Bu, R^3 = H
64 R^1 = *o*Tol, R^2 = *i*Pr, R^3 = Ph

Scheme 38.

^{1}H NMR spectra of the crude products generated by cycloaddition of substrate **169** showed that the reaction was not diastereoselective in contrast to the analogous reactions with substrates **155**, **159**, **163**, and **164**. The cycloaddition which proceeded under the influence of ligand **63** gave the tricyclic products **170a** and **170b** with a ratio of 1 : 1.3 whereas the employment of ligand **64** gave an *endo*:*exo* ratio of 1.5 : 1. The enantioselectivity of the *exo* product **170b** was not determined because it was already present in the starting material and can additionally be formed by an uncatalyzed background reaction. Full conversion was obtained after a reaction time of 6 h and the *endo* product **170a** was generated with high enantioselectivity (Table 23). Surprisingly, the application of ligand **63** resulted in formation of the tricyclic product **170a** with high enantioselectivity in constrast to the reaction with substrate **159** which gave low enantioselectivity with this ligand (compare Table 23, entry 1, with Table 21, ligand **63**).

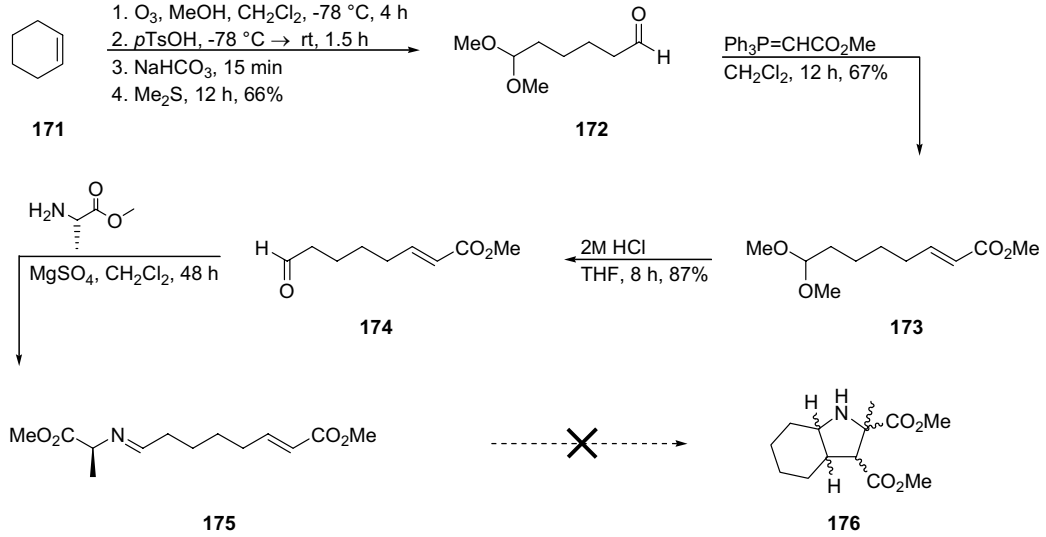
Table 23.

Entry	**Ligand**	**Conversion** (%)[a]	***ee*** (%)[b]
1	**63**	>95	80[c]
2	**64**	>95	90[c]

[a] Determined by ^{1}H NMR.
[b] Determined by chiral HPLC.
[c] Absolute configuration not determined.
Reaction conditions: AgOAc (3 mol%), ligands **63**, **64** (3.3 mol%), substrate **169** (1.0 eq), toluene, 0 °C, 6 h.

9.7 Aliphatic Substrates for the Intramolecular [3+2] Cycloaddition

In order to extend the scope of the intramolecular [3+2] cycloaddition to aliphatic substrates, imine **175** was synthesized.



Scheme 39.

Imine **175** was prepared following the reaction sequence illustrated in Scheme 39. Addition of *p*-toluenesulfonic acid to the ozonolysis reaction medium led to the formation of an acetal-alkoxy hydroperoxide. Prior to reduction of the alkoxy hydroperoxide with dimethylsulfide to the acetal-aldehyde **172**, the acid had to be neutralized with $NaHCO_3$ to avoid bisacetal formation.[80] Subsequent *Wittig* reaction selectively gave the unsaturated ester **173** with *trans* stereochemistry.[81] Hydrolysis of the acetal with a 2M HCl-solution yielded the aldehyde **174**.[82] The usual reaction procedure for imine formation had to be slightly modified. The addition of the aldehyde **174** in dichloromethane to a suspension of the amino ester hydrochloride, triethylamine and $MgSO_4$ in dichloromethane, which was already stirred for one hour, led even after a reaction time of two days only to a conversion of 50%. For that reason the amino ester hydrochloride was extracted first with a concentrated aqueous ammonia solution to obtain the free amine. The aldehyde **174** was subsequently added to a concentrated solution of the free amine and $MgSO_4$ in dichloromethane. After a reaction time of 2 days ^{1}H NMR studies showed that the aldehyde **174** was only present to an extent of 8 mol%.

Attempts to cyclize imine **175** to the bicyclic product **176** were not successful, neither by application of AgOAc nor by employment of Ag(I)-PHOX-complexes. After a reaction time

of 12 h the crude product was purified by column chromatography but none of the isolated compounds corresponded to the desired product **176**.

9.8 Conclusion

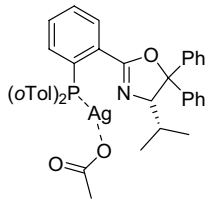
Although Ag(I)-PHOX complexes gave only moderate to good asymmetric induction in intermolecular [3+2] cycloadditions, they are efficient catalysts for intramolecular [3+2] cycloadditions of azomethine ylides with aryl backbones, giving access to tricylic products with almost complete diastereocontrol and enantiomeric excesses of up to 99%.

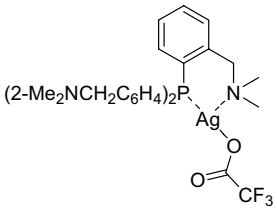
Chapter 10

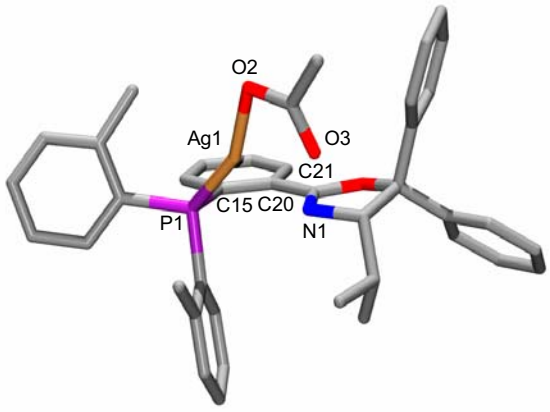
Structural Elucidation of a Ag(I)-PHOX Complex

10 Structural Elucidation of a Ag(I)-PHOX Complex

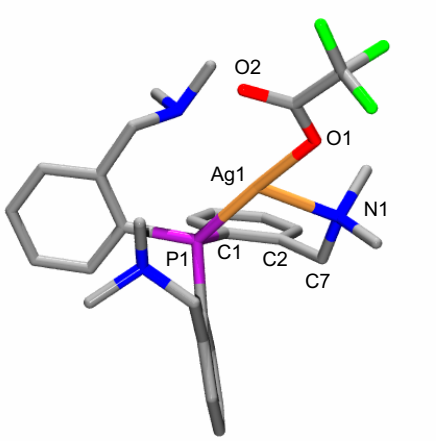
In order to gain insight into the coordination mode of the silver metal ion to PHOX ligands, attempts to grow crystals suitable for X-ray analysis were pursued. Single crystals of complex **216** were obtained from a solution of toluene/pentane. Its solid-state structure is shown in Figure 37 with some relevant structural parameters.







216



217

Selected bond length [Å] and angles [°]:

Ag1-P1:	2.3530(11)	Ag1-P1:	2.3659(6)
Ag1-O2:	2.166(3)	Ag1-O1:	2.183(2)
Ag1··N1:	2.640(3)	Ag1-N1:	2.478(2)
P1-Ag1-O2:	158.27(8)	P1-Ag1-O2:	174.70(7)

Figure 37. X-ray structures of complexes **216** and **217** (POV-Ray[83] view, datasets for the preparation of the pictures were generated with ORTEP[84]). Hydrogen atoms have been omitted for clarity reasons.

The silver metal ion of complex **216** adopts a distorted linear twofold coordination, which represents a common geometry of silver complexes. The tendency of this metal type to twofold linear coordination can be explained by hybridization of the $4d_{z^2}$- and s-orbitals

generating an sd-hybrid-orbital in which the electron density is shifted from the lobes of the d_{z^2}-orbital to the lobe of the xy-plane. Thus, coordination along the z-axis is favored. This is realized by a second hybridization of the sd-hybrid-orbital with a p_z-orbital forming the hybrid orbitals suitable for covalent bond formation. The metal center of complex **216** is bound to the soft phosphorous atom of the PHOX ligand on the one hand and to an oxygen atom of the acetate on the other hand. The Ag1-O2 bond length is slightly shorter than the one found in other related complexes.[85] Coordination of the silver ion to the second oxygen atom O3 (Ag1-O3 2.641(3)) is not assumed since the *van der Waals* radius[86] of the oxygen and the ionic radius[87] of metal ion do not indicate an interaction. Nonetheless, the linear geometry is largely distorted, as indicated by the P1Ag1O2 angle of 158.27(8)°; a peculiarity that could be indicative for an allylic coordination mode of the acetate. Finally, the large distance between the Ag1 and N1 and the dihedral angle of 48.7° found between N1-C21-C20 and C15-P1-Ag1 exclude the existence of a chemical bond.

These findings stand in sharp contrast to the structural properties of the most closely related silver complex **217** found in the Cambridge Crystallographic Data Center (CCDC) whose solid structure is illustrated in Figure 37.[88] The silver metal center of this complex adopts a less common trigonal T-shaped geometry defined by the atoms Ag1, P1, N1 and O1. The angle defined by P1, Ag1, and O1 is almost linear (174.70(7)°). Interestingly, the Ag1-P1 bond length of both complexes is similar as well as the torsion angle defined by the atoms C2, C1, P1, Ag1, 46.77°, and C20, C15, P1, Ag1, 43.6°, for **217** and **216**, respectively.

Chapter 11

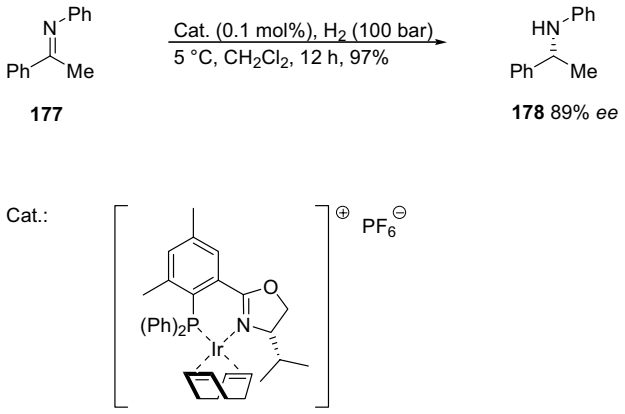
Ir(I)-Complexes of C5-Substituted PHOX Ligands as Catalysts for the Asymmetric Hydrogenation of Olefins and Imines

11 Ir(I)-Complexes of C5-Substituted PHOX Ligands as Catalysts for the Asymmetric Hydrogenation of Olefins and Imines

11.1 Introduction

Ir(I)-PHOX complexes are efficient catalysts for enantioselective hydrogenations of unfunctionalized olefins and imines.[89] They do not require a coordination group next to the double bond for efficient asymmetric induction, which distinguishes them from chiral rhodium and ruthenium catalysts.[90]

Initially, these complexes were applied to the asymmetric hydrogenation of imines.[89d] Up to 89% enantiomeric excess and high turn over numbers (TON) could be achieved with *N*-phenylimine **177** derived from phenyl methyl ketone (Scheme 40).

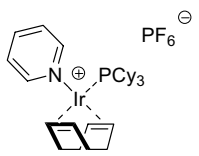


Scheme 40.

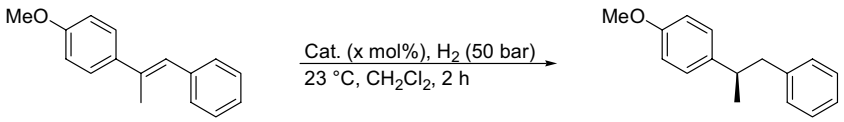
Since the coordination sphere of Ir-PHOX complexes resembles that of the Crabtree's catalyst **179** (Scheme 41) which efficiently catalyzes the hydrogenation of unfunctionalized tri- and tetrasubstituted olefins,[91] Pfaltz and co-workers used these complexes also in carbon-carbon double bond hydrogenation of this kind. First studies with the catalyst **182** using substrate **180** showed promising results (Scheme 41). With 4 mol% of catalyst at 50 bar hydrogen pressure the desired product **181** was obtained with an enantioselectivity of 75% and a conversion of 78%.[89c] Systematic variation of the PHOX ligand substitution pattern successively improved the enantioselectivity (Table 24). Thus catalyst **185** incorporating two *ortho*-tolyl groups at the phosphorous atom and a tertiary butyl group at the C4 position of the oxazoline ring gave the product **181** with an enantioselectivity of 97%. The moderate conversion could be

improved by replacing the PF_6^- anion with $B(Ar_F)_4^-$ (Table 24, compare entries 4 and 5). Catalysts with this counter ion did not suffer from deactivation before the reaction was finished and were less sensitive against moisture.[89c]

Crabtree catalyst:

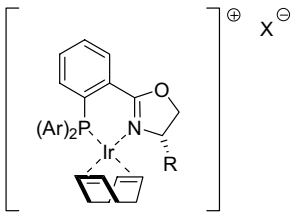


179



180 **181**

Cat.:



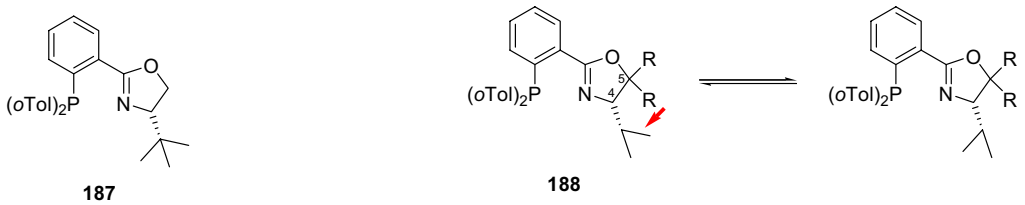
182 Ar = Ph, R = *i*Pr, X = PF_6
183 Ar = Ph, R = *t*Bu, X = PF_6
184 Ar = *o*Tol, R = *i*Pr, X = PF_6
185 Ar = *o*Tol, R = *t*Bu, X = PF_6
186 Ar = *o*Tol, R = *t*Bu, X = $B(Ar_F)_4$

Table 24.

Entry	**Cat.** (mol%)	**Conversion** (%)	***ee*** (%) (**181**)
1	**182** (4)	78	75 (*R*)
2	**183** (4)	98	90 (*R*)
3	**184** (4)	>99	91 (*R*)
4	**185** (4)	57	97 (*R*)
5	**186** (0.3)	>99	98 (*R*)

Scheme 41.

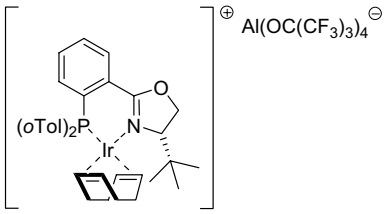
Further investigations showed that the Ir(I)-complex derived from ligand **187** is suitable for the asymmetric hydrogenation of various aryl substituted olefins forming the products with good enantioselectivity.[89a] However, the precursor of this ligand, *tert*-leucine, is expensive. Therefore, it was of interest to test, whether the C5-substituted PHOX ligands **188** derived from inexpensive (*S*)-valine could be used as substitutes of ligand **187**. The steric bulk caused by the groups at C5 should direct the methyl groups of the C4 isopropyl substituent towards the coordination center producing a similar effect to a *tert*-butyl group (Figure 38).



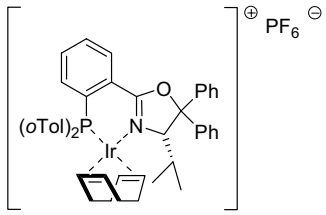
187 **188**

Figure 38.

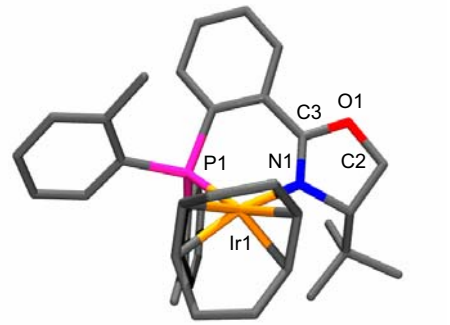
This assumption was at least confirmed by the solid state structures of the Ir(I)-complexes of ligand **187** and one representative of the C5-substituted PHOX ligands **188** (Figure 39).

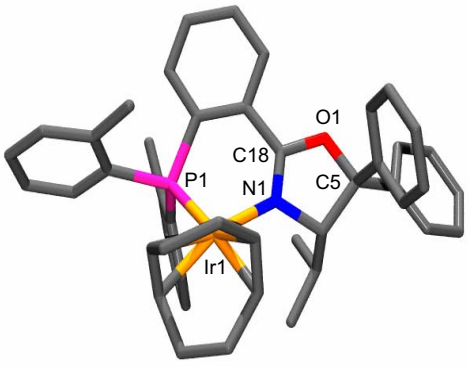


218



219





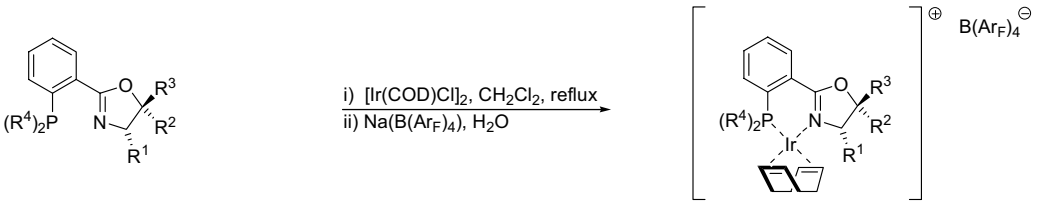
Selected bond length [Å] and angles [°]:

Ir1-P1:	2.292(1)	Ir1-P1:	2.3047(9)
Ir1-N1:	2.102(3)	Ir1-N1:	2.095(3)
P1-Ir1-N1:	85.15(3)	P1-Ir1-N1:	87.54(8)
N1-C3-O1-C2:	-7.82	N1-C18-O1-C5:	-9.95

Figure 39. X-ray structures of complexes **218**[89e] and **219** (POV-Ray[83] view, datasets for the preparation of the pictures were generated with ORTEP[84]). Hydrogen atoms have been omitted for clarity reasons.

11.2 Application of Ir(I)-Complexes Derived from C5-Substituted PHOX Ligands to Asymmetric Hydrogenation

Several PHOX ligands bearing substituents at the C5 position of the oxazoline moiety which were initially prepared for the [3+2] cycloaddition reaction (Chapter 6) were transformed to the corresponding iridium catalysts. The desired oxygen and moisture stable complexes were obtained by refluxing $[Ir(COD)Cl]_2$ and the ligand in dichloromethane and subsequent exchange of the chloride ion by $Na(B(Ar_F)_4)$ (Scheme 42).[89c]



187 R^1 = *t*Bu, R^2 = R^3 = H, R^4 = *o*Tol
40 R^1 = *i*Pr, R^2 = R^3 = H, R^4 = *o*Tol
70 R^1 = *i*Pr, R^2 = R^3 = Et, R^4 = Ph
71 R^1 = *i*Pr, R^2 = R^3 = Et, R^4 = *o*Tol
72 R^1 = *i*Pr, R^2 = R^3 = Cy, R^4 = *o*Tol
41 R^1 = *i*Pr, R^2 = R^3 = R^4 = Ph
64 R^1 = *i*Pr, R^2 = R^3 = Ph, R^4 = *o*Tol
114 R^1 = *i*Pr, R^2 = H, R^3 = Ph, R^4 = *o*Tol
111 R^1 = *i*Pr, R^2 = Ph, R^3 = H, R^4 = *o*Tol
74 R^1 = *i*Pr, R^2 = R^3 = 2-Naph, R^4 = *o*Tol
76 R^1 = *i*Pr, R^2 = R^3 = R^4 = *o*Tol
77 R^1 = *i*Pr, R^2 = R^3 = 3,5-dimethylphenyl, R^4 = *o*Tol

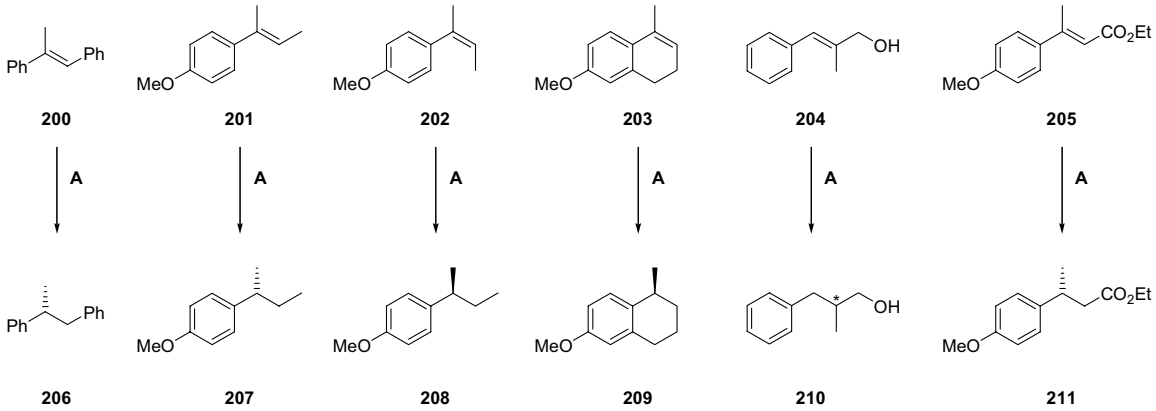
186 R^1 = *t*Bu, R^2 = R^3 = H, R^4 = *o*Tol
189 R^1 = *i*Pr, R^2 = R^3 = H, R^4 = *o*Tol
190 R^1 = *i*Pr, R^2 = R^3 = Et, R^4 = Ph
191 R^1 = *i*Pr, R^2 = R^3 = Et, R^4 = *o*Tol
192 R^1 = *i*Pr, R^2 = R^3 = Cy, R^4 = *o*Tol
193 R^1 = *i*Pr, R^2 = R^3 = R^4 = Ph
194 R^1 = *i*Pr, R^2 = R^3 = Ph, R^4 = *o*Tol
195 R^1 = *i*Pr, R^2 = H, R^3 = Ph, R^4 = *o*Tol
196 R^1 = *i*Pr, R^2 = Ph, R^3 = H, R^4 = *o*Tol
197 R^1 = *i*Pr, R^2 = R^3 = 2-Naph, R^4 = *o*Tol
198 R^1 = *i*Pr, R^2 = R^3 = R^4 = *o*Tol
199 R^1 = *i*Pr, R^2 = R^3 = 3,5-dimethylphenyl, R^4 = *o*Tol

Scheme 42.

These complexes were applied to the asymmetric hydrogenation of trisubstituted and tetrasubstituted olefins as well as imines. The hydrogenations were usually performed in dichloromethane at room temperature and a hydrogen pressure of 50 bar using 1 mol% of catalyst.

Hydrogenation of trisubstituted olefins

Initially the Ir(I)-PHOX complexes illustrated in Scheme 42 were tested in the hydrogenation of six trisubstituted olefins **200**-**205** (Scheme 43).



A = [Ir(L*)(COD)][B(Ar_F)$_4$], 50 bar H_2, CH_2Cl_2, RT
L* = **40**, **41**, **64**, **70-72**, **74**, **76**, **77**, **111**, **114**, **187**

Scheme 43.

The results in Table 25 demonstrate that the Ir(I)-catalyst **186** derived from the *tert*-leucine-derived PHOX ligand **187** induces higher enantioselectivity in the hydrogenation of the substrates **200**-**205** than its analog **189** bearing an isopropyl group instead of a *tert*-butyl group (Table 25, compare columns A with B). Introduction of substituents at the C5 position of the oxazoline moiety in catalyst **189** showed various trends.

The application of this ligand type to the hydrogenation of (*E*)-1,2-diphenyl-1-propene (**200**) or the allylic alcohol **204** led to the formation of products **206** and **210** with enantiomeric excesses comparable to those obtained with the reference catalyst **189** (Table 25, rows 1 and 5). Replacement of the *ortho*-tolyl groups at the phosphorous atom by phenyl substituents led to lower asymmetric induction in the formation of product **206** (Table 25, compare 1F with 1G, and 1C with 1D). *Ortho*-tolyl substituents at the C5 position of the oxazoline moiety also gave relatively low enantiomeric excess (Table 25, entry 1L).

A more pronounced effect of the C5 substituents on enantioselectivity was observed for the hydrogenation of (*Z*)-2-(4-methoxyphenyl)-2-butene (**202**) or the acrylic ester **205** (Table 25, rows 3 and 6). In comparison to the reference catalyst **189** the hydrogenation products of **208** were formed with higher enantioselectivity except for catalysts bearing phenyl groups instead of *ortho*-tolyl groups at the phosphorous atom or only one substituent at the C5 position (Table 25, entries 3C, 3F and 3H). In the case of the acrylic ester **205,** catalyst **190** containing ethyl substituents at the C5 position and phenyl substituents at the phosphorous atom afforded superior enantioselectivity than the *tert*-leucine-derived catalyst **186** (Table 25, compare entries 6A and 6C). Surprisingly, its analog **193** bearing phenyl substituents at the C5 position gave almost racemic product (Table 25, entry 6F).

Hydrogenation of 6-methoxy-1-methyl-3,4-dihydronaphthalene (**203**) and (*E*)-2-(4-methoxyphenyl)-2-butene (**201**) proceeded with substantial higher asymmetric induction using some of the complexes bearing C5 substituents instead of the reference catalyst **189** (Table 25, rows 2 and 4). In some cases, the enantiomeric excesses were even higher than those induced by the *tert*-leucine derived ligand **186** (Table 25, compare entries 2A with 2M and 4A with 4E). In case of the cyclic substrate **203**, it was found to be crucial that the catalyst incorporates *ortho*-tolyl substituents at the phosphorous atom and aliphatic groups at the C5 position of the oxazoline ring to reach high enantiomeric excesses.

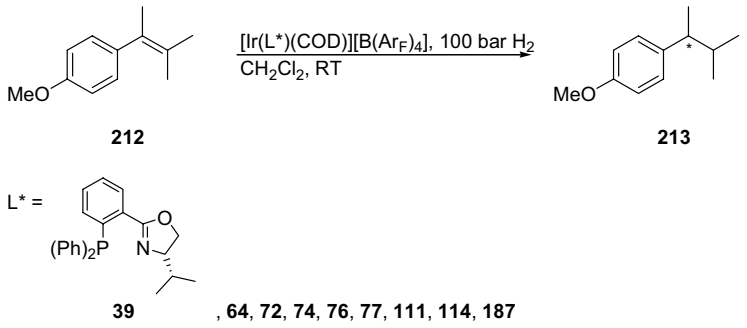
Table 25.

Catalyst		**186**	**189**	**190**	**191**	**192**	**193**	**194**	**195**	**196**	**197**	**198**	**199**
Compound		A	B	C	D	E	F	G	H	I	K	L	M
206[a] (*R*) ***ee*** (%)[b]	1	**98**	94	89	93	92	69	94	94	96	93	43	93
207[a] (*R*) ***ee*** (%)[b]	2	73[d]	55	78	64	85	76	85	48	55	86	28	**90**
208[a] (*S*) ***ee*** (%)[b]	3	**58**[d]	24	17	28	46	22	40	14	40	49	39	51
209[a] (*S*) ***ee*** (%)[b]	4	75[d]	47	30	63	**78**	12	53	46	65	51	52	55
210[a] (–) ***ee*** (%)[b]	5	**95**[d]	93	89	92	88	91	92	92	93	92	87	94
211[a] (*R*) ***ee*** (%)[b]	6	84	82	**86**	84	71	5	79	84	81	69	18[c]	75

[a] Product was obtained with full conversion.
[b] Determined by chiral HPLC.
[c] Conversion: 40%.
[d] Values are not in accordance to those published in reference 89f.
Reaction conditions: Substrates **200**-**205** (1 eq), catalysts illustrated in Scheme 42 (1 mol%), 50 bar H_2, dichloromethane, rt, 2 h.

Hydrogenation of a tetrasubstituted olefin

The tetrasubstituted olefine **212** is a more challenging substrate for asymmetric hydrogenation than the trisubstituted alkenes **200**-**205**. It is known that less bulky ligands as diphenylphosphino-isopropyloxazoline **39** are more suitable for the reaction of Scheme 44 than sterically more demanding analogs like the bis(*ortho*-tolyl)phosphino-*tert*-butyloxazoline ligand **187** (Table 26, compare entries 1A and 1B).



212 **213**

39 , **64**, **72**, **74**, **76**, **77**, **111**, **114**, **187**

Scheme 44.

This trend was also observed for ligands listed in Scheme 44 (Table 26). Since the C5-substituted ligands are sterically more demanding than the diphenylphosphino-isopropyloxazoline ligand **39**, low enantiomeric excess and conversion were obtained in the reaction shown in Scheme 44 (Table 26, row 1).

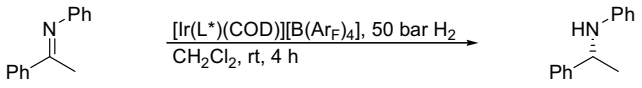
Table 26.

Ligand		**187**	**39**	**72**	**64**	**114**	**111**	**74**	**76**	**77**
Compound		A	B	C	D	E	F	G	H	I
213 (–) ***ee*** (%)[a]	1	3[c]	60[c]	18[d]	34	12	19[d]	28	23	19
(conversion)[b]		(37)	(>99)	(12)	(85)	(>99)	(91)	(95)	(53)	(79)

[a] Determined by chiral HPLC.
[b] Conversion determined by GC.
[c] 2 mol% of catalyst were used.
[d] Opposite enantiomer was formed.
Reaction conditions: Substrate **212** (1 eq), catalysts illustrated in Scheme 44 (1 mol%), 50 bar H_2, dichloromethane, rt, 2 h.

Hydrogenation of an imine

The Ir(I)-catalysts listed in Scheme 42 were also applied to the asymmetric hydrogenation of imine **177** (Scheme 45).



177 **178**

L* = **40, 41, 64, 70-72, 74, 76, 77, 111, 114, 187**

Scheme 45.

In contrast to the hydrogenation of the trisubstituted olefins, the bis(*ortho*-tolyl)phosphino-isopropyloxazoline ligand **40** induced higher enantioselectivity in the reduction of substrate **177** than the analogous *tert*-butyl-substituted ligand **187** (Table 27, compare entries 1A and 1B). A slight negative effect on asymmetric induction was generally observed if substituents were introduced at the C5 position of the oxazoline ring of ligand **40.** However, ligand **77** did not follow this trend since its use led to the formation of the desired product **178** with the highest enantioselectivity in this series (Table 27, entry 1M).

Table 27.

Ligand		**187**	**40**	**70**	**71**	**72**	**41**	**64**	**114**	**111**	**74**	**76**	**77**
Compound		A	B	C	D	E	F	G	H	I	K	L	M
178[a] (*R*) ***ee*** (%)[b]	1	77	83	76	71	65	76	76	76	70	83	83	**87**

[a] Product was obtained with full conversion.
[b] Determined by chiral HPLC.
Reaction conditions: Substrate **177** (1 eq), catalysts illustrated in Scheme 42 (1 mol%), 50 bar H_2, dichloromethane, rt, 4 h.

11.3 Conclusion

For each of the test substrates listed in Schemes 43 and 45 at least one representative of the C5-disubstituted bis(*aryl*)phosphino-isopropyloxazoline ligands was found that induced higher enantioselectivity than its unsubstituted analog **40**. This can be explained by the steric bulk at the C5 position of the oxazoline ring which directs the methyl groups of the isopropyl substituent at the C4 position to the coordination center creating a “tertiary butyl substitute“, as previously mentioned. Thus, C5-disubstituted isopropyloxazoline ligands, derived from inexpensive (*R*)- or (*S*)-valine, are an attractive alternative to the more expensive *tert*-leucine-derived PHOX ligands.

Chapter 12

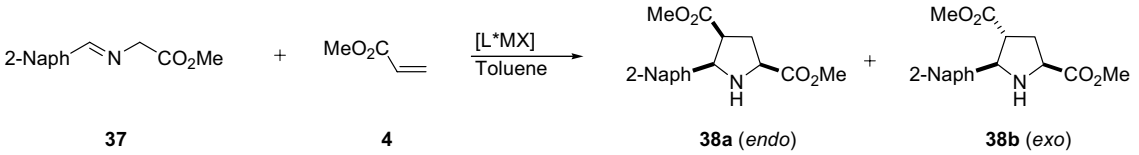
Asymmetric Metal-Catalyzed [3+2] Cycloadditions of Azomethine Ylides

12 Asymmetric Metal-Catalyzed [3+2] Cycloadditions of Azomethine Ylides

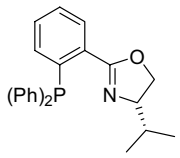
(Synopsis)

Cycloadditions of azomethine ylides with olefins provide a short, attractive route to pyrrolidine units with the potential to control the relative and absolute configuration by means of a chiral catalyst. Grigg and co-workers have pioneered the use of chiral transition metal complexes to induce enantioselective cycloadditions of this type. However, stoichiometric amounts of metal complexes were employed in this work.[39a,41]

Paying regard to Griggs investigations it was intended to develop a system which gives asymmetric induction using catalytic amounts of chiral transition metal complexes. A first screening of different transition metal sources showed promising results for Cu(I) and Ag(I) species. The application of their complexes with several members of different ligand classes to the 1,3-dipolar cycloaddition reaction directed the interest towards phosphinooxazoline (PHOX) ligands. The catalysts derived from the two different metals and PHOX ligand **39** induced enantioselectivity in both cases (Scheme 46, Table 28). Subsequent investigations demonstrated that also the use of the analogous Au(I) catalyst led to the formation of enantioenriched pyrrolidines.



37 **4** **38a** (*endo*) **38b** (*exo*)

L* = 

39

Table 28.

Entry[a]	Metal	X	Cat. (mol%)	t (h)	Conv. (%)[b]	**38a** : **38b**[b]	*ee* (**38a**) (%)[c]
1	Cu(I)	OAc	5	12	85	1.5 : 1	70 (–)
2	Ag(I)	OAc	3	4	>95	>40.0 : 1	22 (+)
3	Au(I)	O*t*Bu	5	10	80	7.0 : 1	16 (–)

[a] Imine (**37**) : dipolarophile (**4**) = 1 : 1.2. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

Scheme 46.

Although the Cu(I)-PHOX catalyst generated the five-membered heterocycle **38a** with higher enantiomeric excess than the other two catalysts (Table 28, compare entries 1 with 2 and 3) the focus was directed to the Ag(I) system. Firstly, because a further screening with differently substituted PHOX ligands indicated only for the Ag(I) system the chance of substantial improvement of the enantioselectivity. Secondly, much higher *endo:exo* selectivity could be observed than for the other two systems. Optimization of the substitution pattern of the PHOX ligand (Figure 40) showed that particularly the variation of the substituents at the phosphorous atom and the C5 position of the oxazoline moiety had a positive effect on asymmetric induction.

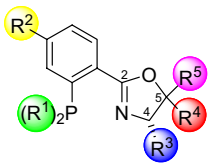
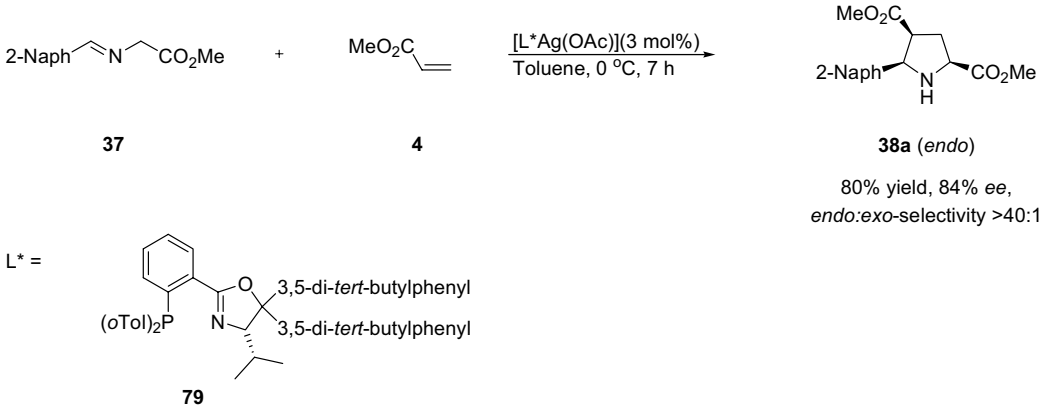


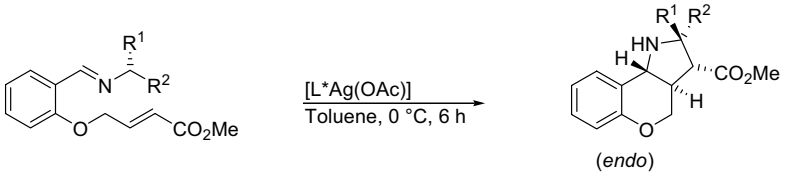
Figure 40.

Scheme 47 shows the most selective PHOX ligand (**79**) found to date which resulted in formation of the pyrrolidine product **38a** with 84% enantiomeric excess.



Scheme 47.

Although Ag(I)-PHOX complexes gave only moderate to good asymmetric induction in intermolecular [3+2] cycloadditions, they demonstrated to be efficient catalysts for intramolecular [3+2] cycloadditions of azomethine ylides, giving access to tricylic products with almost complete diastereocontrol and enantiomeric excesses of up to 99% (Scheme 48, Table 29, entry 2).[48e]



159 R^1 = H, R^2 = CO_2Me
163 R^1 = H, R^2 = CO_2tBu
164 R^1 = Me, R^2 = CO_2Me
155 R^1 = H, R^2 = Py

161 R^1 = H, R^2 = CO_2Me
165 R^1 = H, R^2 = CO_2tBu
166 R^1 = Me, R^2 = CO_2Me
156 R^1 = H, R^2 = Py

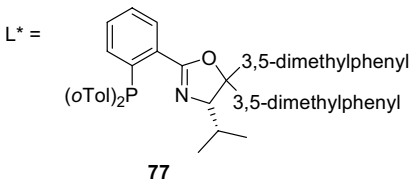


Table 29.

Entry	Product	Yield (%)[a]	*ee* (*endo*) (%)[b]
1	**161**	68	98 (+)
2	**165**	62	99 (+)
3	**166**	60	96 (+)
4	**156**	67	85 (–)

[a] After column chromatography. [b] Determined by chiral HPLC.

Scheme 48.

Additionally the C5-substituted PHOX ligands, originally synthesized for the [3+2] cycloaddition reaction, were applied to the Ir(I)-catalyzed asymmetric hydrogenation of an imine as well as tri- and tetrasubstituted olefins. They induced similar or superior enantioselectivity than the best PHOX ligand (bis(*ortho*-tolyl)phosphino-*tert*-butyloxazoline). This confirmed the preliminary assumption that the steric bulk caused by the substituents at the C5 position of the oxazoline ring might direct the methyl groups of the isopropyl substituent at the C4 position to the coordination center creating a "tertiary butyl substitute". Thus, this ligand type represents a less expensive substitute of the *tert*-leucine-derived PHOX ligand.

Chapter 13

Experimental Part

13 Experimental Part

13.1 Analytical Methods

NMR-Spectrometry: NMR spectra were recorded on Bruker Advance 400 (400 MHz) and Bruker Advance DRX 500 (500 MHz) NMR spectrometers, equipped with BBO broadband probeheads. The chemical shift δ is given in ppm. References were 7.26 ppm (^{1}H NMR) and 77.16 ppm (^{13}C NMR) for $CHCl_3$, 5.32 ppm (^{1}H NMR) and 54.0 ppm (^{13}C NMR) for CH_2Cl_2, 2.09 ppm (^{1}H NMR) and 20.40 ppm (^{13}C NMR) for toluene and 2.50 ppm (^{1}H NMR) and 39.51 ppm (^{13}C NMR) for DMSO.[92] 85% phosphoric acid (0 ppm) was taken as an external standard in a capillary for ^{31}P NMR. For spectra that were measured on the 500 MHz NMR spectrometer, the shifts were corrected (–0.209 ppm for CD_2Cl_2, 0.640 ppm for toluene-D_8). For spectra that were measured on the 400 MHz NMR spectrometer, the shifts were corrected (–3.592 ppm for CD_2Cl_2, –3.626 ppm for $CDCl_3$). $CFCl_3$ was taken as an external standard in a capillary for ^{19}F NMR. For spectra that were measured on the 400 MHz NMR spectrometer, the shifts were corrected (–0.851 ppm for CD_2Cl_2, –0.884 ppm for $CDCl_3$). The assignment of ^{1}H- and ^{13}C-signals was made by 2D-NMR, namely COSY, HMQC, HMBC, TOCSY and difference NOESY-spectrometry. ^{13}C and ^{31}P, until otherwise noted, were recorded ^{1}H-decoupled. Multiplets were assigned with s (singlet), d (doublet), t (triplet), ds (doublet of septet), m (multiplet). The relative configuration of the pyrrolidine compounds was determined by NOESY experiments.

Mass Spectrometry (MS): Mass spectra were recorded by Dr. H. Nadig. Electron ionization (EI) was measured on VG70-250, fast atom bombardment (FAB) was measured on MAR 312, Electron spray ionization (ESI) was measured on Finnigan MAT LCQ by A. Teichert. FAB was performed with 3-nitrobenzyl alcohol as matrix. The signals are given in mass-to-charge ratio (m/z). The fragment and intensities of the signals are given in brackets.

Infrared Spectrometry (IR): Infrared spectra were measured on a Perkin Elmer 1600 series FTIR spectrometer. Solid samples were prepared as KBr wafers, liquid samples were prepared between NaCl plates. For air and moisture sensitive compounds KBr was thoroughly dried under high vacuum and samples were prepared in the glove box. Absorption bands are given in wave numbers $\tilde{\upsilon}$ [cm^{-1}]. The peak intensity is assigned with s (strong), m (medium) and w (weak).^

Melting Point (m.p.): The melting point was measured in a Büchi 535 melting point apparatus. The values are not corrected.

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

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

Gas Chromatography (GC): The gas chromatographs in use were Carlo Erba HRGC Mega2 Series 800 (HRGC Mega 2). Achiral separations were performed with Macherey-Nagel Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm). For chiral separations β-cyclodextrine columns (30 m × 0.25 mm × 0.25 μm) were used.

High Performance Liquid Chromatography (HPLC): For HPLC analysis Shimadzu systems with SCL-10A System Controller, CTO-10AC column oven, LC10-AD pump system, DGU-14A degasser, and SPD-M10A Diode Array- or UV-vis detector were used. Chiral columns Chiracel OD-H, OB-H, OJ, AS, AD-H and Chiralpak AD from Daicel Chemical Industries Ltd. were used.

Elemental Analysis (EA): Elemental analyses were carried out by Mr. W. Kirsch at the Department of Chemistry at the University of Basel, on Leco CHN-900 (C-, H-, N-detection) and Leco RO-478 (O-detection) analysers. The data are indicated in mass percent.

13.2 Working Techniques

Sensitive Compounds: Syntheses of air- and moisture-sensitive compounds were carried out under inert atmosphere in a glove box (MBRAUN labmaser 130, N_2) or using standard Schlenk techniques (Ar).

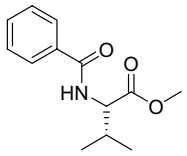
Solvents: Dichloromethane, diethyl ether, pentane, tetrahydrofuran, and toluene were dried and degassed by reflux over an adequate drying agent under nitrogen.[93] Other solvents were purchased dry at Fluka or Aldrich in septum sealed bottles, kept under inert atmosphere and over molecular sieves. If necessary, solvents were degassed by three freeze-pump-thaw cycles. Deuterated solvents were degassed and stored over activated molecular sieves (4Å).

Column Chromatography: Silica gel was obtained from CU Chemie Uetikon (C-560 D, 0.040-0.063 mm) or Merck (silica gel 60, 0.040-0.063 mm). Generally, the *flash column chromatography* according to Still[94] was performed.

13.3 Synthesis of PHOX Ligands

13.3.1 Synthesis of C5-Disubstituted PHOX Ligands

(*S*)-methyl 2-benzamido-3-methylbutanoate (85)



General Procedure I:

To a solution of L-valine methyl ester hydrochloride (3.10 g, 18.3 mmol) and triethylamine (7.60 mL, 54.6 mmol) in dichloromethane (25.0 mL) a solution of the benzoylchloride (2.10 mL, 18.3 mmol) in dichloromethane (15.0 mL) was added within 55 min. at 0 °C. The resulting suspension was stirred at rt over night. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate and filtered over silica gel, which was washed with ethyl acetate. The solvent was removed under reduced pressure and the obtained colorless solid (4.20 g, 97%) was pure enough to be used in the following step.

$C_{13}H_{17}NO_3$ (235.28).

R_f = 0.34 (EtOAc : Hx 1 : 3).

m.p. 110-112 °C.

$[\alpha]_D^{20}$ = +40.6° (c = 0.870, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.99 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 1.01 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 2.28 (ds, *J*(H,H)= 6.8 Hz, *J*(H,H)= 4.8 Hz, 1H, C**H**(CH$_3$)$_2$), 3.78 (s, 3H, C**H**$_3$), 4.79 (dd, *J*(H,H) = 8.7 Hz, *J*(H,H) = 4.9 Hz, 1H, NHC**H**), 6.62 (d, *J*(H,H) = 8.4 Hz, 1H, N**H**), 7.42-7.47 (m, 2H, Ph-**H**), 7.50-7.54 (m, 1H, Ph-**H**), 7.80-7.82 (m, 2H, Ph-**H**).

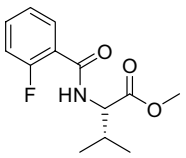
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 18.1 (CH(**C**H$_3$)$_2$), 19.1 (CH(**C**H$_3$)$_2$), 31.8 (**C**H(CH$_3$)$_2$), 52.4 (O**C**H$_3$), 57.5 (N**C**H), 127.2 (2C, **Ph**-H), 128.8 (2C, **Ph**-H), 131.9 (**Ph**-H). 134.3 (**Ph**-C), 167.4 (**C**ONH), 172.8 (**C**O$_2$CH$_3$).

MS (FAB) m/z (rel int %): 236 (M + H, 81), 176 (23), 105 (100), 77 (20).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3347s, 3074w, 2967w, 2872w, 1739s, 1641s, 1603m, 1581m, 1522s, 1490s, 1460m, 1431m, 1392w, 1361m, 1328m, 1297m, 1204s, 1152s, 1067w, 994m, 928w, 892w, 803w, 750m, 734m, 714m, 693m.

EA % found (calcd): C: 66.41 (66.36), H: 7.25 (7.28), N: 5.95 (5.95).

(*S*)-methyl 2-(2-fluorobenzamido)-3-methylbutanoate (89)



Product **89** was prepared according to **general procedure I** (page 133) from L-valine methyl ester hydrochlorid (1.67 g, 10.0 mmol), triethylamine (4.18 mL, 30.0 mmol) and 2-fluorobenzoyl chloride (1.18 mL, 10.0 mmol) in dichloromethane (20.0 mL). The obtained colorless solid (2.20 g, 93%) was pure enough to be used in the following step.

$C_{13}H_{16}NO_3F$ (253.27).

$\mathbf{R}_f$ = 0.43 (EtOAc : Hx 1 : 3).

m.p. 59-60 °C.

$[\alpha]_D^{20}$ = +32.9° (c = 0.500, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 1.00 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 1.03 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 2.30 (ds, *J*(H,H)= 6.8 Hz, *J*(H,H)= 4.7 Hz, 1H, C**H**(CH$_3$)$_2$), 3.77 (s, 3H, C**H**$_3$), 4.79 (dd, *J*(H,H) = 8.7 Hz, *J*(H,H) = 4.9 Hz, 1H, NHC**H**), 7.11-7.27 (m, 3H, Ph-**H** and N**H**), 7.48-7.53 (m, 1H, Ph-**H**), 7.89-8.19 (m, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 18.3 (CH(**C**H$_3$)$_2$), 19.4 (CH(**C**H$_3$)$_2$), 31.7 (**C**H(CH$_3$)$_2$), 52.6 (O**C**H$_3$), 58.1 (N**C**H), 116.6 (d, *J*(C,F) = 24.6 Hz, **Ph**-H), 121.2 (d, *J*(C,F) = 11.3 Hz, **Ph**-H), 125.2 (d, *J*(C,F) = 3.1 Hz, **Ph**-H), 132.5 (d, *J*(C,F) = 1.9 Hz, **Ph**-H), 133.9 (d, *J*(C,F) = 9.2 Hz, **Ph**-C), 159.4 (d, *J*(C,F) = 246.2 Hz, **Ph**-F), 163.5 (d, *J*(C,F) = 3.2 Hz, **C**ONH), 172.6 (**C**O$_2$CH$_3$).

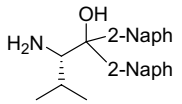
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -114.5 (m).

MS (FAB) m/z (rel int %): 254 (M + H, 100), 194 (41), 123 (62).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3350s, 2966w, 2879w, 1739s, 1645s, 1631m, 1614m, 1484s, 1455m, 1429m, 1362m, 1315m, 1262m, 1240s, 1219m, 1204m, 1159s, 1149m, 1097w, 996m, 893w, 843w, 805w, 766m.

EA % found (calcd): C: 61.84 (61.65), H: 6.29 (6.37), N: 5.54 (5.53).

((S)-2-Amino-3-methyl-1,1-di-naphthalen-2-yl-butan-1-ol)[95] (86)



L-valine methyl ester hydrochloride (3.07g, 18.0 mmol) was added portionwise over 20 min to a 2M *Grignard* solution (55.0 mL, 110 mmol) in THF at 0 °C. The reaction mixture was stirred for 4 h at rt before it was quenched by a 2M HCl-solution at 0 °C. The mixture was basified by the addition of aqueous ammonia. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude amino alcohol was purified by column chromatography (DCM : MeOH 20 : 1, $\mathbf{R}_f$ = 0.56) over silica gel to afford a colorless solid (2.00 g, 31%).

$C_{25}H_{25}NO$ (355.47).

m.p. 199-201 °C.

$[\alpha]_D^{20}$ = -281.5° (c = 0.505, CH_2Cl_2).

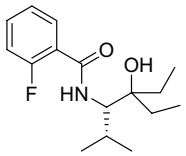
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.94 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.98 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 1.29 (br s, 2H, N**H**$_2$), 1.78 (ds, *J*(H,H) = 6.9 Hz, *J*(H,H) = 2.0 Hz, 1H, C**H**(CH$_3$)$_2$), 4.17 (d, *J*(H,H) = 2.3 Hz, 1H, H$_2$NC**H**), 4.81 (br s, 1H, O**H**), 7.39-7.51 (m, 4H, Naph-**H**), 7.55 (dd, *J*(H,H) = 8.6 Hz, *J*(H,H) = 1.77 Hz, 1H, Naph-**H**), 7.72-7.79 (m, 5H, Naph-**H**), 7.85-7.90 (m, 2H, Naph-**H**), 8.16 (d, J(H,H) = 12.1 Hz, 2H, Naph-**H**).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 15.8 (CH(**C**H$_3$)$_2$), 22.6 (CH(**C**H$_3$)$_2$), 28.2 (**C**H(CH$_3$)$_2$), 59.4 (H$_2$N**C**H), 79.9 (**C**(Naph)$_2$OH), 123.6 (**Naph**-H), 123.9 (**Naph**-H), 124.3 (**Naph**-H), 125.5 (**Naph**-H), 125.7 (**Naph**-H), 125.9 (**Naph**-H), 126.0 (**Naph**-H), 126.1 (**Naph**-H), 127.4 (2C, **Naph**-H), 127.5 (**Naph**-H), 128.1 (**Naph**-H), 128.2 (2C, **Naph**-H), 132.1 (**Naph**-C), 132.3 (**Naph**-C), 133.2 (**Naph**-C), 133.3 (**Naph**-C), 142.4 (**Naph**-C), 145.5 (**Naph**-C).

MS (FAB) m/z (rel int %): 356 (M + H, 9), 338 (18), 127 (11), 72 (100), 55 (13);

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3407s, 3338s, 3060m, 2952s, 2926s, 2875m, 1627m, 1597s, 1505s, 1466m, 1435m, 1394m, 1376s, 1293m, 1272m, 1248m, 1164m, 1121s, 1015m, 982m, 905m, 861s, 814s, 754s.

(*S*)-*N*-(4-Ethyl-4-hydroxy-2-methylhexan-3-yl)-2-fluorobenzamide (90)



General Procedure II:

A 3M *Grignard* solution (5.60 mL, 16.8 mmol) in THF was added drop wise to a solution of (*S*)-methyl 2-(2-fluorobenzamido)-3-methylbutanoate (700 mg, 2.80 mmol) in THF (15.0 mL) at 0 °C. After full addition of the *Grignard* reagent the reaction mixture was stirred over night at rt. The resulting suspension was quenched with a saturated NH_4Cl-solution (10 mL) and water (10 mL). The water phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (Hx : EtOAc 4 : 1, $\mathbf{R}_f$ = 0.29) over silica gel to afford a colorless solid (590 mg, 75%).

$C_{16}H_{24}FNO_2$ (281.37).

m.p. 80–81 °C.

$[\alpha]_D^{20}$ = -4.0° (c = 0.620, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.86 (t, *J*(H,H) = 7.6 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.92 (t, *J*(H,H) = 7.6 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.99 (d, *J*(H,H) = 7.1 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 1.01 (d, *J*(H,H) = 7.1 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 1.43 (br s, 1H, O**H**), 1.45-1.72 (m, 4H, $C\mathbf{H}_2CH_3$), 2.20 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 2.3 Hz, 1H, $C\mathbf{H}(CH_3)_2$), 4.18 (dd, *J*(H,H) = 9.8 Hz, *J*(H,H) = 2.6 Hz, 1H, NHC**H**), 7.05-7.15 (m, 2H, Ph-**H,** N**H**), 7.26 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.0 Hz, 1H, Ph-**H**), 7.43-7.47 (m, 1H, Ph-**H**), 8.08 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.7 Hz, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 7.9 ($CH_2\mathbf{C}H_3$), 8.2 ($CH_2\mathbf{C}H_3$), 17.2 ($CH(\mathbf{C}H_3)_2$), 22.4 ($CH(\mathbf{C}H_3)_2$), 28.0 ($\mathbf{C}H_2CH_3$), 28.2 ($\mathbf{C}H(CH_3)_2$), 28.9 ($\mathbf{C}H_2CH_3$), 57.3 (N**C**H), 77.9 (**C**OH), 116.2 (d, *J*(C,F) = 24.9 Hz, **Ph**-H), 121.7 (d, *J*(C,F) = 11.9 Hz, **Ph**-C), 124.9 (d, *J*(C,F) = 3.5 Hz, **Ph**-H), 132.3 (d, *J*(C,F) = 2.3 Hz, **Ph**-H), 133.1 (d, *J*(C,F) = 9.2 Hz, **Ph**-H), 160.7 (d, *J*(C,F) = 247.3 Hz, **Ph**-F), 163.9 (d, *J*(C,F) = 3.5 Hz, **C**=O).

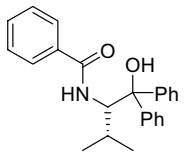
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -115.9 (m).

MS (FAB) m/z (rel int %): 282 (M + H, 58), 264 (100), 194 (25), 140 (31), 123 (91), 87 (11), 83 (12), 69 (26).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3465s, 3088w, 2963m, 2885w, 1654s, 1614w, 1530s, 1477m, 1450w, 1374w, 1315m, 1244w, 1204m, 1138m, 1095w, 1035w, 932w, 884w, 818w, 788w, 757m.

EA % found (calcd): C: 68.27 (68.30), H: 8.60 (8.60), N: 5.00 (4.98).

***(S)*-*N*-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)benzamide (91)**



Product **91** was prepared according to **general procedure II** (page 136) from (*S*)-methyl 2-benzamido-3-methylbutanoate (3.50 g, 14.9 mmol), 3M *Grignard* solution (18.3 mL, 55.0 mmol) in THF and THF as a solvent (20.0 mL). After column chromatography (Hx : EtOAc 4 : 1, $\mathbf{R}_f$ = 0.29) on silica compound **91** (4.23 g, 79%) was isolated as a colorless solid.

$C_{24}H_{25}NO_2$ (359.47).

m.p. 233-235 °C.

$[\alpha]_D^{20}$ = -118.5° (c = 0.375, $CHCl_3$).

^{1}H NMR (400.1 MHz, DMSO, 300 K): δ = 0.75 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 0.98 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.81 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 2.0 Hz, 1H, C**H**(CH$_3$)$_2$), 5.14 (dd, *J*(H,H) = 9.8 Hz, *J*(H,H) = 1.8 Hz, 1H, NHC**H**), 5.86 (s, 1H, O**H**), 7.07 (t, *J*(H,H) = 7.3 Hz, 1H, Ph-**H**), 7.15 (t, *J*(H,H) = 7.3 Hz, 1H, Ph-**H**), 7.21 (t, *J*(H,H) = 7.5 Hz, 2H, Ph-**H**), 7.30 (t, *J*(H,H) = 7.5 Hz, 2H, Ph-**H**), 7.41-7.51 (m, 3H, Ph-**H**), 7.54-7.57 (m, 4H, Ph-**H**), 7.61-7.63 (m, 2H, Ph-**H**), 7.79 (d, *J*(H,H) = 9.8 Hz, 1H, N**H**).

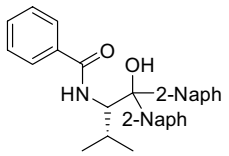
^{13}C{^{1}H} NMR (100.6 MHz, DMSO, 300 K): δ = 18.4 (CH(**C**H$_3$)$_2$), 23.2 (CH(**C**H$_3$)$_2$), 28.6 (**C**H(CH$_3$)$_2$), 58.2 (NH**C**H), 80.9 (**C**OH), 125.0 (2C, **Ph**-H), 125.4 (2C, **Ph**-H), 126.1 (**Ph**-H), 126.3 (**Ph**-H), 127.0 (2C, **Ph**-H), 127.8 (2C, **Ph**-H), 128.1 (2C, **Ph**-H), 128.3 (2C, **Ph**-H), 131.1 (**Ph**-H), 135.2 (**Ph**-C), 146.2 (**Ph**-C), 147.8 (**Ph**-C), 167.1 (**C**O).

MS (FAB) m/z (rel int %): 360 (M + H, 4), 342 (23), 176 (19), 105 (100), 77 (16).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3417s, 3062w, 3024w, 2960w, 1630s, 1521s, 1489m, 1449m, 1366m, 1324m, 1162m, 1061m, 898w, 749m, 700s.

EA % found (calcd): C: 79.84 (80.19), H: 7.25 (7.01), N: 4.04 (3.90).

***(S)*-*N*-(1-hydroxy-3-methyl-1,1-di(naphthalen-2-yl)butan-2-yl)benzamide (87)**



Product **87** was prepared according to **general procedure II** (page 136) from (*S*)-methyl 2-benzamido-3-methylbutanoate (0.97 g, 4.1 mmol), 3M *Grignard* solution (8.00 mL, 24.1 mmol) in THF and THF as a solvent (22.0 mL). After column chromatography (Hx : EtOAc 3 : 1, $\mathbf{R}_f$ = 0.71) on silica compound **87** (1.69 g, 90%) was isolated as a colorless solid.

$C_{32}H_{29}NO_2$ (459.58).

m.p. 230-232 °C.

$[\alpha]_D^{20}$ = -150.0° (c = 0.555, CH_2Cl_2).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.98 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.10 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 2.07 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 2.3 Hz, 1H, C**H**(CH$_3$)$_2$), 3.85 (br s, 1H, O**H**), 5.49 (dd, *J*(H,H) = 10.0 Hz, *J*(H,H) = 2.3 Hz, 1H, NHC**H**), 7.06 (d, *J*(H,H) = 9.8 Hz, 1H, N**H**), 7.09-7.13 (m, 2H, Ar-**H**), 7.27-7.30 (m, 1H, Ar-**H**), 7.37-7.42 (m, 2H, Ar-**H**), 7.44-7.53 (m, 4H, Ar-**H**), 7.60-7.70 (m, 4H, Ar-**H**), 7.80-7.83 (m, 3H, Ar-**H**), 7.91 (d, *J*(H,H) = 7.6 Hz, 1H, Ar-**H**), 8.28-8.29 (m, 2H, Ar-**H**).

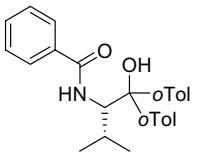
^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 17.8 (CH(**C**H$_3$)$_2$), 22.8 (CH(**C**H$_3$)$_2$), 29.6 (**C**H(CH$_3$)$_2$), 58.3 (HN**C**H), 82.8 (**C**OH), 123.7 (**Ar**-H), 124.2 (**Ar**-H), 124.3 (**Ar**-H), 124.3 (**Ar**-H), 126.1 (**Ar**-H), 126.2 (2C, **Ar**-H), 126.4 (**Ar**-H), 126.7 (2C, **Ar**-H), 127.3 (**Ar**-H), 127.5 (**Ar**-H), 128.2 (**Ar**-H), 128.2 (**Ar**-H), 128.3 (**Ar**-H), 128.3 (2C, **Ar**-H), 128.5 (**Ar**-H), 131.2 (**Ar**-H), 132.3 (**Ar**-C), 132.4 (**Ar**-C), 133.2 (**Ar**-C), 133.3 (**Ar**-C), 135.0 (**Ar**-C), 143.0 (**Ar**-C), 143.5 (**Ar**-C), 168.2 (**C**O).

MS (FAB) m/z (rel int %): 460 (M + H, 1), 442 (22), 177 (23), 127 (10), 105 (100), 77 (17).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3417s$_{br}$, 3056m, 2959m, 2872w, 1629s, 1601m, 1578m, 1522s$_{br}$, 1487s, 1357m, 1315m, 1271m, 1244w, 1204w, 1154m, 1122m, 1076w, 1019w, 967w, 903w, 860w, 817m, 783.4m, 758s, 691m, 477m.

EA % found (calcd): C: 83.31 (83.63), H: 6.65 (6.36), N: 2.72 (3.05).

***(S)*-*N*-(1-hydroxy-3-methyl-1,1-di-o-tolylbutan-2-yl)benzamide (92)**



Product **92** was prepared according to **general procedure II** (page 136) from (*S*)-methyl 2-benzamido-3-methylbutanoate (700 mg, 3.00 mmol), 3M *Grignard* solution (3.30 mL, 10.0 mmol) in THF and THF as a solvent (17.0 mL). After column chromatography (Hx : EtOAc 5 : 1, $\mathbf{R}_f$ = 0.29) on silica compound **92** (0.70 g, 60%) was isolated as a colorless solid.

$C_{26}H_{29}NO_2$ (387.51).

m.p. 184-186 °C.

$[\alpha]_D^{20}$ = -210.7° (c = 0.870, $CDCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.91 (d, *J*(H,H) = 6.2 Hz, 3H, CH(C**H**$_3$)$_2$), 0.99 (d, *J*(H,H) = 6.2 Hz, 3H, CH(C**H**$_3$)$_2$), 1.59 (br s, 1H, C**H**(CH$_3$)$_2$), 1.98 (s, 6H, Ph-C**H**$_3$), 2.90 (br s, 1H, O**H**), 5.33 (br s, 1H, NHC**H**), 7.02-7.29 (m, 6H, Ar-**H**), 7.36-7.39 (m, 2H, Ar-**H**), 7.45-7.48 (m, 1H, Ar-**H**), 7.68 (br s, 2H, Ar-**H**), 7.89 (m, 1H, Ar-**H**), 8.17 (br s, 1H, Ar-**H**). (N**H** not visible).

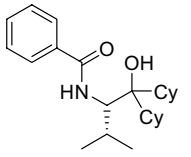
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 300 K): δ = 17.0 (**C**H$_3$), 21.8 (**C**H$_3$), 21.9 (**C**H$_3$), 23.1 (**C**H$_3$), 30.4 (**C**H(CH$_3$)$_2$), 55.8 (NH**C**H), 83.0 (**C**OH), 125.2 (**Ar**-H), 125.7 (**Ar**-H), 126.9 (2C, **Ar**-H), 127.5 (**Ar**-H), 127.8 (**Ar**-H), 128.0 (**Ar**-H), 128.1 (**Ar**-H), 128.6 (2C, **Ar**-H), 131.4 (**Ar**-H), 132.3 (**Ar**-C), 132.4 (**Ar**-H), 133.5 (**Ar**-H), 135.3 (**Ar**-C), 136.1 (**Ar**-C), 142.2 (**Ar**-C), 142.3 (**Ar**-C), 167.6 (**C**=O).

MS (FAB) m/z (rel int %): 388 (M + H, 6), 370 (40), 211 (10), 176 (23), 119 (12), 105 (100).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3428s, 3341s, 3061w, 2959s, 2872w, 1632s, 1575m, 1524s, 1484s, 1459s, 1363m, 1314s, 1165w, 1125m, 1050m, 904w, 745s, 694m, 619w, 571w.

EA % found (calcd): C: 80.70 (80.59), H: 7.52 (7.54), N: 3.58 (3.61).

***(S)*-*N*-(1,1-dicyclohexyl-1-hydroxy-3-methylbutan-2-yl)benzamide (93)**



General Procedure III:

$CeCl_3 \cdot 7H_2O$ (11.2 g, 30.0 mmol) was heated at 140 °C under high vacuum over night. After cooling the colorless powder to 0 °C it was suspended in THF (80.0 mL) and stirred for 30 min before a 2M *Grignard* solution (15.0 mL, 30.0 mmol) in THF was added drop wise. After the reaction mixture was stirred for 2 h at 0 °C, (*S*)-methyl 2-benzamido-3-methylbutanoate (1.20 g, 5.00 mmol) was added and the mixture was stirred over night at rt. The mixture was carefully quenched by a 1M HCl-solution and the pH-value was adjusted to about 3. The organic layer was separated, the aqueous phase was extracted with ethyl acetate (2 x 30 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Hx : EtOAc 5 : 1, $\mathbf{R}_f$ = 0.29) on silica to give a colorless solid (0.97 g, 52%).

$C_{24}H_{37}NO_2$ (371.56).

m.p. 206-207 °C.

$[\alpha]_D^{20}$ = +17.8° (c = 0.630, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.96 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.00 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.05-1.15 (m, 4H, Cy-**H**), 1.19-1.35 (m, 6H, Cy-**H**), 1.57-1.88 (m, 13H, Cy-**H** and O**H**), 2.20 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 1.8 Hz, 1H, C**H**(CH$_3$)$_2$), 4.36 (dd, *J*(H,H) = 9.8 Hz, *J*(H,H) = 1.5 Hz, 1H, NHC**H**), 6.59 (br d, *J*(H,H) = 9.8 Hz, 1H, N**H**), 7.43-7.53 (m, 3H, Ph-**H**), 7.76-7.78 (m, 2H, Ph-**H**).

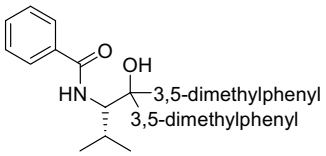
^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 17.9 (CH(**C**H$_3$)$_2$), 23.0 (CH(**C**H$_3$)$_2$), 27.3 (**Cy**$_{(CH2)}$), 27.4 (**Cy**$_{(CH2)}$), 28.0 (**Cy**$_{(CH2)}$), 28.0 (**Cy**$_{(CH2)}$), 28.1 (**Cy**$_{(CH2)}$), 28.5 (**Cy**$_{(CH2)}$), 28.6 (**Cy**$_{(CH2)}$), 29.6 (**C**H(CH$_3$)$_2$), 29.7 (**Cy**$_{(CH2)}$), 29.8 (**Cy**$_{(CH2)}$), 30.2(**Cy**$_{(CH2)}$), 46.1(**Cy**$_{(CH)}$), 47.8(**Cy**$_{(CH)}$), 55.6 (N**C**H), 80.6 (**C**OH), 127.3 (2C, **Ph**-H), 129.1 (2C, **Ph**-H), 131.6 (**Ph**-H), 136.2 (**Ph**-C), 167.2 (**C**ONH).

MS (FAB) m/z (rel int %): 372 (M + H, 11), 354 (20), 176 (29), 105 (100), 83 (13), 77 (17), 55 (20), 41 (14).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3548w, 3427m, 3072w, 2931s, 2853m, 1648s, 1603m, 1578w, 1508s, 1484m, 1450w, 1318w, 1195s, 1039w, 967w, 894w, 718m, 692m.

EA % found (calcd): C: 77.25 (77.58), H: 9.98 (10.04), N: 3.78 (3.77).

***(S)*-*N*-(1,1-bis(3,5-dimethylphenyl)-1-hydroxy-3-methylbutan-2-yl)benzamide (94)**



Product **94** was prepared according to **general procedure III** (page 140) from $CeCl_3 \cdot 7H_2O$ (19.0 g, 51.0 mmol), 2M *Grignard* solution (25.5 mL, 51.0 mmol) in THF, (*S*)-methyl 2-benzamido-3-methylbutanoate (2.00 g, 8.50 mmol), and THF as a solvent (140 mL). After column chromatography (DCM, $\mathbf{R}_f$ = 0.44) on silica compound **94** (2.8 g, 80%) was isolated as a colorless solid.

$C_{28}H_{33}NO_2$ (415.57).

m.p. 203-205 °C.

$[\alpha]_D^{20}$ = -78.0° (c = 0.750, $CDCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.97 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.98 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.91 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 2.0 Hz, 1H, C**H**(CH$_3$)$_2$), 2.21 (s, 6H, Ar-C**H**$_3$), 2.31 (s, 6H, Ar-C**H**$_3$), 5.10 (dd, *J*(H,H) = 9.8 Hz, *J*(H,H) = 2.0 Hz, 1H, NC**H**), 6.62 (d, *J*(H,H) = 9.6 Hz, 1H, N**H**), 6.76 (br s, 1H, Ar-**H**), 6.86 (br s, 1H, Ar-**H**), 7.11-7.13 (m, 4H, Ar-**H**), 7.31-7.35 (m, 2H, Ar-**H**), 7.40-7.44 (m, 1H, Ar-**H**), 7.54-7.58 (m, 2H, Ar-**H**). (O**H** not visible).

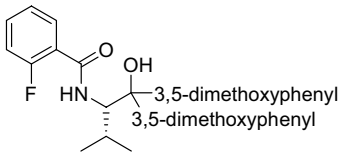
^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 300 K): δ = 18.1 (CH(**C**H$_3$)$_2$), 21.6 (2C, Ar-**C**H$_3$), 21.7 (2C, Ar-**C**H$_3$), 23.2 (CH(**C**H$_3$)$_2$), 29.4 (**C**H(CH$_3$)$_2$), 58.3 (NH**C**H), 82.6 (**C**OH), 123.2 (2C, **Ar**-H), 123.3 (2C, **Ar**-H), 126.9 (2C, **Ar**-H), 128.5 (2C, **Ar**-H), 128.7 (**Ar**-H), 128.8 (**Ar**-H), 131.2 (**Ar**-H), 135.7 (**Ar**-C), 137.9 (2C, **Ar**-C), 138.0 (2C, **Ar**-C), 145.6 (**Ar**-C), 146.2 (**Ar**-C), 168.0 (C=O).

MS (FAB) m/z (rel int %): 416 (M + H, 4), 398 (42), 239 (12), 177 (23), 133 (23), 105 (100), 77 (12), 55 (14), 43 (13).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3425s, 3304m, 3058w, 2958m, 2919m, 2870w, 1628s, 1546m, 1484m, 1367m, 1320m, 1277m, 1152m, 1032w, 851m, 744w.

EA % found (calcd): C: 80.55 (80.93), H: 8.30 (8.00), N: 3.28 (3.37).

***(S)*-*N*-(1,1-bis(3,5-dimethoxyphenyl)-1-hydroxy-3-methylbutan-2-yl)-2-fluorobenzamide (95)**



Product **95** was prepared according to **general procedure III** (page 140) from $CeCl_3 \cdot 7H_2O$ (7.70 g, 20.7 mmol), 2M *Grignard* solution (10.4 mL, 20.7 mmol) in THF, (*S*)-methyl 2-(2-fluorobenzamido)-3-methylbutanoate (875 mg, 3.45 mmol), and THF as a solvent (60.0 mL). After column chromatography (Hx : EtOAc 4 : 1, $\mathbf{R}_f$ = 0.09) on silica compound **95** (1.27 g, 74%) was isolated as a colorless solid.

$C_{28}H_{32}FNO_6$ (497.56).

m.p. 199-200 °C.

$[\alpha]_D^{20}$ = -107.0° (c = 0.820, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.95 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.97 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.89 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 2.0 Hz, 1H, C**H**(CH$_3$)$_2$), 2.70 (br s, 1H, O**H**), 3.72 (s, 6H, OC**H**$_3$), 3.76 (s, 6H, OC**H**$_3$), 5.16 (td, *J*(H,H) = 9.8 Hz, *J*(H,H) = 2.6 Hz, 1H, NHC**H**), 6.25 (t, *J*(H,H) = 2.3 Hz, 1H, Ar-**H**), 6.31 (t, *J*(H,H) = 2.3 Hz, 1H, Ar-**H**), 6.65 (d, *J*(H,H) = 2.3 Hz, 2H, Ar-**H**), 6.73 (d, *J*(H,H) = 2.3 Hz, 2H, Ar-**H**), 7.04 (ddd, *J*(H,F) = 11.9 Hz, *J*(H,H) = 8.1 Hz, *J*(H,H) = 1.0 Hz, 1H, Ar-**H**), 7.18 (dt, *J*(H,H) = 8.0 Hz, *J*(H,H) = 1.0 Hz, 1H, Ar-**H**), 7.22 (d, *J*(H,H) = 9.8 Hz, 1H, N**H**), 7.37–7.43 (m, 1H, Ar-**H**), 7.93 (dt, *J*(H,H) = 7.9 Hz, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 300 K): δ = 17.6 (CH(**C**H$_3$)$_2$), 22.9 (CH(**C**H$_3$)$_2$), 29.4 (**C**H(CH$_3$)$_2$), 55.5 (2C, O**C**H$_3$), 55.5 (2C, O**C**H$_3$), 60.5 (NH**C**H), 82.4 (**C**OH), 98.5 (**Ar**-H), 99.8 (**Ar**-H), 103.7 (2C, **Ar**-H), 103.9 (2C, **Ar**-H), 116.2 (d, *J*(C,F) = 24.5 Hz, **Ar**-H), 121.7 (d, J(C,F) = 11.5 Hz, **Ar**-C), 124.8 (d, *J*(C,F) = 3.1 Hz, **Ar**-H), 131.9 (d, *J*(C,F) = 1.9 Hz, **Ar**-H), 133.1 (d, *J*(C,F) = 9.2 Hz, **Ar**-H), 148.1 (**Ar**-C), 148.9 (**Ar**-C), 160.6 (d, *J*(C,F) = 247.7 Hz, **Ar**-F), 160.9 (2C, **Ar**-OMe), 160.9 (2C, **Ar**-OMe), 163.5 (d, *J*(C,F) = 3.1 Hz, **C**=O).

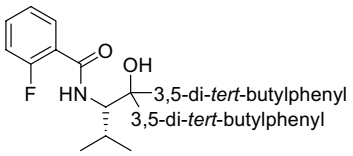
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = - 115.8 (m).

MS (FAB) m/z (rel int %): 480 (M + H, 64), 341 (13), 177 (100), 162 (37), 123 (63), 69 (10), 57 (13), 55 (16), 43 (14), 41 (13).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3444m, 3083w, 2959m, 2837w, 1643s, 1601s, 1529s, 1460s, 1427s, 1311s, 1204s, 1155s, 1061s, 926w, 835m, 752m.

EA % found (calcd): C: 67.50 (67.59), H: 6.40 (6.48), N: 2.90 (2.82).

(*S*)-*N*-(1,1-bis(3,5-di-*tert*-butylphenyl)-1-hydroxy-3-methylbutan-2-yl)-2-fluorobenzamide (96)



Product **96** was prepared according to **general procedure III** (page 140) from $CeCl_3 \cdot 7H_2O$ (6.90 g, 18.6 mmol), 2M *Grignard* solution (9.30 mL, 18.6 mmol) in THF, (*S*)-methyl 2-(2-fluorobenzamido)-3-methylbutanoate (784 mg, 3.10 mmol), and THF as a solvent (55.0 mL). After column chromatography (Hx : EtOAc 8 : 1, $\mathbf{R}_f$ = 0.27) on silica compound **96** (1.72 g, 92%) was isolated as a colorless solid.

$C_{40}H_{56}FNO_2$ (601.88).

m.p. 79-81 °C.

$[\alpha]_D^{20}$ = -10.4° (c = 0.585, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.90 (d, J(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 0.99 (d, J(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.21 (s, 18H, 2 x C(C**H**$_3$)$_3$), 1.29 (s, 18H, 2 x C(C**H**$_3$)$_3$), 1.97 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 2.0 Hz, 1H, C**H**(CH$_3$)$_2$), 2.24 (br s, 1H, OH), 5.25 (td, *J*(H,H) = 9.8 Hz, *J*(H,H) = 2.3 Hz, 1H, NHC**H**), 7.01-7.12 (m, 2H, Ar-**H** and N**H**), 7.15-7.18 (m, 2H, Ar-**H**), 7.25 (t, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**), 7.33 (d, *J*(H,H) = 1.8 Hz, 2H, Ar-**H**), 7.35 (d, *J*(H,H) = 1.8 Hz, 2H, Ar-**H**), 7.36-7.41 (m, 1H, Ar-**H**), 7.86 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): 17.9 (CH(**C**H$_3$)$_2$), 23.2 (CH(**C**H$_3$)$_2$), 29.3 (**C**H(CH$_3$)$_2$), 31.5 (6C, C(**C**H$_3$)$_3$), 31.6 (6C, C(**C**H$_3$)$_3$), 35.0 (2C, **C**(CH$_3$)$_3$), 35.1 (2C, **C**(CH$_3$)$_3$), 59.0 (NH**C**H), 83.1 (**C**-OH), 116.0 (d, *J*(C,F) = 24.5 Hz, Ar-H), 120.1 (2C, Ar-H), 120.1 (2C, Ar-H), 120.5 (Ar-H), 120.6 (Ar-H), 121.9 (d, J(C,F) = 11.9 Hz, Ar-C), 124.6 (d, *J*(C,F) = 3.1 Hz, **Ar**-H), 132.0 (d, *J*(C,F) = 2.3 Hz, **Ar**-H), 132.8 (d, *J*(C,F) = 9.2 Hz, **Ar**-H), 144.7 (**Ar**-C), 145.2 (**Ar**-C), 150.4 (2C, **Ar**-C(CH$_3$)$_3$), 150.5 (2C, **Ar**-C(CH$_3$)$_3$), 160.6 (d, *J*(C,F) = 247.6 Hz, **Ar**-F), 163.2 (d, *J*(C,F) = 3.1 Hz, **C**=O).

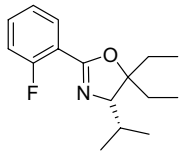
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -115.7.

MS (FAB) m/z (rel int %): 584 (M - OH, 5), 195 (10), 123 (44), 57 (100), 41 (25), 39 (11).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3454m, 3078w, 2961s, 2871s, 1705m, 1657s, 1597m, 1530s, 1478s, 1364s, 1313m, 1250s, 1203m, 1095w, 1141w, 879m, 818w, 756m.

EA % found (calcd): C: 79.45 (79.82), H: 9.47 (9.38), N 2.27 (2.33)

***(S)*-5,5-Diethyl-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (97)**



General Procedure IV:

A solution of (*S*)-*N*-(4-ethyl-4-hydroxy-2-methylhexan-3-yl)-2-fluorobenzamide (1.00 g, 3.60 mmol) and methanesulfonic acid (717 µL, 11.1 mmol) in dichloromethane (65.0 mL) was heated to reflux for 12 h using a Soxhlet kind extractor filled with CaH_2 (4.60 g) to remove the water. The reaction mixture was then quenched with a saturated $NaHCO_3$-solution (55 mL) and the aqueous phase was extracted with dichloromethane (2 x 35 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (Hx : EtOAc 6 : 1, $\mathbf{R}_f$ = 0.37) on silica to afford product 97 (0.8 g, 85%) as a colorless solid.

$C_{16}H_{22}FNO$ (263.35).

$[\alpha]_D^{20}$ = -65.0° (c = 0.270, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.95 (t, *J*(H,H) = 7.6 Hz, 3H, $CH_2C\mathbf{H}_3$), 1.01 (t, *J*(H,H) = 7.4 Hz, 3H, $CH_2C\mathbf{H}_3$), 1.04 (d, *J*(H,H) = 6.8 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 1.06 (d, *J*(H,H) = 6.6 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 1.60-1.74 (m, 2H, $C\mathbf{H}_2$), 1.84-1.92 (m, 2H, $C\mathbf{H}_2$), 1.94 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 6.7 Hz, 1H, $C\mathbf{H}(CH_3)_2$), 3.65 (d, *J*(H,H) = 7.0 Hz, 1H, NC**H**), 7.12 (ddd, *J*(H,F) = 10.8 Hz, *J*(H,H) = 8.3 Hz, *J*(H,H) = 1.2 Hz, 1H, Ph-**H**), 7.19 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.2 Hz, 1H, Ph-**H**), 7.41-7.46 (m, 1H, Ph-**H**), 7.86 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.2 Hz, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 8.1 ($\mathbf{C}H_3$), 8.9 ($\mathbf{C}H_3$), 20.6 ($CH(\mathbf{C}H_3)_2$), 22.1 ($CH(\mathbf{C}H_3)_2$), 25.6 ($\mathbf{C}H_2$), 29.0 ($\mathbf{C}H(CH_3)_2$), 30.2 ($\mathbf{C}H_2$), 77.8 (N**C**H), 91.1 (O**C**), 117.0 (d, *J*(C,F) = 21.9 Hz, **Ph**-H), 117.8 (d, *J*(C,F) = 11.1 Hz, **Ph**-C), 124.4 (d, *J*(C,F) = 4.8 Hz, **Ph**-H), 131.6 (d, *J*(C,F) = 2.3 Hz, **Ph**-H), 132.8 (d, *J*(C,F) = 8.8 Hz, **Ph**-H), 158.9 (d, *J*(C,F) = 4.6 Hz, **C**=N), 161.6 (d, *J*(C,F) = 256.3 Hz, **Ph**-F).

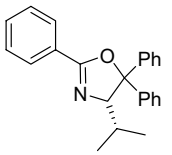
^{19}F{^{1}H} NMR (376.5 MHz, CD_2Cl_2, 300 K): δ = -112.7 (m).

MS (FAB) m/z (rel int %): 264 (M + H, 100), 220 (16), 140 (18), 83 (14), 69 (35), 57 (40).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3078w, 2968s, 2880m, 2868m, 1649s, 1614w, 1582w, 1495m, 1459s, 1342m, 1276m, 1228m, 1112w, 1061m, 1034m, 929m, 765m, 669w.

EA % found (calcd): C: 72.91 (72.97), H: 8.46 (8.42), N: 5.43 (5.32).

(*S*)-4-isopropyl-2,5,5-triphenyl-4,5-dihydrooxazole (98)



Product **98** was prepared according to **general procedure IV** (page 144) from *(S)*-*N*-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)benzamide (4.00 g, 11.1 mmol), methanesulfonic acid (2.20 mL, 34.4 mmol), CaH_2 (10.0 g) and dichloromethane as a solvent (240 mL). After column chromatography (Hx : EtOAc 8 : 1, $\mathbf{R}_f$ = 0.5) on silica compound **98** (3.10 g, 82%) was isolated as a colorless solid.

$C_{24}H_{23}NO$ (341.45).

m.p. 93-95 °C.

$[\alpha]_D^{20}$ = -354.6° (c = 0.945, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.58 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.04 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.89 (ds, *J*(H,H) = 6.6 Hz, *J*(H,H) = 4.5 Hz, 1H, C**H**(CH$_3$)$_2$), 4.79 (d, *J*(H,H) = 4.2 Hz, 1H, NC**H**), 7.23–7.40 (m, 8H, Ph-**H**), 7.45-7.55 (m, 3H, Ph-**H**), 7.59-7.61 (m, 2H, Ph-**H**), 8.11 (m, 2H, Ph-**H**).

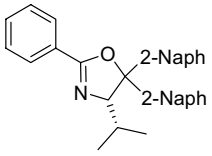
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 17.1 (CH(**C**H$_3$)$_2$), 22.2 (CH(**C**H$_3$)$_2$), 31.0 (**C**H(CH$_3$)$_2$), 80.5 (N**C**H), 93.0 (O**C**Ph$_2$), 126.5 (2C, **Ph**-H), 127.4 (2C, **Ph**-H), 127.7 (**Ph**-H), 128.3 (**Ph**-H), 128.3 (2C, **Ph**-H), 128.7 (**Ph**-C), 128.8 (2C, **Ph**-H), 128.9 (2C, **Ph**-H), 128.9 (2C, **Ph**-H), 131.9 (**Ph**-H), 141.6 (**Ph-**C), 146.5 (**Ph**-C), 161.6 (**C**=N).

MS (FAB) m/z (rel int %): 342 (M + H, 49), 159 (44), 144 (16), 105 (100), 77 (21).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3426m, 3057m, 2952m, 2865m, 1662s, 1582w, 1494m, 1448m, 1330s, 1286m, 1177w, 1104s, 1070w, 1026m, 950s, 896w, 765m, 695s.

EA % found (calcd): C: 84.41 (84.42), H: 6.84 (6.79), N: 4.10 (4.10).

(*S*)-4-isopropyl-5,5-di(naphthalen-2-yl)-2-phenyl-4,5-dihydrooxazole (88)



Product **88** was prepared according to **general procedure IV** (page 144) from *(S)*-*N*-(1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)benzamide (1.50 g, 3.30 mmol), methanesulfonic

acid (0.66 mL, 10.2 mmol), CaH_2 (4.00 g) and dichloromethane as a solvent (66.0 mL). After column chromatography (Hx : EtOAc 6 : 1, $\mathbf{R}_f$ = 0.5) on silica compound **88** (1.20 g, 82%) was isolated as a colorless solid.

$C_{32}H_{27}NO$ (441.56).

m.p. 76-79 °C.

$[\alpha]_D^{20}$ = -499.0° (c = 0.530, CH_2Cl_2).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.62 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.11 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.95 (ds, *J*(H,H) = 6.6 Hz, *J*(H,H) = 4.3 Hz, 1H, C**H**(CH$_3$)$_2$), 5.09 (d, *J*(H,H) = 4.3 Hz, 1H, NC**H**), 7.45-7.54 (m, 8H, Ar-**H**), 7.69 (dd, *J*(H,H) = 8.7 Hz, *J*(H,H) = 2.0 Hz, 1H, Ar-**H**), 7.78 (d, *J*(H,H) = 8.6 Hz, 1H, Ar-**H**), 7.80-7.83 (m, 4H, Ar-**H**), 7.88-7.91 (m, 1H, Ar-**H**), 7.99-8.00 (m, 1H, Ar-**H**), 8.13-8.18 (m, 3H, Ar-**H**).

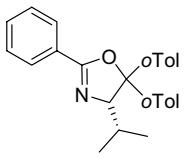
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 17.1 (CH(**C**H$_3$)$_2$), 22.3 (CH(**C**H$_3$)$_2$), 31.1 (**C**H(CH$_3$)$_2$), 79.6 (N**C**H), 93.4 (**C**(Naph)$_2$), 125.0 (**Ar**-H), 125.0 (**Ar**-H), 125.8 (**Ar**-H), 125.9 (**Ar**-H), 126.0 (**Ar**-H), 126.8 (**Ar**-H), 126.8 (**Ar**-H), 126.9 (**Ar**-H), 126.9 (**Ar**-H), 127.9 (**Ar**-H), 127.9 (**Ar**-H), 128.0 (**Ar**-H), 128.7 (**Ar**-H), 128.8 (**Ar**-H), 128.8 (**Ar**-H), 128.8 (**Ar**-C), 128.9 (**Ar**-H), 129.0 (2C, **Ar**-H), 131.9 (**Ar**-H), 133.0 (**Ar**-C), 133.4 (2C, **Ar**-C), 133.4 (**Ar**-C), 138.9 (**Ar**-C), 143.2 (**Ar**-C), 161.8 (**C**=N).

MS (FAB) m/z (rel int %): 442 (M + H, 51), 321 (5), 267 (8), 159 (84), 144 (38), 127 (10), 105 (100), 77 (19).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3462w$_{br}$, 3057m, 2957m, 2870m, 1654s, 1600w, 1579w, 1506m, 1450m, 1340s, 1272m, 1175m, 1118m, 1062m, 1024m, 968m, 938m, 904m, 858m, 813s, 772m, 746s, 693s.

EA % found (calcd): C: 86.81 (87.04), H: 6.43 (6.16), N: 3.09 (3.17).

(*S*)-4-isopropyl-2-phenyl-5,5-di*o*-tolyl-4,5-dihydrooxazole (99)



Product **99** was prepared according to **general procedure IV** (page 144) from *(S)*-*N*-(1-hydroxy-3-methyl-1,1-di-*o*-tolylbutan-2-yl)benzamide (3.20 g, 8.26 mmol), methanesulfonic acid (1.66 mL, 25.6 mmol), CaH_2 (10.0 g) and dichloromethane as a solvent (180 mL). After

column chromatography (Hx : EtOAc 8 : 1, $\mathbf{R}_f$ = 0.4) on silica compound **99** (2.20 g, 71%) was isolated as a colorless solid.

$C_{26}H_{27}NO$ (369.5).

m.p. 39-42 °C.

$[\alpha]_D^{20}$ = -601.8° (c = 0.940, $CDCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.59 (d, *J*(H,H)= 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.11 (d, *J*(H,H)= 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.42 (ds, *J*(H,H)= 6.8 Hz, *J*(H,H)= 2.5 Hz, 1H, C**H**(CH$_3$)$_2$), 1.83 (s, 3H, *o*Tol-C**H**$_3$), 2.05 (s, 3H, *o*Tol-C**H**$_3$), 5.22 (d, *J*(H,H)= 2.5 Hz, 1H, NC**H**), 7.06-7.08 (m, 2H, Ar-**H**), 7.15-7.24 (m, 4H, Ar-**H**), 7.39-7.42 (m, 2H, Ar-**H**), 7.45-7.49 (m, 1H, Ar-**H**), 7.70-7.72 (m, 1H, Ar-**H**), 7.92 (bs, 1H, Ar-**H**), 7.97-7.99 (m, 2H, Ar-**H**).

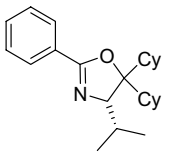
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 16.5 (**C**H$_3$), 22.0 (**C**H$_3$), 22.7 (**C**H$_3$), 23.1 (**C**H$_3$), 30.4 (**C**H(CH$_3$)$_2$), 74.8 (NH**C**H), 94.7 (**C**(*o*Tol)$_2$), 125.4 (**Ar**-H), 125.6 (**Ar**-H), 127.1 (**Ar**-H), 128.0 (**Ar**-H), 128.6 (**Ar**-H), 128.7 (2C, **Ar**-H), 128.8 (**Ar**-H), 128.9 (2C, **Ar**-H), 128.9 (**Ar**-C), 131.8 (**Ar**-H), 131.9 (**Ar**-H), 133.6 (**Ar**-H), 135.2 (**Ar**-C), 139.0 (**Ar**-C), 139.5 (**Ar**-C), 140.6 (**Ar**-C), 161.6 (**C**=O).

MS (FAB) m/z (rel int %): 370 (M + H, 68), 195 (9), 159 (70), 144 (17), 119 (13), 105 (100).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3420w, 3061w, 3021w, 2962s, 2871m, 1649s, 1578w, 1487m, 1453s, 1382w, 1341s, 1296m, 1230w, 1172w, 1064m, 1027m, 954s, 820w, 754s, 693s.

EA % found (calcd): C: 84.36 (84.51), H: 7.46 (7.36), N: 3.86 (3.79).

(*S*)-5,5-dicyclohexyl-4-isopropyl-2-phenyl-4,5-dihydrooxazole (100)



Product **100** was prepared according to **general procedure IV** (page 144) from *(S)*-*N*-(1,1-dicyclohexyl-1-hydroxy-3-methylbutan-2-yl)benzamide (1.78 g, 4.80 mmol), methane-sulfonic acid (0.98 mL, 15.1 mmol), CaH_2 (3.30 g) and dichloromethane as a solvent (50.0 mL). After column chromatography (Hx : EtOAc + 3% Et_3N 50 : 1, $\mathbf{R}_f$ = 0.23 and Pe : Diethyl ether 40 : 1, $\mathbf{R}_f$ = 0.15) on silica compound **100** (1.04 g, 61%) was isolated as a colorless solid.

$C_{24}H_{35}NO$ (353.54).

m.p. 110-115 °C.

$[\alpha]_D^{20}$ = -5.4° (c = 0.790, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 1.00-1.33 (m, 10H, Cy-**H**), 1.06 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.21 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.53-1.57 (m, 1H, Cy-**H**), 1.62-1.82 (m, 10H, Cy-**H**), 1.93-2.01 (m, 1H, Cy-**H**), 2.07 (ds, *J*(H,H) = 9.4 Hz, *J*(H,H) = 6.6 Hz, 1H, C**H**(CH$_3$)$_2$), 3.72 (d, *J*(H,H) = 9.4 Hz, 1H, NC**H**), 7.37-7.47 (m, 3H, Ph-**H**), 7.89-7.91 (m, 2H, Ph-**H**).

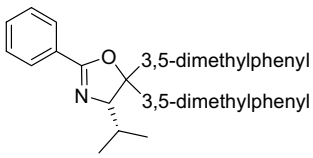
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 22.9 (CH(**C**H$_3$)$_2$), 24.3 (CH(**C**H$_3$)$_2$), 27.0 (**Cy**$_{(CH2)}$), 27.1 (**Cy**$_{(CH2)}$), 27.2 (**Cy**$_{(CH2)}$), 27.2 (**Cy**$_{(CH2)}$), 27.3 (**Cy**$_{(CH2)}$), 27.3 (**Cy**$_{(CH2)}$), 27.8 (**Cy**$_{(CH2)}$), 28.2 (**Cy**$_{(CH2)}$), 28.6 (**Cy**$_{(CH2)}$), 29.4 (**C**H(CH$_3$)$_2$), 29.5 (**Cy**$_{(CH2)}$), 41.5 (**Cy**$_{(CH)}$), 43.4 (**Cy**$_{(CH)}$), 76.4 (N**C**H), 94.0 (**C**(Cy)$_2$), 128.5 (2C, **Ph**-H), 128.7 (2C, **Ph**-H), 129.2 (**Ph**-C). 131.2 (**Ph**-H), 161.0 (**C**=N).

MS (FAB) m/z (rel int %): 354 (67), 310 (11), 176 (27), 159 (29), 144 (10), 122 (14), 105 (100), 95 (32), 83 (51), 77 (20), 69 (27), 55 (60), 41 (38).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3449w, 3066w, 2927s, 2849s, 1657s, 1580w, 1451s, 1337s, 1300m, 1263m, 1169w, 1101m, 1023w, 964m, 891w, 766m, 695s.

EA % found (calcd): C: 81.52 (81.53), H: 9.87 (9.98), N: 3.97 (3.96).

(*S*)-5,5-bis(3,5-dimethylphenyl)-4-isopropyl-2-phenyl-4,5-dihydrooxazole (101)



Product **101** was prepared according to **general procedure IV** (page 144) from *(S)*-*N*-(1,1-bis(3,5-dimethylphenyl)-1-hydroxy-3-methylbutan-2-yl)benzamide (1.50 g, 3.61 mmol), methanesulfonic acid (0.73 mL, 11.2 mmol), CaH_2 (4.50 g) and dichloromethane as a solvent (80.0 mL). After column chromatography (Hx : EtOAc 8 : 1, $\mathbf{R}_f$ = 0.38) on silica compound **101** (1.20 g, 84%) was isolated as a colorless solid.

$C_{28}H_{31}NO$ (397.55).

m.p. 42-44 **°C**.

$[\alpha]_D^{20}$ = -333.2° (c = 1.210, $CDCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.53 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.06 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.90 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 4.0 Hz, 1H,

C**H**$(CH_3)_2$), 2.27 (s, 6H, 3,5-dimethylphenyl-C**H**$_3$), 2.29 (s, 6H, 3,5-dimethylphenyl-C**H**$_3$), 4.62 (d, *J*(H,H) = 4.0 Hz, 1H, NC**H**), 6.88-6.90 (m, 2H, Ar-**H**), 7.01 (s, 2H, Ar-**H**), 7.19 (s, 2H, Ar-**H**), 7.44-7.54 (m, 3H, Ar-**H**), 8.09-8.12 (m, 2H, Ar-**H**).

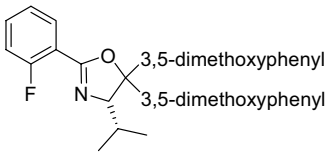
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 16.7 (CH(**C**$H_3)_2$), 21.8 (2C, 3,5-dimethylphenyl-**C**H_3), 21.8 (2C, 3,5-dimethylphenyl-**C**H_3), 22.2 (CH(**C**$H_3)_2$), 30.8 (**C**$H(CH_3)_2$), 79.7 (N**C**H), 93.0 (**C**(3,5-dimethylphenyl)$_2$), 124.1 (2C, **Ar**-H), 124.9 (2C, **Ar**-H), 128.8 (2C, **Ar**-H), 128.9 (2C, **Ar**-H), 128.9 (**Ar**-C), 129.0 (**Ar**-H), 129.7 (**Ar**-H), 131.7 (**Ar**-H), 137.8 (2C, **Ar**-C), 138.3 (2C, **Ar**-C), 141.5 (**Ar**-C), 146.7 (**Ar**-C), 162.0 (**C**=N).

MS (FAB) m/z (rel int %): 398 (M + H, 57), 223 (11), 159 (73), 144 (31), 133 (20), 133 (20), 105 (100), 77 (25), 57 (13), 55 (15), 43 (15), 41 (15).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3444w, 3033w, 2956s, 2919s, 2869m, 1655s, 1603s, 1451s, 1342s, 1294m, 1239w, 1177m, 1107m, 1060m, 1025m, 979m, 852m.

EA % found (calcd): C: 84.51 (84.59), H: 7.90 (7.86), N: 3.60 (3.52).

(*S*)-5,5-Bis(3,5-dimethoxyphenyl)-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (102)



Product **102** was prepared according to **general procedure IV** (page 144) from *(S)*-*N*-(1,1-bis(3,5-dimethoxyphenyl)-1-hydroxy-3-methylbutan-2-yl)-2-fluorobenzamide (0.90 g, 1.80 mmol), methanesulfonic acid (365 µL, 5.58 mmol), CaH_2 (2.50 g) and dichloromethane as a solvent (45.0 mL). After column chromatography (Hx : EtOAc 4 : 1, $\mathbf{R}_f$ = 0.21) on silica compound **102** (600 mg, 70%) was isolated as a colorless solid.

$C_{28}H_{30}FNO_5$ (479.54).

m.p. 85-86 °C.

$[\alpha]_D^{20}$ = -303.3° (c = 0.650, $CHCl_3$).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.66 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3)_2$), 1.09 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3)_2$), 2.00 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H)= 4.4 Hz, 1H, C**H**$(CH_3)_2$), 3.75 (s, 6H, 3,5-dimethoxyphenyl-OC**H**$_3$), 3.77 (s, 6H, 3,5-dimethoxyphenyl-OC**H**$_3$), 4.78 (d, *J*(H,H) = 4.1 Hz, 1H, NC**H**), 6.35 (t, *J*(H,H) = 2.3 Hz, 1H, Ar-**H**), 6.36 (t, *J*(H,H) = 2.3 Hz,

1H, Ar-**H**), 6.59 (d, *J*(H,H) = 2.3 Hz, 2H, Ar-**H**), 6.76 (d, *J*(H,H) = 2.3 Hz, 2H, Ar-**H**), 7.14-7.23 (m, 2H, Ar-**H**), 7.45-7.50 (m, 1H, Ar-**H**), 8.02 (br s, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 17.0 (CH(**C**H_3)$_2$), 22.2 (CH(**C**H_3)$_2$), 30.3 (**C**H(CH_3)$_2$), 55.5 (2C, 3,5-dimethoxyphenyl-O**C**H_3), 55.5 (2C, 3,5-dimethoxyphenyl-O**C**H_3), 79.6 (N**C**H), 93.1 (**C**(3,5-dimethoxyphenyl)$_2$), 98.6 (**Ar**-H), 99.4 (**Ar**-H), 104.8 (2C, **Ar**-H), 105.8 (2C, **Ar**-H), 116.8 (d, *J*(C,F) = 21.5 Hz, **Ph**-H), 124.2 (d, *J*(C,F) = 3.8 Hz, **Ph**-H), 131.6 (d, *J*(C,F) = 2.3 Hz, **Ph**-H), 133.0 (d, *J*(C,F) = 8.8 Hz, **Ph**-H), 142.6 (C(**3,5-dimethoxyphenyl$_{(ipso)}$**)$_2$), 147.8 (C(**3,5-dimethoxyphenyl$_{(ipso)}$**)$_2$), 160.3 (**C**=N), 160.2 (2C, **3,5-dimethoxyphenyl**-OCH_3), 160.7 (2C, **3,5-dimethoxyphenyl**-OCH_3), 161.5 (d, *J*(C,F) = 257.6 Hz, **Ph**-F). (One quaternary C-atom is not visible).

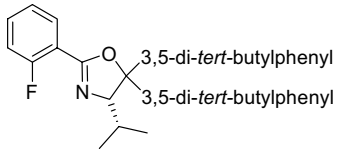
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -111.5 (m).

MS (FAB) m/z (rel int %): 480 (M + H, 64), 341 (13), 177 (100), 162 (37), 123 (63), 69 (10), 57 (17), 55 (16), 43 (14), 41 (13).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3076w, 2964m, 2936m, 2873w, 2838w, 1647s, 1599s, 1459s, 1431s, 1317s, 1206s, 1158s, 1115m, 1062s, 1023s, 990m, 972m, 859m, 821m, 747m.

EA % found (calcd): C: 69.93 (70.13), H: 6.35 (6.31), N: 3.05 (2.92).

(*S*)-5,5-Bis(3,5-di-*tert*-butylphenyl)-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (103)



Product **103** was prepared according to **general procedure IV** (page 144) from *(S)*-*N*-(1,1-bis(3,5-dimethoxyphenyl)-1-hydroxy-3-methylbutan-2-yl)-2-fluorobenzamide (1.20 g, 2.00 mmol), methanesulfonic acid (400 µL, 6.20 mmol), CaH_2 (2.50 g) and dichloromethane as a solvent (45.0 mL). After column chromatography (Hx : EtOAc 25 : 1, $\mathbf{R}_f$ = 0.15) on silica compound **103** (978 mg, 84%) was isolated as a colorless solid.

$C_{40}H_{54}FNO$ (583.86).

m.p. 139-141 °C.

$[\alpha]_D^{20}$ = -158.6° (c = 0.635, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.61 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 0.98 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.26 (s, 18H, 2 x C(C**H**$_3$)$_3$), 1.30 (s, 18H, 2 x C(C**H**$_3$)$_3$),

1.91 (ds, *J*(H,H) = 6.6 Hz, *J*(H,H)= 5.1 Hz, 1H, C**H**$(CH_3)_2$), 4.68 (d, *J*(H,H) = 5.0 Hz, 1H, NC**H**), 7.19-7.27 (m, 2H, Ar-**H**), 7.25 (d, *J*(H,H) = 1.8 Hz, 2H, Ar-**H**), 7.29 (t, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**), 7.35 (t, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**), 7.47 (d, *J*(H,H) = 1.8 Hz, 2H, Ar-**H**), 7.49-7.53 (m, 1H, Ar-**H**), 8.04 (dt, *J*(H,H) = 7.4 Hz, *J*(H,H) = 2.0 Hz, 1H, Ar-**H**).

$^{13}C\{^1H\}$ NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 17.5 (CH(**C**$H_3)_2$), 22.1 (CH(**C**$H_3)_2$), 31.2 (**C**H$(CH_3)_2$), 31.7 (6C, C(**C**$H_3)_3$), 31.8 (6C, C(**C**$H_3)_3$), 35.3 (2C, **C**$(CH_3)_3$), 35.5 (2C, **C**$(CH_3)_3$), 82.0 (N**C**H), 94.0 (O**C**), 117.2 (d, *J*(C,F) = 21.9 Hz, **Ar**-H), 117.4 (d, *J*(C,F) = 11.1 Hz, **Ar**-C), 120.5 (2C, **Ar**-H), 121.2 (**Ar**-H), 121.8 (2C, **Ar**-H), 122.1 (**Ar**-H), 124.6 (d, *J*(C,F) = 3.8 Hz, **Ar**-H), 131.7 (d, *J*(C,F) = 1.9 Hz, **Ar**-H), 133.3 (d, *J*(C,F) = 8.4 Hz, **Ar**-H), 140.3 (C(**3,5-di-*tert*-butylbenzene$_{(ipso)}$**$)_2$), 146.0 (C(**3,5-di-*tert*-butylbenzene$_{(ipso)}$**$)_2$), 150.5 (2C, **Ar**-C$(CH_3)_3$), 151.1 (2C, **Ar**-C$(CH_3)_3$), 159.1 (d, *J*(C,F) = 4.2 Hz, **C**=N), 161.8 (d, *J*(C,F) = 256.8 Hz, **Ar**-F).

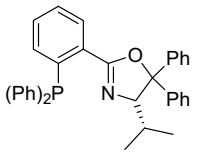
$^{19}F\{^1H\}$ NMR (376.5 MHz, CD_2Cl_2, 300 K): δ = -112.2 (m).

MS (FAB) m/z (rel int %): 584 (M + H, 10), 177 (30), 162 (11), 123 (31), 57 (100), 41 (24).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3423w, 3078w, 2960s, 2870s, 1661s, 1598s, 1460s, 1342s, 1249m, 1222m, 1117s, 1030w, 980m, 820w, 768m, 717m.

EA % found (calcd): C: 82.24 (82.28), H: 9.16 (9.32), N: 2.55 (2.40).

(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (41)



General Procedure V:

A 1.3M solution of *sec*-BuLi in cyclohexane (1.20 mL, 1.61 mmol) was added within 10 min to a solution of (*S*)-4-isopropyl-2,5,5-triphenyl-4,5-dihydrooxazole (500 mg, 1.46 mmol) and TMEDA (242 μL, 1.61 mmol) in pentane (14.0 mL) at –78 °C. The reaction mixture was stirred for a further 5 min at –78 °C before the cooling bath was replaced by an ice-bath. After 10 min a solution of chlorodiphenylphosphine (420 mg, 1.90 mmol) in pentane (8.00 mL) was added over 10 min. After 10 min the ice-bath was removed and the solution was stirred over night at rt. The resulting suspension was filtered, the solvent was removed by high vacuum and the crude product was purified by column chromatography (Hx : EtOAc 8 : 1, $\mathbf{R}_f$ = 0.45) on silica to afford a colorless solid (613 mg, 80%).

$C_{36}H_{32}NOP$ (525.22).

$[\alpha]_D^{20}$ = -315.0° (c = 0.150, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.41 (d, *J*(H,H) = 6.5 Hz, 3H, CH(C**H**$_3$)$_2$), 0.82 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.70 (ds, *J*(H,H) = 6.6 Hz, *J*(H,H)= 4.9 Hz, 1H, C**H**(CH$_3$)$_2$), 4.63 (d, *J*(H,H) = 4.9 Hz, 1H, NC**H**), 6.95 (ddd, *J*(H,H) = 7.7 Hz, *J*(H,H) = 3.6 Hz, *J*(H,H) = 1.3 Hz, 1H, Ph-**H**), 7.20-7.25 (m, 9H, Ph-**H**), 7.26-7.36 (m, 10H, Ph-**H**), 7.43-7.47 (m, 3H, Ph-**H**), 8.17 (ddd, *J*(H,H) = 7.7 Hz, *J*(H,H) = 3.6 Hz, *J*(H,H) = 1.3 Hz, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 17.4 (d, *J*(C,P) = 2.4 Hz, CH(**C**H$_3$)$_2$), 21.9 (CH(**C**H$_3$)$_2$), 30.8 (**C**H(CH$_3$)$_2$), 81.5 (N**C**H), 92.8 (**C**O), 126.8 (2C, **Ph**-H), 127.5 (2C, **Ph**-H), 128.1 (2C, **Ph**-H), 128.2 (**Ph**-H), 128.7 (**Ph**-H), 128.8-128.9 (9C, **Ph**-H), 130.4 (d, J(C,P) = 2.9 Hz, **Ph**-H), 131.0 (**Ph**-H), 132.6 (d, *J*(C,P) = 20.6 Hz, **Ph**-CN), 134.4 (**Ph**-H), 134.5 (**Ph**-H), 134.5 (**Ph**-H), 134.6 (**Ph**-H), 135.2 (**Ph**-H), 139.5 (d, *J*(C,P) = 12.0 Hz, **Ph**-P), 139.5 (d, *J*(C,P) = 12.0 Hz, **Ph**-P), 139.6 (d, *J*(C,P) = 27.4 Hz, **Ph**-P), 141.6 (C(**Ph$_{(ipso)}$**)$_2$), 146.3 (C(**Ph$_{(ipso)}$**)$_2$), 160.7 (d, *J*(C,P) = 2.9 Hz, **C**=N).

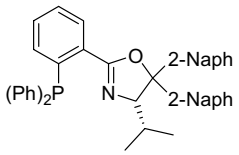
^{31}P{^{1}H} NMR (162.0 MHz, $CDCl_3$, 300 K): δ = -13.4.

MS (FAB) m/z (rel int %): 526 (M + H, 17), 304 (100), 289 (12), 55 (16), 43 (16).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3423w, 3061w, 2954s, 2925m, 2867s, 1659s, 1584s, 1491s, 1471s, 1446s, 1434m,1384s, 1282m, 1138m, 1099s, 1063w, 1038w, 974m, 773w, 761m.

EA % found (calcd): C: 81.67 (82.26), H: 6.19 (6.14), N: 2.42 (2.66).

(*S*)-2-(2-(Diphenylphosphino)phenyl)-4-isopropyl-5,5-di(naphthalen-2-yl)-4,5-dihydrooxazole (73)



Product **73** was prepared according to **general procedure V** (page 151) from (*S*)-4-isopropyl-5,5-di(naphthalen-2-yl)-2-phenyl-4,5-dihydrooxazole (200 mg, 0.45 mmol), *sec*-BuLi in cyclohexane (0.39 mL, 0.50 mmol), TMEDA (75.0 µL, 1.25 mmol), chlorodiphenylphosphine (110 µL, 0.59 mmol) and pentane as a solvent (12.0 mL). After column chromatography (Hx : EtOAc 10 : 1, **R**$_f$ = 0.32) on silica compound **73** (200 mg, 71%) was isolated as a colorless solid.

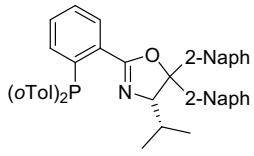
$C_{44}H_{36}NOP$ (625.71).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.48 (d, *J*(H,H) = 6.5 Hz, 3H, CH(C**H**$_3$)$_2$), 0.91 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.79 (ds, *J*(H,H) = 6.6 Hz, *J*(H,H) = 4.6 Hz, 1H, C**H**(CH$_3$)$_2$), 4.93 (d, *J*(H,H) = 4.6 Hz, 1H, NC**H**), 6.97 (dddd, *J*(H,H) = 7.8 Hz, *J*(H,H) = 3.6 Hz, *J*(H,H) = 1.3 Hz, *J*(H,H) = 0.4 Hz, 1H, Ar-**H**), 7.22-7.28 (m, 7H, Ar-**H**), 7.28-7.32 (m, 3H, Ar-**H**), 7.34 (m, 2H, Ar-**H**), 7.44-7.48 (m, 3H, Ar-**H**), 7.49-7.51 (m, 3H, Ar-**H**), 7.72 (d, *J*(H,H) = 8.8 Hz, 1H, Ar-**H**), 7.76-7.82 (m, 4H, Ar-**H**), 7.85-7.88 (m, 2H, Ar-**H**), 8.00 (d, *J*(H,H) = 2.0 Hz, 1H, Ar-**H**), 8.22 (dddd, *J*(H,H) = 7.8 Hz, *J*(H,H) = 3.6 Hz, *J*(H,H) = 1.3 Hz, *J*(H,H) = 0.4 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 17.4 (**C**H$_3$), 22.1 (**C**H$_3$), 30.9 (**C**H(CH$_3$)$_3$), 80.5 (N**C**H), 93.4 (**C**(Naph)$_2$), 125.2 (**Ar**-H), 126.1 (**Ar**-H, 2C), 126.3 (**Ar**-H), 126.7 (**Ar**-H), 126.7 (**Ar**-H), 126.8 (**Ar**-H), 126.9 (**Ar**-H), 127.7 (**Ar**-H), 127.9 (**Ar**-H), 128.0 (**Ar**-H), 128.6 (**Ar**-H), 128.7 (**Ar**-H), 128.8 (**Ar**-H), 128.8 (**Ar**-H, 2C), 128.9 (**Ar**-H, 2C), 128.9 (**Ar**-H), 128.9 (**Ar**-H), 129.0 (**Ar**-H), 130.6 (d, *J*(C,P) = 3.4 Hz, **Ar**-H), 131.1 (**Ar**-H), 132.8 (d, *J*(C, P) = 21.2 Hz, **Ar**-CN), 132.9 (**Ar**-C), 133.3 (**Ar**-C), 133.4 (**Ar**-C), 133.4 (**Ar**-C), 134.5 (**Ar**-H), 134.4 (**Ar**-H), 134.5 (**Ar**-H), 134.6 (**Ar**-H), 135.2 (**Ar**-H), 139.0 (C(**Naph$_{(ipso)}$**)$_2$), 139.4 (d, *J*(C,P) = 12.5 Hz, **Ar**-P), 139.5 (d, *J*(C,P) = 12.0 Hz, **Ar**-P), 139.6 (d, *J*(C,P) = 27.4 Hz, **Ar**-P), 143.0 (C(**Naph$_{(ipso)}$**)$_2$), 161.0 (d, *J*(C,P) = 2.8 Hz, **C**=N).

^{31}P{^{1}H} NMR (202.5 MHz, CD_2Cl_2, 295 K): δ = -7.1.

(*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-di(naphthalen-2-yl)-4,5-dihydrooxazole (74)



Product **74** was prepared according to **general procedure V** (page 151) from (*S*)-4-isopropyl-5,5-di(naphthalen-2-yl)-2-phenyl-4,5-dihydrooxazole (500 mg, 1.13 mmol), *sec*-BuLi in cyclohexane (0.96 mL, 1.25 mmol), TMEDA (190 µL, 1.25 mmol), chlorodi*ortho*-tolylphosphine (366 mg, 1.47 mmol) and pentane as a solvent (20.0 mL). After column chromatography (Hx : EtOAc 10 : 1, $\mathbf{R}_f$ = 0.30) on silica compound **74** (518 mg, 70%) was isolated as a colorless solid.

$C_{46}H_{40}NOP$ (653.79).

m.p. 114-118 °C.

$[\alpha]_D^{20}$ = -294.6° (c = 0.970, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.45 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.93 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.83 (ds, *J*(H,H) = 6.7 Hz, *J*(H,H)= 4.4 Hz, 1H, C**H**(CH$_3$)$_2$), 2.29 (d, *J*(H,H) = 1.3 Hz, 3H, *o*Tol-C**H**$_3$), 2.33 (d, *J*(H,H) = 1.3 Hz, 3H, *o*Tol-C**H**$_3$), 4.97 (d, *J*(H,H) = 4.6 Hz, 1H, NC**H**), 6.70-6.77 (m, 2H, Ar-**H**), 6.95-7.08 (m, 3H, Ar-**H**), 7.18-7.25 (m, 4H, Ar-**H**), 7.33-7.40 (m, 2H, Ar-**H**), 7.43-7.51 (m, 6H, Ar-**H**), 7.70-7.86 (m, 7H, Ar-**H**), 8.02 (d, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**), 8.19-8.21 (m, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 16.6 (d, *J*(C,P) = 2.9 Hz, CH(**C**H$_3$)$_2$), 20.8 (d, *J*(C,P) = 5.3 Hz, *o*Tol-**C**H$_3$), 21.0 (d, *J*(C,P) = 5.7 Hz, *o*Tol-**C**H$_3$), 21.5 (CH(**C**H$_3$)$_2$), 30.3 (**C**H(CH$_3$)$_2$), 80.4 (N**C**H), 93.6 (**C**O), 124.6 (**Ar**-H), 125.5 (**Ar**-H), 125.6 (d, *J*(C,P) = 1.0 Hz, **Ar**-H), 125.7 (**Ar**-H), 125.9 (**Ar**-H), 126.0 (**Ar**-H), 126.1 (**Ar**-H), 126.1 (**Ar**-H), 126.2 (**Ar**-H), 126.3 (**Ar**-H), 127.1 (**Ar**-H), 127.3 (**Ar**-H), 127.4 (**Ar**-H), 128.0 (**Ar**-H), 128.1 (**Ar**-H), 128.3 (**Ar**-H), 128.4 (2C, **Ar**-H), 128.4 (**Ar**-H), 129.9 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 130.0 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 130.3 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 130.7 (**Ar**-H), 132.3 (**Ar**-C), 132.7 (**Ar**-C), 132.8 (**Ar**-C), 132.8 (**Ar**-C), 133.1 (**Ar**-H), 133.1 (**Ar**-H), 133.2 (d, *J*(C,P) = 21.3 Hz, **Ar**-CN), 134.9 (**Ar**-H), 136.7 (d, *J*(C,P) = 13.4 Hz, ***o*Tol**-P), 136.7 (d, *J*(C,P) = 13.4 Hz, ***o*Tol**-P), 137.5 (d, *J*(C,P) = 25.4 Hz, **Ar**-P), 138.4 (C(**Naph$_{(ipso)}$**)$_2$), 142.3 (d, *J*(C,P) = 26.9 Hz, ***o*Tol**-CH$_3$), 142.3 (d, *J*(C,P) = 26.9 Hz, ***o*Tol**-CH$_3$), 142.6 (C(**Naph$_{(ipso)}$**)$_2$), 161.5 (d, *J*(C,P) = 2.0 Hz, **C**=N).

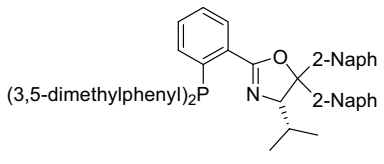
^{31}P{^{1}H} NMR (202.5 MHz, CD_2Cl_2, 295 K): δ = -26.0.

MS (FAB) m/z (rel int %): 654 (M + H, 13), 332 (100), 317 (30), 179 (19), 165 (10), 141 (10), 105 (7), 91 (13), 77 (10), 57 (15), 55 (17), 43 (14).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3433w$_{br}$, 3052m, 2956s, 2869m, 1649s, 1591m, 1503m, 1462s, 1378m, 1333s, 1270m, 1166w, 1127m, 1093m, 1036s, 966m, 938m, 899m, 856m, 812s, 745s.

EA % found (calcd): C: 84.15 (84.51), H: 6.32 (6.17), N: 1.90 (2.14).

(*S*)-2-(2-(bis(3,5-dimethylphenyl)phosphino)phenyl)-4-isopropyl-5,5-di(naphthalen-2-yl)-4,5-dihydrooxazole (75)



Product **75** was prepared according to **general procedure V** (page 151) from (*S*)-4-isopropyl-5,5-di(naphthalen-2-yl)-2-phenyl-4,5-dihydrooxazole (300 mg, 0.68 mmol), *sec*-BuLi in cyclohexane (0.58 mL, 0.75 mmol), TMEDA (113 µL, 0.75 mmol), chlorobis(3,5-dimethylphenyl)phosphine (236 mg, 0.88 mmol) and pentane as a solvent (18.0 mL). After column chromatography (Tol : Diethyl ether : Pe 5 : 1 : 5, $\mathbf{R}_f$ = 0.25) on silica compound **75** (270 mg, 58%) was isolated as a colorless solid.

$C_{48}H_{44}NOP$ (681.84).

m.p. 91-100 °C.

$[\alpha]_D^{20}$ = -258.2° (c = 0.370, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.52 (d, *J*(H,H) = 6.5 Hz, 3H, CH(C**H**$_3$)$_2$), 0.93 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.81 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 4.6 Hz, 1H, C**H**(CH$_3$)$_2$), 2.17 (s, 6H, 3,5-dimethylphenyl-C**H**$_3$), 2.21 (s, 6H, 3,5-dimethylphenyl-C**H**$_3$), 4.89 (d, *J*(H,H) = 4.5 Hz, 1H, NC**H**), 6.87-6.89 (m, 5H, Ar-**H**), 6.95 (br s, 1H, Ar-**H**), 7.01 (dd, *J*(H,H) = 7.7 Hz, *J*(H,H) = 3.6 Hz, 1H, Ar-**H**), 7.34 (dd, *J*(H,H) = 8.6 Hz, *J*(H,H) = 1.9 Hz, 1H, Ar-**H**), 7.35 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**), 7.43-7.53 (m, 6H, Ar-**H**), 7.71 (d, *J*(H,H) = 8.6 Hz, 1H, Ar-**H**), 7.75-7.82 (m, 4H, Ar-**H**), 7.86-7.88 (m, 2H, Ar-**H**), 7.99 (d, *J*(H,H) = 1.6 Hz, 1H, Ar-**H**), 8.18 (ddd, *J*(H,H) = 7.7 Hz, *J*(H,H) = 3.8 Hz, *J*(H,H) = 1.6 Hz, 1H, Ar-**H**).

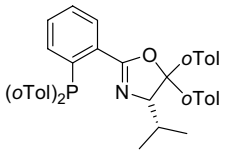
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 17.4 (d, *J*(C,P) = 2.9 Hz, CH(**C**H$_3$)$_2$), 21.5 (2C, 3,5-di**methyl**phenyl), 21.6 (2C, 3,5-di**methyl**phenyl), 22.1 (CH(**C**H$_3$)$_2$), 30.8 (**C**H(CH$_3$)$_2$), 80.2 (N**C**H), 93.4 (O**C**), 125.1 (**Ar**-H), 126.1 (**Ar**-H), 126.2 (**Ar**-H), 126.3 (d, *J*(C,P)= 1.4 Hz, **Ar**-H), 126.7 (2C, **Ar**-H), 126.8 (**Ar**-H), 126.9 (**Ar**-H), 127.7 (**Ar**-H), 127.9 (**Ar**-H), 127.9 (**Ar**-H), 128.5 (**Ar**-H), 128.6 (**Ar**-H), 128.7 (**Ar**-H), 129.0 (**Ar**-H), 130.5 (d, *J*(C,P)= 3.4 Hz, **Ar**-H), 130.6 (**Ar**-H), 130.7 (**Ar**-H), 130.9 (**Ar**-H), 132.1 (**Ar**-H), 132.2 (**Ar**-H), 132.3 (**Ar**-H), 132.3 (**Ar**-H), 132.9 (d, *J*(C,P) = 21.1 Hz, **Ar**-CN), 132.9 (**Naph**$_{(Cq)}$), 133.2 (**Naph**$_{(Cq)}$), 133.3 (**Naph**$_{(Cq)}$), 132.3 (**Naph**$_{(Cq)}$), 135.2 (**Ar**-H), 138.2 (d, *J*(C,P) = 1.9 Hz, 2C, **3,5-dimethylphenyl**-CH$_3$), 138.3 (d, *J*(C,P) = 1.9 Hz, 2C, **3,5-dimethylphenyl**-CH$_3$), 138.9 (d, *J*(C,P) = 11.5 Hz, **Ar**-P), 138.9 (d, *J*(C,P) = 12.0 Hz, **Ar**-P), 139.1 (C(**Naph$_{(ipso)}$**)$_2$), 140.1 (d, *J*(C,P) = 27.4 Hz, **Ar**-P), 143.1 (C(**Naph$_{(ipso)}$**)$_2$), 161.3 (d, *J*(C,P)= 2.9 Hz, **C**=N).

^{31}P{^{1}H} NMR (202.5 MHz, CD_2Cl_2, 295 K): δ = -10.2.

MS (FAB) m/z (rel int %): 682 (M + H, 8), 360 (100), 345 (17), 179 (20), 165 (13), 141 (11), 136 (18), 127 (14), 115 (11), 105 (12), 91 (21), 89 (25), 77 (39), 65 (18), 63 (17), 57 (21), 55 (20), 51 (21), 43 (21), 41 (30), 39 (34).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3427w_{br}, 3020w, 2917s, 2864m, 1652s, 1593m, 1500w, 1462s, 1333s, 1264s, 1168w, 1093m, 1036s, 967m, 938w, 898w, 847m, 811s, 741s, 690s.
EA % found (calcd): C: 84.77 (84.55), H: 6.76 (6.50), N: 1.77 (2.05).

(*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-di*o*-tolyl-4,5-dihydrooxazole (76)



Product **76** was prepared according to **general procedure V** (page 151) from (*S*)-4-isopropyl-2-phenyl-5,5-di*o*-tolyl-4,5-dihydrooxazole (500 mg, 1.35 mmol), *sec*-BuLi in cyclohexane (1.10 mL, 1.49 mmol), TMEDA (224 µL, 1.49 mmol), chlorodi*ortho*-tolylphosphine (438 mg, 1.76 mmol) and pentane as a solvent (32.0 mL). After column chromatography (Hx : EtOAc 10 : 1, $\mathbf{R}_f$ = 0.37) on silica compound **76** (510 mg, 65%) was isolated as a colorless solid.

$C_{40}H_{40}NOP$ (581.73).
m.p. 79-82 °C.
$[\alpha]_D^{20}$ = -378.3° (c = 0.540, $CHCl_3$).
^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.52 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.97 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.29 (ds, *J*(H,H) = 6.7 Hz, *J*(H,H) = 4.4 Hz, 1H, C**H**(CH$_3$)$_2$), 1.64 (br s, 3H, *o*Tol-C**H**$_3$), 1.72 (br s, 3H, *o*Tol-C**H**$_3$), 2.29 (br s, 3H, *o*Tol-C**H**$_3$), 2.44 (br s, 3H, *o*Tol-C**H**$_3$), 5.12 (br s, 1H, NC**H**), 6.69 (dd, *J*(H,H) = 7.6 Hz, *J*(H,H) = 4.0 Hz, 2H, Ar-**H**), 6.93 (ddd, *J*(H,H) = 7.0 Hz, *J*(H,H) = 3.5 Hz, *J*(H,H)= 1.1 Hz, 1H, Ar-**H**), 6.95-6.99 (m, 1H, Ar-**H**), 6.99-7.05 (m, 3H, Ar-**H**), 7.11-7.18 (m, 4H, Ar-**H**), 7.20-7.23 (m, 3H, Ar-**H**), 7.24 (dd, *J*(H,H) = 7.3 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**), 7.28 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.5 Hz, 1H, Ar-**H**), 7.37 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**), 7.57 (br s, 1H, Ar-**H**), 7.84-7.85 (m, 1H, Ar-**H**), 7.89 (ddd, *J*(H,H) = 7.8 Hz, *J*(H,H)= 3.8 Hz, *J*(H,H)= 1.4 Hz, 1H, Ar-**H**).
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 16.5 (d, *J*(C,P) = 4.8 Hz, CH(**C**H$_3$)$_2$), 21.3 (d, *J*(C,P) = 3.8 Hz, *o*Tol-**C**H$_3$), 21.5 (d, *J*(C,P) = 3.8 Hz, *o*Tol-**C**H$_3$), 21.8 (*o*Tol-**C**H$_3$), 22.4 (*o*Tol-**C**H$_3$), 23.0 (CH(**C**H$_3$)$_2$), 30.0 (**C**H(CH$_3$)$_2$), 75.4 (N**C**H), 95.1 (O**C**), 125.2 (**Ar**-H), 125.7 (**Ar**-H), 126.5 (**Ar**-H), 126.6 (**Ar**-H), 127.1 (**Ar**-H), 127.9 (**Ar**-H), 128.5 (**Ar**-H), 128.9 (**Ar**-H), 128.9 (**Ar**-H), 129.0 (**Ar**-H), 129.2 (d, *J*(C,P) = 2.9 Hz, **Ar**-H), 130.5 (**Ar**-H), 130.5 (**Ar**-H), 130.7 (d, *J*(C,P) = 4.8 Hz, **Ar**-H), 131.0 (**Ar**-H), 131.6 (**Ar**-H), 133.4 (**Ar**-H), 133.5

(**Ar**-H), 133.7 (**Ar**-H), 134.9 (***o*Tol**-CH_3), 135.6 (**Ar**-H), 137.1-137.4 (3C, **Ar**-P), 139.0 (C(***o*Tol$_{(ipso)}$**)$_2$), 139.6 (C(***o*Tol$_{(ipso)}$**)$_2$), 140.7 (***o*Tol**-CH_3), 142.6-142.8 (2C, ***o*Tol**-CH_3), 161.8 (br s, **C**=N). (**Ar**-CN is not visible).

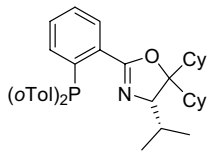
^{31}P{^{1}H} NMR (162.0 MHz, CD_2Cl_2, 300 K): δ = -30.3.

MS (FAB) m/z (rel int %): 582 (M + H, 16), 332 (100), 317 (20), 179 (7), 165 (8), 105 (11), 91 (15), 77 (7), 57 (12), 55 (13), 43 (15), 41 (13).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3433m_{br}, 3054m, 2958s, 2924s, 2867m, 1646s, 1588w, 1459s, 1379w, 1355m, 1303w, 1267w, 1229w, 1202w, 1166w, 1133m, 1091m, 1035s, 951s, 891w, 815w, 749s, 685w.

EA % found (calcd): C: 82.60 (82.59), H: 7.16 (6.93), N: 2.23 (2.41).

(*S*)-5,5-dicyclohexyl-2-(2-(di*o*-tolylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole (72)



Product **72** was prepared according to **general procedure V** (page 151) from (*S*)-5,5-dicyclohexyl-4-isopropyl-2-phenyl-4,5-dihydrooxazole (300 mg, 0.85 mmol), *sec*-BuLi in cyclohexane (692 µL, 0.93 mmol), TMEDA (135 µL, 0.93 mmol), chlorodi*ortho*-tolylphosphine (274 mg, 1.10 mmol) and pentane as a solvent (20.0 mL). After column chromatography (Hx : EtOAc 15 : 1, $\mathbf{R}_f$ = 0.48 and Tol : DCM : Hx 5 : 1 : 1 $\mathbf{R}_f$ = 0.39) on silica compound **72** (252 mg, 52%) was isolated as a colorless solid.

$C_{38}H_{48}NOP$ (565.77).

m.p. 143-145 °C.

$[\alpha]_D^{20}$ = -6.3° (c = 0.530, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.95 (d, *J*(H,H) = 6.5 Hz, 6H, CH(C**H**$_3$)$_2$), 0.91-1.26 (m, 10H, C**H**$_{2(Cy)}$), 1.44 (d, *J*(H,H) = 12.2 Hz, 1H, C**H**$_{2(Cy)}$), 1.57-1.82 (m, 11H, C**H**$_{2(Cy)}$), 1.91 (br s, 1H, C**H**(CH$_3$)$_2$), 2.30 (d, *J*(H,P) = 1.6 Hz, 3H, Ph-C**H**$_3$), 2.33 (d, *J*(H,P) = 1.5 Hz, 3H, Ph-C**H**$_3$), 3.61 (d, J(H,H) = 9.6 Hz, 1H, NC**H**), 6.69 (m, 2H, Ar-**H**), 6.87 (ddd, *J*(H,H) = 7.8 Hz, *J*(H,H) = 3.4 Hz, *J*(H,H) = 1.0 Hz, 1H, Ar-**H**), 7.00-7.06 (m, 2H, Ar-**H**), 7.15-7.28 (m, 5H, Ar-**H**), 7.38 (td, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 7.99 (ddd, *J*(H,H) = 7.8 Hz, *J*(H,H) = 3.4 Hz, *J*(H,H) = 1.0 Hz, 1H, Ar-**H**).

$^{13}C\{^1H\}$ NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 21.3 (d, *J*(C,P) = 1.6 Hz, *o*Tol-**C**H_3), 21.5 (d, *J*(C,P) = 1.6 Hz, *o*Tol-**C**H_3), 22.9 (CH(**C**H_3)$_2$), 24.2 (CH(**C**H_3)$_2$), 27.0 (**C**$H_{2(Cy)}$), 27.1 (**C**$H_{2(Cy)}$), 27.2 (**C**$H_{2(Cy)}$), 27.2 (**C**$H_{2(Cy)}$), 27.3 (**C**$H_{2(Cy)}$), 27.3 (**C**$H_{2(Cy)}$), 27.7 (**C**$H_{2(Cy)}$), 28.1 (**C**$H_{2(Cy)}$), 28.2 (**C**$H_{2(Cy)}$), 29.3 (**C**H$(CH_3)_2$), 29.6 (**C**$H_{2(Cy)}$), 41.3 (**C**$H_{(Cy)}$),43.3 (**C**$H_{(Cy)}$), 76.7 (N**C**H), 94.6 (**C**$(Cy)_2$), 126.4 (**Ar**-H), 126.5 (**Ar**-H), 128.6 (**Ar**-H), 128.7 (**Ar**-H), 130.3 (**Ar**-H), 130.3 (**Ar**-H), 130.4 (**Ar**-H), 130.4 (**Ar**-H), 130.7 (**Ar**-H), 133.6 (**Ar**-H), 133.8 (**Ar**-H), 134.4 (d, *J*(C,P) = 23.5 Hz, **Ar**-CN), 135.2 (**Ar**-H), 137.5 (d, *J*(C,P) = 14.0 Hz, ***o*Tol**-P), 137.6 (d, *J*(C,P) = 25.3 Hz, **Ar**-P), 137.8 (d, *J*(C,P) = 13.4 Hz, ***o*Tol**-P), 142.8 (br s, 2C, ***o*Tol**-CH_3), 161.0 (**C**=N).

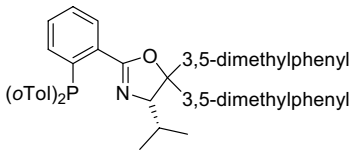
$^{31}P\{^1H\}$ NMR (162.0 MHz, CD_2Cl_2, 300 K): δ = -29.5.

MS (FAB) m/z (rel int %): 566 (M + H, 36), 332 (100), 317 (16), 242 (12), 95 (23), 83 (27), 69 (26), 57 (21), 55 (51), 43 (24), 41 (34), 39 (11).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3447w, 3052w, 2927s, 2850s, 1629s, 1587w, 1450s, 1333m, 1265w, 1201w, 1184w, 1060w, 957w, 892w, 747m, 716w, 686w.

EA % found (calcd): C: 80.71 (80.67), H: 8.57 (8.55), N: 2.27 (2.48).

(*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-bis(3,5-dimethylphenyl)-4-isopropyl-4,5-dihydrooxazole (77)



Product **77** was prepared according to **general procedure V** (page 151) from (*S*)-5,5-bis(3,5-dimethylphenyl)-4-isopropyl-2-phenyl-4,5-dihydrooxazol (600 mg, 1.51 mmol), *sec*-BuLi in cyclohexane (1.30 mL, 1.66 mmol), TMEDA (250 µL, 1.66 mmol), chlorodi*ortho*-tolylphosphine (490 mg, 1.96 mmol) and pentane as a solvent (36.0 mL). After column chromatography (Hx : EtOAc 10 : 1, $\mathbf{R}_f$ = 0.45) on silica compound **77** (770 mg, 84%) was isolated as a colorless solid.

$C_{42}H_{44}NOP$ (609.78).

m.p. 85-90 °C.

$[\alpha]_D^{20}$ = -190.3° (c = 0.780, $CHCl_3$).

^1H NMR (400.1 MHz, CD_2Cl_2, 295 K): δ = 0.32 (br s, 3H, CH(C**H**$_3$)$_2$), 0.84 (br s, 3H, CH(C**H**$_3$)$_2$), 1.72-1.82 (m, 1H, C**H**$(CH_3)_2$), 2.24 (s, 6H, 2 x 3,5-dimethylphenyl-C**H**$_3$), 2.28 (s,

6H, 2 x 3,5-dimethylphenyl-C**H**$_3$), 2.30 (d, *J*(H,H) = 1.6 Hz, 3H, *o*Tol-C**H**$_3$), 2.33 (d, *J*(H,H) = 1.6 Hz, 3H, *o*Tol-C**H**$_3$), 4.68 (d, *J*(H,H) = 3.8 Hz, 1H, NC**H**), 6.65-6.68 (m, 1H, Ar-**H**), 6.70-6.73 (m, 1H, Ar-**H**), 6.84 (br s, 1H, Ar-**H**), 6.90 (br s, 1H, Ar-**H**), 6.94-6.97 (m, 3H, Ar-**H**), 6.99-7.06 (m, 2H, Ar-**H**), 7.10 (br s, 2H, Ar-**H**), 7.17-7.24 (m, 4H, Ar-**H**), 7.33 (td, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.5 Hz, 1H, Ar-**H**), 7.48 (td, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 8.17-8.20 (m, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 16.0 (CH(**C**H$_3$)$_2$), 20.8 (d, *J*(C,P) = 13.0 Hz, Ar-**C**H$_3$), 20.9 (d, *J*(C,P) = 13.0 Hz, Ar-**C**H$_3$), 21.2 (2C, 3,5-dimethylphenyl-**C**H$_3$), 21.2 (2C, 3,5-dimethylphenyl-**C**H$_3$), 21.4 (CH(**C**H$_3$)$_2$), 30.0 (**C**H(CH$_3$)$_2$), 80.2 (N**C**H), 92.3 (O**C**), 123.7 (2C, **Ar**-H), 124.5 (2C, **Ar**-H), 125.9 (**Ar**-H), 125.9 (**Ar**-H), 128.2 (**Ar**-H), 128.3 (**Ar**-H), 128.3 (**Ar**-H), 128.3 (**Ar**-H), 129.0 (**Ar**-H), 129.9 (d, *J*(C,P) = 8.1 Hz, **Ar**-H), 129.9 (d, *J*(C,P) = 8.1 Hz, **Ar**-H), 130.1 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 130.5 (**Ar**-H), 132.9 (**Ar**-H), 133.1 (**Ar**-H), 133.2 (d, *J*(C,P) = 23.0 Hz, **Ar**-CN), 134.9 (**Ar**-H), 136.9 (d, *J*(C,P) = 12.5 Hz, ***o*Tol**-P), 137.0 (d, *J*(C,P) = 12.5 Hz, ***o*Tol**-P), 137.0 (2C, **3,5-dimethylphenyl**-CH$_3$), 137.5 (d, *J*(C,P) = 25.9 Hz, **Ar**-P), 137.7 (2C, **3,5-dimethylphenyl**-CH$_3$), 141.0 (C(**3,5-dimethylphenyl$_{(ipso)}$**)$_2$), 142.2 (d, *J*(C,P) = 26.9 Hz, ***o*Tol**-CH$_3$), 142.2 (d, *J*(C,P) = 26.9 Hz, ***o*Tol**-CH$_3$), 146.1 (C(**3,5-dimethylphenyl$_{(ipso)}$**)$_2$), 160.5 (d, *J*(C,P) = 2.0 Hz, **C**=N).

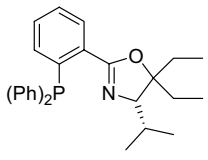
^{31}P{^{1}H} NMR (162.0 MHz, CD_2Cl_2, 300 K): δ = -29.8.

MS (FAB) m/z (rel int %): 610 (M + H, 14), 332 (100), 317 (20), 263 (8), 157 (10), 133 (8), 91 (7), 57 (14), 55 (15), 43 (18), 41 (14).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448w, 3051w, 2955s, 2918s, 2866m, 1651m, 1601s, 1463s, 1378w, 1337m, 1306w, 1274w, 1167w, 1134m, 1107m, 1095m, 1037s, 976m, 851m.

EA % found (calcd): C: 82.54 (82.73), H: 7.50 (7.27), N: 2.02 (2.30).

(*S*)-2-(2-(Diphenylphosphino)phenyl)-5,5-diethyl-4-isopropyl-4,5-dihydrooxazole (70)



General Procedure VI:

A 1.6M solution of *n*-BuLi in hexane (1.30 mL, 2.09 mmol) was added drop wise to a solution of diphenylphosphane (389 mg, 2.09 mmol) in THF (20.0 mL) at 0 °C. The reaction mixture was stirred for 30 min before it was added drop wise to a solution of (*S*)-5,5-Diethyl-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (500 mg, 1.90 mmol) in THF (20 mL) at 0 °C.

After 10 min the cooling bath was removed and the reaction solution was stirred over night at rt. The solvent was removed under reduced pressure before dichloromethane (20 mL) was added and the resulting solution was washed with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (Hx : EtOAc 15 : 1, $\mathbf{R}_f$ = 0.44) on silica to afford a colorless oil **70** (555 mg, 68%).

$C_{28}H_{32}NOP$ (429.53).

$[\alpha]_D^{20}$ = -30.0° (c = 0.200, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.82 (t, *J*(H,H) = 7.4 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.87 (d, *J*(H,H) = 6.5 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 0.88 (t, *J*(H,H) = 7.5 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.89 (d, *J*(H,H) = 6.5 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 1.50 (dq, *J*(H,H) = 14.8 Hz, *J*(H,H) = 7.4 Hz, 1H, $C\mathbf{H}_2CH_3$), 1.52 (dq, *J*(H,H) = 14.8 Hz, *J*(H,H) = 7.6 Hz, 1H, $C\mathbf{H}_2CH_3$), 1.63 (dq, *J*(H,H) = 14.7 Hz, *J*(H,H) = 7.4 Hz, 1H, $C\mathbf{H}_2CH_3$), 1.68 (ds, *J*(H,H) = 7.8 Hz, *J*(H,H) = 6.5 Hz, 1H, $C\mathbf{H}(CH_3)_2$), 1.76 (dq, *J*(H,H) = 14.8 Hz, *J*(H,H) = 7.6 Hz, 1H, $C\mathbf{H}_2CH_3$), 3.40 (d, *J*(H,H) = 7.9 Hz, 1H, NC**H**), 6.86 (ddd, *J*(H,H) = 7.9 Hz, *J*(H,H) = 4.0 Hz, *J*(H,H) = 1.3 Hz, 1H, Ph-**H**), 7.21-7.32 (m, 11H, Ph-**H**), 7.36 (dt, *J*(H,H) = 7.4 Hz, *J*(H,H) = 1.5 Hz, 1H, Ph-**H**), 7.89 (ddd, *J*(H,H) = 7.6 Hz, *J*(H,H) = 3.7 Hz, *J*(H,H) = 1.4 Hz, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 8.2 ($CH_2\mathbf{C}H_3$), 8.7 ($CH_2\mathbf{C}H_3$), 21.2 ($CH(\mathbf{C}H_3)_2$), 21.8 ($CH(\mathbf{C}H_3)_2$), 25.5 ($\mathbf{C}H_2CH_3$), 28.9 ($\mathbf{C}H(CH_3)_2$), 30.0 ($\mathbf{C}H_2CH_3$), 78.4 (N**C**H), 91.1 (O**C**), 128.4 (**Ph**-H), 128.7 (**Ph**-H), 128.8 (**Ph**-H), 128.8 (2C, **Ph**-H), 128.8 (**Ph**-H), 128.8 (**Ph**-H), 129.9 (d, *J*(C,P) =2.9 Hz, **Ph**-H), 130.5 (**Ph**-H), 133.5 (d, *J*(C,P) = 19.7 Hz, **Ph**-CN), 134.4 (**Ph**-H), 134.4 (**Ph**-H), 134.6 (**Ph**-H), 134.6 (2C, **Ph**-H), 139.4 (d, *J*(C,P) = 26.8 Hz, **Ph**-P), 139.6 (d, *J*(C,P) = 13.4 Hz, **Ph**-P), 139.7 (d, *J*(C,P) = 13.4 Hz, **Ph**-P), 161.1 (d, *J*(C,P) = 3.4 Hz, **C**=N).

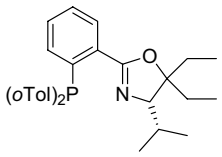
^{31}P{^{1}H} NMR (162.0 MHz, $CDCl_3$, 300 K): δ = -12.4.

MS (FAB) m/z (rel int %): 430 (M + H, 31), 304 (100), 289 (9), 317(10), 246 (50), 202 (10), 155 (10), 137 (20), 105 (25).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3380w_{br}, 3056m, 2967s, 2876m, 1652s, 1586w, 1465s, 1435s, 1382m, 1355s, 1302m, 1277m, 1180w, 1090s, 1046s, 928s, 746s.

EA % found (calcd): C: 78.29 (77.50), H: 7.54 (7.51), N: 3.09 (3.26).

(*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-diethyl-4-isopropyl-4,5-dihydrooxazole (71)



Product **71** was prepared according to **general procedure VI** (page 159) from (*S*)-5,5-Diethyl-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (500 mg, 1.90 mmol), 1.6M *n*-BuLi in hexane (1.30 mL, 2.09 mmol), di*ortho*-tolylphosphane (447 mg, 2.09 mmol) and THF as a solvent (40.0 mL). After column chromatography (Hx : EtOAc 10 : 1, $\mathbf{R}_f$ = 0.53) on silica compound **71** (478 mg, 55%) was isolated as a colorless solid.

$C_{30}H_{36}NOP$ (457.58).

m.p. 68-73 °C.

$[\alpha]_D^{20}$ = -45.0° (c = 0.200, $CHCl_3$).

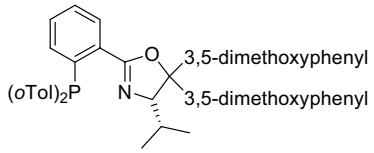
^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.84 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 0.84 (t, *J*(H,H) = 7.4 Hz, 3H, CH_2C**H**$_3$), 0.85 (t, *J*(H,H) = 7.5 Hz, 3H, CH_2C**H**$_3$), 0.90 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.52 (dq, *J*(H,H) = 14.8 Hz, *J*(H,H) = 7.4 Hz, 1H, C**H**$_2$CH$_3$), 1.55 (dq, *J*(H,H) = 14.8 Hz, *J*(H,H) = 7.4 Hz, 1H, C**H**$_2$CH$_3$), 1.67-1.79 (m, 3H, C**H**$_2$CH$_3$ & C**H**(CH$_3$)$_2$), 2.34 (d, *J*(H,H) = 1.8 Hz, 3H, *o*Tol-C**H**$_3$), 2.35 (d, *J*(H,H) = 1.8 Hz, 3H, *o*Tol-C**H**$_3$), 3.48 (d, *J*(H,H) = 7.3 Hz, 1H, NC**H**), 6.71-6.73 (m, 2H, Ar-**H**), 6.88 (dddd, *J*(H,H) = 7.7 Hz, *J*(H,H) = 3.5 Hz, *J*(H,H) = 1.3 Hz, *J*(H,H) = 0.5 Hz, 1H, Ar-**H**) 7.01-7.06 (m, 2H, Ar-**H**), 7.17-7.24 (m, 4H, Ar-**H**), 7.28 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**), 7.38 (dt, *J*(H,H) = 7.4 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 7.89 (dddd, *J*(H,H) = 7.7 Hz, *J*(H,H) = 4.0 Hz, *J*(H,H) = 1.7 Hz, *J*(H,H) = 0.5 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 8.2 (CH_2**C**H$_3$), 8.7 (CH_2**C**H$_3$), 20.7 (CH(**C**H$_3$)$_2$), 21.3 (d, *J*(C,P) = 5.6 Hz, *o*Tol-**C**H$_3$), 21.5 (d, *J*(C,P) =5.8 Hz, *o*Tol-**C**H$_3$), 22.0 (CH(**C**H$_3$)$_2$), 25.4 (**C**H$_2$CH$_3$), 29.0 (**C**H(CH$_3$)$_2$), 30.0 (**C**H$_2$CH$_3$), 78.4 (N**C**H), 91.2 (O**C**), 126.4 (**Ar**-H), 126.5 (**Ar**-H), 128.6 (**Ar**-H), 128.8 (**Ar**-H), 128.8 (**Ar**-H), 130.2 (d, *J*(C,P) = 3.8 Hz, **Ar**-H), 130.4 (d, *J*(C,P) = 4.8 Hz, **Ar**-H), 130.4 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 130.6 (**Ar**-H), 133.5 (**Ar**-H), 133.7 (**Ar**-H), 134.7 (d, *J*(C,P) = 23.5 Hz, **Ar**-CN), 134.9 (**Ar**-H), 137.4 (d, *J*(C,P) = 13.0 Hz, ***o*Tol**-P), 137.5 (d, *J*(C,P) = 13.9 Hz, ***o*Tol**-P), 137.7 (d, *J*(C,P) = 24.5 Hz, **Ph**-P), 142.8 (d, *J*(C,P) = 26.9 Hz, ***o*Tol**-CH$_3$), 142.8 (d, *J*(C,P) = 26.9 Hz, ***o*Tol**-CH$_3$), 161.5 (d, J(C,P) = 1.9 Hz, **C**=N).

^{31}P{^{1}H} NMR (162.0 MHz, $CDCl_3$, 300 K): δ = -28.9.

MS (FAB) m/z (rel int %): 458 (M + H, 43), 366 (11), 332 (100), 317(10), 242 (13).
IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3424w_{br}, 3053w, 2942s, 2876m, 1649s, 1586w, 1462s, 1379m, 1333m, 1273m, 1132w, 1088m, 1046s, 925s, 888m, 863w, 751s, 716w.
EA % found (calcd): C: 78.66 (78.74), H: 7.88 (7.93), N: 2.86 (3.06).

(*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-bis-(3,5-dimethoxyphenyl)-4-isopropyl-4,5-dihydrooxazole (78)



Product **78** was prepared according to **general procedure VI** (page 159) from (*S*)-5,5-bis-(3,5-dimethoxyphenyl)-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (200 mg, 0.42 mmol), 1.6M *n*-BuLi in hexane (288 µL, 0.46 mmol), di*ortho*-tolylphosphane (100 mg, 0.46 mmol) and THF as a solvent (10.0 mL). After column chromatography (Hx : EtOAc 3 : 1, $\mathbf{R}_f$ = 0.38) on silica compound **78** (150 mg, 53%) was isolated as a colorless solid.

$C_{42}H_{44}NO_5P$ (673.78).
m.p. 77-78 °C.
$[\alpha]_D^{20}$ = -212.5° (c = 0.410, $CHCl_3$).
^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.32 (br s, 3H, CH(C**H**$_3$)$_2$), 0.82 (br s, 3H, CH(C**H**$_3$)$_2$), 1.84 (br s, 1H, C**H**(CH$_3$)$_2$), 2.30 (d, *J*(H,H) = 1.6 Hz, *o*Tol-C**H**$_3$), 2.33 (d, *J*(H,H) = 1.8 Hz, *o*Tol-C**H**$_3$), 3.72 (s, 6H, 2 x OC**H**$_3$), 3.74 (s, 6H, 2 x OC**H**$_3$), 4.63 (d, *J*(H,H) = 4.0 Hz, 1H, NC**H**), 6.32 (t, *J*(H,H) = 2.4 Hz, 3,5-dimethoxyphenyl-**H**), 6.36 (t, *J*(H,H) = 2.4 Hz, 3,5-dimethoxyphenyl-**H**), 6.53 (d, *J*(H,H) = 2.4 Hz, 3,5-dimethoxyphenyl-**H**), 6.65 (d, *J*(H,H) = 2.2 Hz, 3,5-dimethoxyphenyl-**H**), 6.65-6.67 (m, 1H, Ar-**H**), 6.69-6.71 (m, 1H, Ar-**H**), 6.96 (ddd, *J*(H,H) = 7.9 Hz, *J*(H,H) = 3.3 Hz, *J*(H,H) = 1.0 Hz, 1H, Ar-**H**), 6.97-7.04 (m, 2H, Ar-**H**), 7.16-7.22 (m, 4H, Ar-H), 7.34 (td, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**), 7.47 (td, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.5 Hz, 1H, Ar-**H**), 8.17 (br s, 1H, Ar-**H**).
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 16.8 (CH(**C**H$_3$)$_2$), 21.3 (d, *J*(C,P) = 8.6 Hz, *o*Tol-**C**H$_3$), 21.5 (d, *J*(C,P) = 8.6 Hz, *o*Tol-**C**H$_3$), 22.0 (CH(**C**H$_3$)$_2$), 30.6 (**C**H(CH$_3$)$_2$), 55.8 (2C, O**C**H$_3$), 55.9 (2C, O**C**H$_3$), 81.4 (N**C**H), 92.5 (O**C**), 98.6 (**methoxyphenyl**-H), 99.5 (**methoxyphenyl**-H), 105.1 (2C, **methoxyphenyl**-H), 106.3 (2C, **methoxyphenyl**-H), 126.4 (2C, **Ar**-H), 128.8 (2C, **Ar**-H), 128.9 (**Ar**-H), 130.4 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 130.5 (d,

J(C,P) = 5.3 Hz, **Ar**-H), 130.6 (**Ar**-H), 131.1 (**Ar**-H), 133.3 (d, *J*(C,P) = 19.5 Hz, **Ar**-CN), 133.4 (**Ar**-H), 133.7 (**Ar**-H), 135.5 (**Ar**-H), 137.4 (d, *J*(C,P) = 13.0 Hz, ***o*Tol**-P), 137.5 (d, *J*(C,P) = 12.9 Hz, ***o*Tol**-P), 138.4 (d, *J*(C,P) = 25.4 Hz, **Ph**-P), 142.8 (d, *J*(C,P) = 25.4 Hz, ***o*Tol**-CH_3), 142.8 (d, *J*(C,P) = 25.4 Hz, ***o*Tol**-CH_3), 143.6 (C(**3,5-dimethoxyphenyl**$_{(ipso)}$)$_2$), 148.8 (C(**3,5-dimethoxyphenyl**$_{(ipso)}$)$_2$), 160.6 (d, *J*(C,P) = 2.4 Hz, **C**=N), 160.8 (2C, **3,5-dimethoxyphenyl**-OCH_3), 161.2 (2C, **3,5-dimethoxyphenyl**-OCH_3).

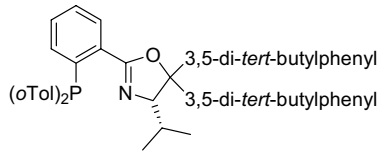
^{31}P{^{1}H} NMR (162.0 MHz, CD_2Cl_2, 295 K): δ = -30.0.

MS (FAB) m/z (rel int %): 674 (M + H, 11), 342 (24), 332 (100), 317 (19), 165 (12), 91 (14), 89 (16), 77 (20), 65 (11), 63 (10), 51 (12), 41 (12), 39 (21).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3424w, 3054w, 2954m, 2836w, 1654w, 1598s, 1460s, 1426s, 1333m, 1203s, 1156s, 1062m, 977w, 928w, 837w, 748m.

EA % found (calcd): C: 74.80 (74.87), H: 6.80 (6.58), N: 1.81 (2.08).

(*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-bis-(3,5-di-*tert*-butylphenyl)-4-isopropyl-4,5-dihydrooxazole (79)



Product **79** was prepared according to **general procedure VI** (page 159) from (*S*)-5,5-bis-(3,5-di-*tert*-butylphenyl)-2-(2-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (200 mg, 0.34 mmol), 1.6M *n*-BuLi in hexane (236 µL, 0.38 mmol), di*ortho*-tolylphosphane (81.0 mg, 0.38 mmol) and THF as a solvent (10.0 mL). After column chromatography (Hx : EtOAc 100 : 1, $\mathbf{R}_f$ = 0.10) on silica compound **79** (142 mg, 54%) was isolated as a colorless solid.

$C_{54}H_{68}NOP$ (778.10).

m.p. 205 °C.

$[\alpha]_D^{20}$ = -87.1° (c = 0.480, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.22 (br s, 3H, CH(C**H**$_3$)$_2$), 0.66 (br s, 3H, CH(C**H**$_3$)$_2$), 1.24 (s, 18H, 2 x C(C**H**$_3$)$_3$), 1.30 (s, 18H, 2 x C(C**H**$_3$)$_3$), 1.84 (br s, 1H, C**H**(CH$_3$)$_2$), 2.29 (d, *J*(H,H) = 1.8 Hz, 3H, *o*Tol-C**H**$_3$), 2.35 (d, *J*(H,H) = 1.8 Hz, 3H, *o*Tol-C**H**$_3$), 4.52 (d, *J*(H,H) = 5.0 Hz, 1H, NC**H**), 6.65-6.68 (m, 1H, Ar-**H**), 6.70-6.73 (m, 1H, Ar-**H**), 6.95-6.98 (m, 1H, Ar-**H**), 6.99-7.03 (m, 2H, Ar-**H**), 7.15-7.19 (m, 4H, Ar-**H**), 7.20 (d, *J*(H,H) = 1.8 Hz, 2H, Ar-**H**), 7.27 (t, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**), 7.35 (td, *J*(H,H) = 6.3 Hz,

J(H,H) = 1.3 Hz, 1H, Ar-**H**), 7.27 (t, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**), 7.40 (d, *J*(H,H) = 1.8 Hz, 2H, Ar-**H**), 7.47 (td, *J*(H,H) = 6.3 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 8.25 (br s, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 16.7 ($CH(\mathbf{C}H_3)_2$), 20.8 (d, *J*(C,P) = 13.4 Hz, *o*Tol-$\mathbf{C}H_3$), 21.0 (d, *J*(C,P) = 14.4 Hz, *o*Tol-$\mathbf{C}H_3$), 21.1 ($CH(\mathbf{C}H_3)_2$), 30.5 ($\mathbf{C}H(CH_3)_2$), 31.1 (6C, $C(\mathbf{C}H_3)_3$), 31.2 (6C, $C(\mathbf{C}H_3)_3$), 34.7 (2C, $\mathbf{C}(CH_3)_3$), 34.8 (2C, $\mathbf{C}(CH_3)_3$), 83.1 (N**C**H), 92.5 (O**C**), 120.1 (2C, **3,5-di-*tert*-butylphenyl**-H), 120.5 (**3,5-di-*tert*-butylphenyl**-H), 121.4 (**3,5-di-*tert*-butylphenyl**-H), 121.5 (2C, **3,5-di-*tert*-butylphenyl**-H), 125.8 (**Ar**-H), 125.9 (**Ar**-H), 128.1 (**Ar**-H), 128.1 (**Ar**-H), 128.3 (**Ar**-H), 129.6 (**Ar**-H), 129.7 (**Ar**-H), 129.8 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 129.8 (d, *J*(C,P) = 4.3 Hz, **Ar**-H), 130.3 (**Ar**-H), 132.8 (**Ar**-H), 133.1 (**Ar**-H), 134.8 (**Ar**-H), 137.0 (d, *J*(C,P) = 14.4 Hz, ***o*Tol**-P), 137.2 (d, *J*(C,P) = 11.5 Hz, ***o*Tol**-P), 137.9 (d, *J*(C,P) = 24.0 Hz, **Ph**-P), 140.1 ($C(\mathbf{3,5\text{-}di\text{-}}\mathit{tert}\mathbf{\text{-}butylphenyl}_{(ipso)})_2$), 142.1 (d, *J*(C,P) = 22.6 Hz, ***o*Tol**-CH_3), 142.1 (d, *J*(C,P) = 22.7 Hz, ***o*Tol**-CH_3), 145.4 ($C(\mathbf{3,5\text{-}di\text{-}}\mathit{tert}\mathbf{\text{-}butylphenyl}_{(ipso)})_2$), 149.7 (2C, $C(\mathbf{3,5\text{-}di\text{-}}\mathit{tert}\mathbf{\text{-}butylphenyl}_{(meta)})_2$), 150.5 (2C, $C(\mathbf{3,5\text{-}di\text{-}}\mathit{tert}\mathbf{\text{-}butylphenyl}_{(meta)})_2$), 159.8 (br s, **C**=N). (**Ar**-CN not visible).

^{31}P{^{1}H} NMR (162.0 MHz, CD_2Cl_2, 295 K): δ = -29.3.

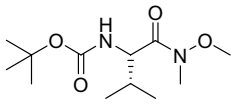
MS (FAB) m/z (rel int %): 779 (M + H, 1), 332 (21), 77 (9), 57 (100), 41 (21), 39 (10).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3425w, 3056w, 2960s, 2867m, 1653m, 1596m, 1467m, 1362w, 1333w, 1247w, 1134w, 1092w, 1038m, 967w, 880w, 749m, 718w.

EA % found (calcd): C: 83.33 (83.35), H: 8.90 (8.81), N: 1.57 (1.80).

13.3.2 Synthesis of PHOX Ligands Bearing Two Chirality Centers at the Oxazoline Unit

(*S*)-*tert*-butyl 1-(methoxy(methyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate (106)



A solution of (*S*)-2-(*tert*-butoxycarbonylamino)-3-methylbutanoic acid (23.5 g, 108 mmol) in dichloromethane (50.0 mL) was successively added to a stirred suspension of *O*,*N*-dimethylhydroxylamine hydrochloride (11.6 g, 119 mmol) and triethylamine (16.6 mL, 119 mmol) in dichloromethane (200 mL). After adding a solution of *N*,*N*'-dicyclohexylcarbodiimide (24.6 g, 119 mL) in dichloromethane (50.0 mL) over 30 min the reaction mixture was stirred for 3 h. The suspension was filtered over Celite, the solvent

was removed under reduced pressure and the crude product was purified by column chromatography (Hx : EtOAC 4 : 1, $KMnO_4$ and Ninhydrin dips, $\mathbf{R}_f$ = 0.25 ($KMnO_4$)) on silica to afford a colorless oil (19.1 g, 68%).

$C_{12}H_{24}N_2O_4$ (260.33).

$[\alpha]_D^{20}$ = +11.2° (c = 0.860, CH_2Cl_2).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.90 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.95 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.43 (s, 9H, C(C**H**$_3$)$_3$), 1.98 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 6.6 Hz, 1H, C**H**(CH$_3$)$_2$), 3.21 (s, 3H, NC**H**$_3$), 3.76 (s, 3H, OC**H**$_3$), 4.57 (br s, 1H, NHC**H**), 5.13 (d, *J*(H,H) = 9.1 Hz, 1H, N**H**).

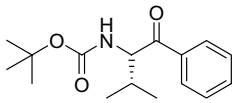
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 17.6 (CH(**C**H$_3$)$_2$), 19.5 (CH(**C**H$_3$)$_2$), 28.5 (3C, C(**C**H$_3$)$_3$), 31.5 (**C**H(CH$_3$)$_2$), 32.0 (N**C**H$_3$), 55.1 (N**C**H), 61.7 (O**C**H$_3$), 79.5 (**C**(CH$_3$)$_3$), 156.0 (**C**ON(Me)OMe), 173.1 (**C**OOC(CH$_3$)$_3$).

MS (FAB) m/z (rel int %): 261 (M + H, 74), 205 (100), 161 (44), 144 (12), 116 (29), 72 (41), 62 (55), 57 (41).

IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3327m, 2970s, 2936s, 2876m, 2823w, 1713s, 1657s, 1498s, 1389m, 1367s, 1304m, 1242s, 1172s, 1117w, 1084w, 1042w, 1015m, 966w, 875w, 830w.

EA % found (calcd): C: 55.45 (55.36), H: 9.02 (9.29), N: 10.86 (10.72).

(*S*)-*tert*-butyl 3-methyl-1-oxo-1-phenylbutan-2-ylcarbamate (107)



1M Phenylmagnesiumbromide-solution (158 mL, 134 mmol) in THF was added over 30 min. to a solution of the Weinreb amide **106** (12.4 g, 46.1 mmol) in THF (110 mL) at 0 °C. The reaction mixture was stirred over night at rt and was subsequently quenched with a 10% HCl-solution (115 mL) at 0 °C. The resulting solution was extracted with ethyl acetate (3 x 280 mL), the combined organic layers were washed with water (2 x 120 mL) and brine (80 mL) and were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Hx : EtOAc 8 : 1, $\mathbf{R}_f$ = 0.30) on silica to afford a colorless solid (10.5 g, 82%).

$C_{16}H_{23}NO_3$ (277.36).

m.p. 38-40 °C.

$[\alpha]_D^{20}$ = +82.8° (c = 0.950, CH_2Cl_2).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.74 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.03 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.45 (s, 9H, C(C**H**$_3$)$_3$), 2.15 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 4.3 Hz, 1H, C**H**(CH$_3$)$_2$), 5.23 (dd, *J*(H, H) = 8.8 Hz, *J*(H, H) = 4.1 Hz, 1H, NHC**H**), 5.41 (d, *J*(H, H) = 8.6 Hz, 1H, N**H**), 7.48 (t, *J*(H, H) = 7.7 Hz, 2H, Ph-**H**), 7.59 (t, *J*(H,H) = 7.3 Hz, 1H, Ph-**H**), 7.97 (d, *J*(H ,H) = 7.3 Hz, 2H, Ph-**H**).

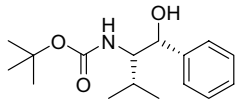
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 16.6 (CH(**C**H$_3$)$_2$), 20.2 (CH(**C**H$_3$)$_2$), 28.5 (3C, C(**C**H$_3$)$_3$), 31.8 (**C**H(CH$_3$)$_2$), 59.7 (NH**C**H), 79.7 (**C**(CH$_3$)$_3$), 128.7 (2C, **Ph**-H), 128.9 (2C, **Ph**-H), 133.7 (**Ph**-H), 135.6 (**Ph**-C), 156.1 (O**C**O), 199.9 (**C**OPh).

MS (FAB) m/z (rel int %): 278 (M + H, 22), 222 (72), 178 (51), 172 (19), 116 (36), 105 (26), 72 (52), 57 (100), 41 (16).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3368s, 2973m, 2954w, 2903w, 1704s, 1681s, 1595w, 1521s, 1451w, 1390w, 1365s, 1301w, 1245m, 1217m, 1160s, 1094m, 1002w, 877m, 774w, 693m.

EA % found (calcd): C: 69.25 (69.29), H: 8.20 (8.36), N: 4.96 (5.05).

***Tert*-butyl (1*R*,2*S*)-1-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate (108)**



Sodium borohydride (2.70 g, 72.1 mmol) was added to a stirred solution of (*S*)-*tert*-butyl 3-methyl-1-oxo-1-phenylbutan-2-ylcarbamate (10.0 g, 36.1 mmol) in dry methanol (450 mL) at –20 °C. After a stirring period of 3.5 h the reaction solution was quenched with water (90 mL) and the resulting mixture was concentrated under reduced pressure until a colorless solid precipitated. The suspension was diluted with ethyl acetate (900 mL), was successively washed with water and brine and was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Hx : EtOAc 4 : 1, **R**$_f$ = 0.25) on silica to afford a colorless solid (8.5 g, 84%).

$C_{16}H_{25}NO_3$ (279.37).

m.p. 101-103 °C.

$[\alpha]_D^{20}$ = -80.8° (c = 0.570, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.87 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.02 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.35 (s, 9H, C(C**H**$_3$)), 1.70-1.79 (m, 1H, C**H**(CH$_3$)$_2$), 3.02 (d, *J*(H,H) = 4.5 Hz, 1H, O**H**), 3.70-3.76 (m, 1H, NHC**H**), 4.38 (d, *J*(H,H) = 9.1 Hz, 1H, N**H**), 4.79 (t, *J*(H,H) = 4.8 Hz, 1H, C**H**(OH)Ph), 7.25-7.34 (m, 5H, Ph-**H**).

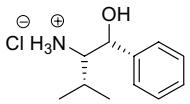
^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 18.1 (CH(**C**H$_3$)$_2$), 21.1 (CH(**C**H$_3$)$_2$), 28.6 (3C, C(**C**H$_3$)$_3$), 28.8 (**C**H(CH$_3$)$_2$), 61.6 (NH**C**H), 75.7 (**C**H(OH)Ph), 79.7 (**C**(CH$_3$)$_3$), 127.4 (2C, **Ph**-H), 128.1 (**Ph**-H), 128.6 (2C, **Ph**-H), 142.1 (**Ph**-C), 157.3 (**C**O).

MS (FAB) m/z (rel int %): 280 (M + H, 25), 224 (25), 206 (85), 172 (23), 145 (17), 116 (49), 91 (13), 72 (64), 57 (100), 41 (12).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3383s, 3067w, 3033w, 2963m, 2944w, 2933w, 2894w, 1688s, 1521s, 1458m, 1389w, 1366m, 1306m, 1253m, 1172s, 1114w, 1046m, 988m, 873w, 812w, 761w, 702w.

EA % found (calcd): C: 68.59 (68.79), H: 8.89 (9.02), N: 4.91 (5.01).

(1*R*, 2*S*)-2-Amino-3-methyl-1-phenylbutan-1-ol hydrochloride (109)



A 4M HCl-solution (88.4 mL, 354 mmol) in dioxane was added to *tert*-butyl (1*R*,2*S*)-1-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate (7.80 g, 27.9 mmol). The reaction mixture was stirred for 3 h before the solvent was removed under reduced pressure. The residue was diluted in absolute diethyl ether whereupon the product precipitated as a colorless solid. It was filtered and washed with cold absolute diethyl ether and pentane to afford the pure product **109** (5.78 g, 96 %).

$C_{11}H_{17}NO{\cdot}HCl$ (215.72).

m.p. 193–195 °C (decomp.).

$[\alpha]_D^{20}$ = -32.5° (c = 0.540, MeOH, *syn*:*anti* 98:2).

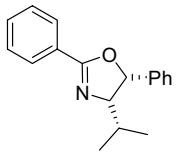
^{1}H NMR (400.1 MHz, $(CD_3)_2SO$, 300 K): δ = 0.89 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 0.92 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 1.66-1.75 (m, 1H, C**H**(CH$_3$)$_2$), 3.11 (t, *J*(H,H) = 4.8 Hz, 1H, C**H**NH), 4.98-4.99 (m, 1H, O**H**), 6.08 (d, *J*(H,H) = 4.0 Hz, 1H, C**H**OH), 7.28-7.32 (m, 1H, Ph-**H**), 7.36-7.44 (m, 4H, Ph-**H**), 7.94 (br s, 3H, $^+$N**H**$_3$)

^{13}C{^{1}H} NMR (100.6 MHz, $(CD_3)_2SO$, 300 K): δ = 18.0 ($CH(\mathbf{C}H_3)_2$), 20.5 ($CH(\mathbf{C}H_3)_2$), 26.1 ($\mathbf{C}H(CH_3)_2$), 60.9 (**C**HNH), 71.0 (**C**HOH), 126.5 (2C, **Ph**-H), 127.5 (**Ph**-H), 128.2 (2C, **Ph**-H), 140.7 (**Ph**-C).

MS (FAB) m/z (rel int %):180 (M^+-Cl, 100), 162 (M-OH, 23), 72 (M-CH(OH)Ph, 11).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3328s, 3032s, 2964s, 1603m, 1560w, 1508m, 1451m, 1405w, 1376w, 1203w, 1139w, 1027m, 753m, 703s.

(4*S*,5*R*)-4-Isopropyl-2,5-diphenyl-4,5-dihydrooxazole (110)



Ethyl benzimidate hydrochloride (2.00 g, 4.21 mmol) was dissolved in dichloromethane (50.0 mL) and was extracted with a saturated $NaHCO_3$-solution (2 x 50 mL) and brine. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford a colorless oil (1.60 g).

(1*R*,2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol hydrochloride (1.00 g, 4.64 mmol) was added to a solution of the imidate (0.63 g, 4.21 mmol) in dichloroethane (35.0 mL). The reaction solution was heated to reflux for 20 h before the precipitate which was formed during the reaction was filtered off and washed with dichloroethane. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Hx : EtOAc 5 : 1, $\mathbf{R}_f$ = 0.50) on silica to afford a colorless solid (0.77 g, 69%) with a *de*-value of 92%. By means of semipreperative HPLC (OD, Hep : IPA 95 : 5, 0.5 mL/min, 20 °C, 220 nm and 254 nm, 7.8 min and 13.8 min) the pure diastereomer **110** (0.50 g, 45%) could be isolated as a colorless solid.

$C_{18}H_{19}NO$ (265.35).

m.p. 86-89 °C.

$[\alpha]_D^{20}$ = -238.1° (c = 0.640, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.77 (d, *J*(H,H) = 6.6 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 0.91 (d, *J*(H,H) = 6.6 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 1.58 (ds, *J*(H,H) = 6.6 Hz, *J*(H,H)= 6.6 Hz, 1H, $C\mathbf{H}(CH_3)_2$), 4.21 (dd, *J*(H,H) = 9.1 Hz, *J*(H,H) = 6.8 Hz, 1H, NC**H**), 5.73 (d, *J*(H,H) = 9.6 Hz, 1H, OC**H**), 7.33 (br s, 5H, Ph-**H**), 7.43-7.47 (m, 2H, Ph-**H**), 7.45-7.54 (m, 1H, Ph-**H**), 8.01-8.03 (m, 2H, Ph-**H**).

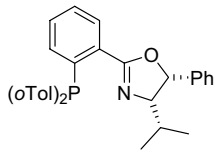
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 19.9 (CH(**C**H_3)$_2$), 21.3 (CH(**C**H_3)$_2$), 29.8 (**C**H(CH$_3$)$_2$), 77.3 (N**C**H), 84.8 (O**C**H), 127.8 (2C, **Ph**-H), 128.5 (**Ph**-H), 128.7 (2C, **Ph**-H), 128.7 (**Ph**-C), 128.8 (2C, **Ph**-H), 128.9 (2C, **Ph**-H), 131.8 (**Ph**-H), 138.2 (**Ph**-C), 163.3 (**C**=N).

MS (FAB) m/z (rel int %): 266 (M + H, 75), 222 (10), 159 (17), 144 (13), 105 (100), 91 (11), 77 (25).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3451w, 3062w, 3033w, 2956m, 2868m, 1646s, 1575m, 1493m, 1450m, 1358m, 1327s, 1301m, 1267m, 1209w, 1178w, 1059s, 1021m, 944s, 768m, 698s.

EA % found (calcd): C: 81.35 (81.48), H: 7.26 (7.22), N: 5.17 (5.28).

(4*S*,5*R*)-2-(2-(Dio-t*o*lylphosphino)phenyl)-4-isopropyl-5-phenyl-4,5-dihydrooxazole (111)



Product **111** was prepared according to **general procedure V** (page 149) from (4*S*,5*R*)-4-isopropyl-2,5-diphenyl-4,5-dihydrooxazole (0.50 g, 1.88 mmol), *sec*-BuLi in cyclohexane (1.60 mL, 2.07 mmol), TMEDA (0.31 mL, 2.07 mmol), chlorodi*ortho*-tolylphosphine (0.61 g, 2.45 mmol) and pentane as a solvent (28.0 mL). After column chromatography (Hx : EtOAc 15 : 1, $\mathbf{R}_f$ = 0.25) on silica compound **111** (635 mg, 71%) was isolated as a colorless solid.

$C_{32}H_{32}NOP$ (477.58).

m.p. 52-54 °C.

$[\alpha]_D^{20}$ = -158.6° (c = 0.590, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.58 (d, *J*(H,H) = 6.5 Hz, 3H, CH(C**H**$_3$)$_2$), 0.60 (d, *J*(H,H) = 6.6 Hz, 3H, CH(C**H**$_3$)$_2$), 1.39 (ds, *J*(H,H) = 7.2 Hz, *J*(H,H) = 6.6 Hz, 1H, C**H**(CH$_3$)$_2$), 2.35 (br s, 6H, *o*Tol-C**H**$_3$), 4.06 (dd, *J*(H,H) = 9.7 Hz, *J*(H,H) = 7.9 Hz, 1H, NC**H**), 5.56 (d, *J*(H,H) = 9.8 Hz, 1H, OC**H**), 6.74-6.78 (m, 2H, Ar-**H**), 6.95 (dddd, *J*(H,H) = 7.6 Hz, *J*(H,H) = 3.5 Hz, *J*(H,H) = 1.5 Hz, *J*(H,H) = 0.5 Hz, 1H, Ar-**H**), 7.05-7.08 (m, 2H, Ar-**H**), 7.18-7.26 (m, 6H, Ar-**H**), 7.27-7.31 (m, 3H, Ar-**H**), 7.33 (dt, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**), 7.43 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**), 7.99 (ddd, *J*(H,H) = 7.9 Hz, *J*(H,H) = 3.9 Hz, *J*(H,H) = 1.4 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 19.4 (d, *J*(C,P) = 1.0 Hz, CH(**C**H_3)$_2$), 21.1 (CH(**C**H_3)$_2$), 21.4 (d, *J*(C,P) = 3.8 Hz, *o*Tol-**C**H_3), 21.6 (d, *J*(C,P) = 3.8 Hz, *o*Tol-**C**H_3), 29.7

(**C**H(CH_3)$_2$), 77.8 (N**C**H), 84.4 (O**C**H), 126.5 (**Ar**-H), 126.5 (**Ar**-H), 127.8 (**Ar**-H), 127.8 (**Ar**-H), 128.3 (**Ar**-H), 128.5 (2C, **Ar**-H), 128.8 (**Ar**-H), 128.9 (**Ar**-H), 128.9 (**Ar**-H), 130.4 (d, *J*(C,P)=3.3 Hz, **Ar**-H), 130.5 (d, *J*(C,P) = 4.8 Hz, **Ar**-H), 130.5 (d, *J*(C,P) = 4.8 Hz, **Ar**-H), 131.5 (**Ar**-H), 133.5 (d, *J*(C,P) = 22.6 Hz, **Ar**-CN), 133.6 (**Ar**-H), 133.7 (**Ar**-H), 135.1 (**Ar**-H), 137.3 (d, *J*(C,P) = 11.5 Hz, ***o*Tol**-P), 137.3 (d, *J*(C,P) = 13.4 Hz, ***o*Tol**-P), 138.0 (**Ar**-CHO), 138.3 (d, *J*(C,P) = 24.5 Hz, **Ar**-P), 142.8 (d, *J*(C,P) = 27.8 Hz, ***o*Tol**-CH_3), 142.9 (d, *J*(C,P) = 27.9 Hz, ***o*Tol**-CH_3), 162.6 (d, *J*(C,P) = 2.4 Hz, **C**=N).

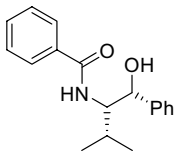
^{31}P{^{1}H} NMR (162.0 MHz, CD_2Cl_2, 300 K): δ = -29.5.

MS (FAB) m/z (rel int %): 478 (M + H, 25), 332 (100), 317 (14), 165 (5), 145 (6), 105 (12), 91 (19), 57 (7), 55 (8), 43 (9), 41 (9).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3432m, 3052m, 3003w, 2955s, 2870m, 1650s, 1586w, 1493w, 1451s, 1376w, 1322m, 1302m, 1202w, 1162w, 1130m, 1086m, 1036s, 961m, 748s, 695s.

EA % found (calcd): C: 80.41 (80.48), H: 7.00 (6.75), N: 2.73 (2.93).

N-((1*R*, 2*S*)-1-hydroxy-3-methyl-1-phenylbutan-2-yl)benzamide 112



A solution of benzoylchloride (0.50 mL, 4.60 mmol) in dioxane (5.10 mL) was added within 40 min to a solution of (1*R*,2*S*)-2-amino-3-methyl-1-phenylbutan-1-ol hydrochloride (1.00 g, 4.60 mmol) and triethylamine (2.15 mL, 15.5 mmol) in dioxane (7.70 mL) at 0 °C. The resulting suspension was stirred for 1.5 h at rt. The solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (13 mL) and filtered over silica gel, which was washed with ethyl acetate (64 mL). The solvent was removed under reduced pressure and the colorless solid (1.27, 97%) was used without further purification in the following step.

$C_{18}H_{21}NO_2$ (283.36).

R$_f$ = 0.28 (Hx : EtOAc 2 : 1).

m.p. 121-123 °C.

$[\alpha]_D^{20}$ = -127.4° (c = 0.510, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.96 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.11 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.83 (ds, *J*(H, H) = 6.8 Hz, *J*(H, H) = 6.8 Hz, 1H, C**H**(CH$_3$)$_2$), 3.56 (d, *J*(H,H) = 4.5 Hz, 1H, O**H**), 4.28-4.33 (m, 1H, NHC**H**), 5.01 (t, *J*(H,H) =

4.5 Hz, 1H, C**H**OH), 5.94 (d, *J*(H,H) = 8.8 Hz, 1H, N**H**), 7.25-7.44 (m, 7H, Ph-**H**), 7.49-7.53 (m, 1H, Ph-**H**), 7.64-7.66 (m, 2H, Ph-**H**).

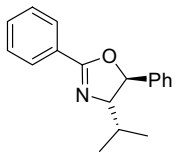
^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 18.9 (**C**H_3), 21.4 (**C**H_3), 29.1 (**C**H$(CH_3)_2$), 61.2 (NH**C**H), 75.7 (**C**HOH), 127.3 (2C, **Ph**-H), 127.4 (2C, **Ph**-H), 128.2 (**Ph**-H), 128.7 (2C, **Ph**-H), 129.1 (2C, **Ph**-H), 132.1 (**Ph**-H), 135.1 (**Ph**-C), 141.7 (**Ph**-C), 169.0 (**C**O).

MS (FAB) m/z (rel int %): 284 (M + H, 26), 266 (26), 176 (20), 105 (100), 77 (26), 51 (15), 39 (16).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3335s, 3062w, 3031w, 2962m, 1637s, 1579s, 1533s, 1490m, 1458m, 1387w, 1320m, 1077m, 1044m, 1028m, 1013w, 915w, 838w, 800m, 756m, 696s.

EA % found (calcd): C: 76.13 (76.30), H: 7.50 (7.47), N: 4.81 (4.94).

(4*S*,5*S*)-4-Isopropyl-2,5-diphenyl-4,5-dihydrooxazole (113)



Product **113** was prepared according to **general procedure IV** (page 142) from *N*-((1*R*,2*S*)-1-hydroxy-3-methyl-1-phenylbutan-2-yl)benzamide (1.00 g, 3.50 mmol), methanesulfonic acid (0.70 mL, 10.9 mmol), CaH_2 (4.50 g) and dichloromethane as a solvent (64.0 mL). After column chromatography (Hx : EtOAc 5 : 1, $\mathbf{R}_f$ = 0.50) on silica compound **113** (0.85 g, 91%) was isolated as a colorless solid with a *de*-value of 96%. By means of semipreperative HPLC (OD, Hep : IPA 95 : 5, 0.5 mL/min, 220 nm and 254 nm, 7.8 min and 13.8 min) the pure diastereomer **113** (0.65 g, 69%) could be isolated as a colorless solid.

$C_{18}H_{19}NO$ (265.35).

m.p. 53-55 °C.

$[\alpha]_D^{20}$ = +54.3° (c = 0.510, $CHCl_3$).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 1.00 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.06 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.96 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 6.8 Hz, 1H, C**H**$(CH_3)_2$), 3.99 (dd, *J*(H,H) = 6.5 Hz, *J*(H,H) = 6.3 Hz, 1H, NC**H**), 5.29 (d, *J*(H,H) = 6.6 Hz, 1H, OC**H**), 7.32-7.39 (m, 5H, Ph-**H**), 7.43-7.46 (m, 2H, Ph-**H**), 7.50-7.53 (m, 1H, Ph-**H**), 8.00-8.02 (m, 2H, Ph-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 18.8 (CH(**C**H_3)$_2$), 18.9 (CH(**C**H_3)$_2$), 33.6 (**C**H$(CH_3)_2$), 82.0 (N**C**H), 84.0 (O**C**H), 126.3 (2C, **Ph**-H), 128.6 (**Ph**-H), 128.8 (2C, **Ph**-H),

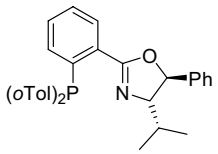
128.9 (2C, **Ph**-H), 129.3 (2C, **Ph**-H), 131.8 (**Ph**-H), 142.6 (**Ph**-C), 162.6 (**C**=N). (One quaternary C-atom is not visible).

MS (FAB) m/z (rel int %): 266 (M + H, 85), 222 (10), 159 (12), 105 (100), 91 (11), 77 (22).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3060w, 3031w, 2954m, 2888m, 2868m, 1648s, 1578m, 1492m, 1466m, 1450m, 1330m, 1278m, 1258m, 1175w, 1080m, 1066s,1024m, 974m, 754m, 693s.

EA % found (calcd): C: 81.17 (81.48), H: 7.15 (7.22), N: 5.16 (5.28).

(4*S*,5*S*)-2-(2-(Dio-tolylphosphino)phenyl)-4-isopropyl-5-phenyl-4,5-dihydrooxazole (114)



Product **114** was prepared according to **general procedure V** (page 149) from (4*S*,5*S*)-4-isopropyl-2,5-diphenyl-4,5-dihydrooxazole (0.50 g, 1.88 mmol), *sec*-BuLi in cyclohexane (1.60 mL, 2.07 mmol), TMEDA (0.31 mL, 2.07 mmol), chlorodi*ortho*-tolylphosphine (0.61 g, 2.45 mmol) and pentane as a solvent (28.0 mL). After column chromatography (Hx : EtOAc 15 : 1, $\mathbf{R}_f$ = 0.25) on silica compound **114** (568 mg, 63%) was isolated as a slightly yellow solid.

$C_{32}H_{32}NOP$ (477.58).

m.p. 153-156 °C.

$[\alpha]_D^{20}$ = -3.8° (c = 0.580, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.81 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.83 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 1.69 (ds, *J*(H,H) = 6.8 Hz, *J*(H,H) = 6.6 Hz, 1H, C**H**(CH$_3$)$_2$), 2.36 (br s, 6H, Ar-C**H**$_3$), 3.85 (dd, *J*(H,H) = 6.8 Hz, *J*(H,H) = 6.6 Hz, 1H, NC**H**), 5.07 (d, *J*(H,H) = 7.0 Hz, 1H, OC**H**), 6.74 (br s, 2H, Ar-**H**), 6.95 (ddd, *J*(H,H) = 7.6 Hz, *J*(H,H) = 3.6 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 7.03-7.08 (m, 2H, Ar-**H**), 7.18-7.27 (m, 6H, Ar-**H**), 7.27-7.34 (m, 4H, Ar-**H**), 7.41 (ddd, *J*(H,H) = 7.5 Hz, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 7.97 (ddd, *J*(H,H) = 7.7 Hz, *J*(H,H) = 3.8 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 18.7 (CH(**C**H$_3$)$_2$), 19.0 (CH(**C**H$_3$)$_2$), 21.4 (d, *J*(C,P) = 4.8 Hz, *o*Tol-**C**H$_3$), 21.6 (d, *J*(C,P) = 4.5 Hz, *o*Tol-**C**H$_3$), 33.4 (**C**H(CH$_3$)$_2$), 82.7 (N**C**H), 83.9 (O**C**H), 126.5 (**Ar**-H), 126.6 (**Ar**-H), 126.6 (**Ar**-H), 128.5 (**Ar**-H), 128.7 (**Ar**-H), 128.9 (**Ar**-H), 129.0 (**Ar**-H), 129.2 (**Ar**-H), 130.5 (d, *J*(C,P) = 4.5 Hz, **Ar**-H), 130.5(d, *J*(C,P) = 4.5 Hz, **Ar**-H), 130.5 (**Ar**-H), 131.0 (**Ar**-H), 133.2 (d, *J*(C,P) = 22.5 Hz, **Ar**-CN),

133.5 (**Ar**-H), 133.9 (**Ar**-H), 134.9 (**Ar**-H), 137.3 (d, *J*(C,P) = 12.8 Hz, ***o*Tol**-P), 137.4 (d, *J*(C,P) = 12.8 Hz, ***o*Tol**-P), 138.5 (d, *J*(C,P) = 25.5 Hz, **Ar**-P), 142.4 (**Ar**-CHO), 143.0 (d, *J*(C,P) = 27.9 Hz, ***o*Tol**-CH_3), 143.1 (d, *J*(C,P) = 27.8 Hz, ***o*Tol**-CH_3), 161.9 (d, *J*(C,P) = 2.4 Hz, **C**=N).

$^{31}P\{^1H\}$ NMR (162.0 MHz, CD_2Cl_2, 300 K): δ = -30.0.

MS (FAB) m/z (rel int %): 478 (M + H, 24), 332 (100), 317 (12), 165 (6), 145 (7), 131 (6), 105 (9), 91 (18), 57 (8), 55 (9), 43 (9), 41 (9).

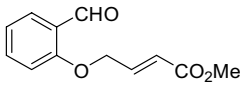
IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3427m, 3048w, 2953m, 2865m, 1647s, 1586w, 1463s, 1379w, 1320s, 1271w, 1202w, 1165w, 1131w, 1087m, 1036s, 955m, 754s, 701m.

EA % found (calcd): C: 80.52 (80.48), H: 6.80 (6.75), N: 2.71 (2.93).

13.4 [3+2] Cycloadditions

13.4.1 Synthesis of Subatrates for [3+2] Cycloadditions

(*E*)-4-(2-Formyl-phenoxy)-but-2-enoic acid methyl ester (158)



General Procedure VII:

Methyl 4-bromobut-2-enoate (1.64 mL, 12.4 mmol) was added to a mixture of 2-hydroxybenzaldehyde (**157**) (1.10 mL, 11.5 mmol) and K_2CO_3 (2.10 g, 15.0 mmol) in DMF (15 mL) at rt. The reaction was closely monitored by TLC and worked up when all 2-hydroxybenzaldehyde (**157**) was consumed (1 h). Toluene (25 mL) and water (25 mL) were added and the aqueous layer was extracted with toluene (3 x 10 mL). The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent the residue was purified by column chromatography (Hx :EtOAc 5 : 1, ; $\mathbf{R}_f$ = 0.15) to afford **158** as a white solid (1.70 g, 66 %).

$C_{12}H_{12}O_4$ (220.07).

m.p. 62-64 °C.

^{1}H NMR (400.1 MHz, CD_2Cl_2, 295 K): δ = 3.74 (s, 3H, C**H**$_3$), 4.84 (app dd, *J*(H,H) = 4.0 Hz, *J*(H,H) = 2.0 Hz, 2H, OC**H**$_2$), 6.23 (dt, *J*(H,H) = 15.9 Hz, *J*(H,H) = 2.0 Hz, 1H, CH_2CH=C**H**), 6.98 (d, *J*(H,H) = 8.3 Hz, 1H, Ph-**H**), 7.06-7.09 (m, 1H, Ph-**H**), 7.10 (dt, *J*(H,H) = 15.9 Hz, *J*(H,H) = 2.0 Hz, 1H, CH_2C**H**=CH), 7.55-7.59 (m, 1H, Ph-**H**), 7.82 (dd, J(H,H) = 7.6 Hz, *J*(H,H) = 1.8 Hz, 1H, Ph-**H**), 10.53 (s, 1H, CO**H**).

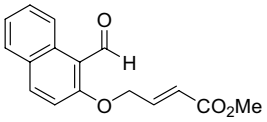
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 52.2 (**C**H_3), 67.2 (**C**H_2), 112.9 (**Ph**-H), 121.8 (**Ph**-H), 122.4 (CH_2CH=**C**H), 125.5 (**Ph**-C), 129.2 (**Ph**-H), 136.3 (**Ph**-H), 141.8 (CH_2**C**H=CH), 160.5 (**Ph**-CO), 166.6 (**C**OOCH_3), 189.6 (**C**OH).

MS (FAB) m/z (rel. Int. %): 221 (M^+ + H, 100), 219 (14), 203 (10), 189 (15), 188 (14), 161 (48), 99 (54), 98 (22), 71 (16).

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 2953w, 2871w, 1641s, 1719s, 1685s, 1662m, 1597s, 1485m, 1442m, 1396m, 1307s, 1242s, 1193m, 1169s, 1079m, 1019w, 956m, 846m, 768m, 662w.

EA % found (calcd): C: 65.37 (65.45), H: 5.42 (5.49).

(*E*)-4-(1-Formylnaphtalen-2-yloxy)-but-2-enoic acid methyl ester (167)



Product **167** was prepared according to **general procedure VII** (page 173) from 2-hydroxy-2-naphthaldehyde (1.98 g, 11.5 mmol), methyl 4-bromobut-2-enoate (1.64 mL, 12.4 mmol), K_2CO_3 (2.10 mL, 15.0 mmol), and DMF as a solvent (15.0 mL). After column chromatography (Hx : EtOAc 1 : 1, $\mathbf{R}_f$ = 0.62) on silica compound **167** (2.80 g, 90%) was isolated as a slightly yellow solid.

$C_{16}H_{14}O_4$ (270.09).

m.p. 96-99 °C.

^{1}H NMR (400.1 MHz, $CDCl_3$, 295 K): δ = 3.78 (s, 3H, C**H**$_3$), 4.98 (app dd, *J*(H,H) = 4.0 Hz, *J*(H,H) = 2.3 Hz, 2H, OC**H**$_2$), 6.25 (dt, *J*(H,H) = 15.9 Hz, *J*(H,H) = 2.0 Hz, 1H, CH_2CH=C**H**), 7.15 (dt, *J*(H,H) = 15.9 Hz, *J*(H,H) = 4.0 Hz, 1H, CH_2C**H**=CH), 7.22 (d, *J*(H,H) = 8.3 Hz, 1H, Naph-**H**), 7.43-7.47 (m, 1H, Naph-**H**), 7.62-7.65 (m, 1H, Naph-**H**), 7.79 (d, *J*(H,H) = 8.3 Hz, 1H, Naph-**H**), 8.06 (d, *J*(H,H) = 9.1 Hz, 1H, Naph-**H**), 9.27 (d, *J*(H,H) = 8.8 Hz, 1H, Naph-**H**), 11.00 (s, 1H, CO**H**).

$^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 295 K): δ = 52.2 (**C**H_3), 68.1 (**C**H_2), 113.5 (**Naph**-H), 117.5 (**Naph**-C), 122.6 (CH_2CH=**C**H), 125.3 (**Naph**-H), 125.5 (**Naph**-H), 128.6 (**Naph**-H), 129.2 (**Naph**-C), 130.4 (**Naph**-H), 131.8 (**Naph**-C), 137.9 (**Naph**-H), 141.8 (CH_2**C**H=CH), 162.5 (**Ph**-CO), 166.5 (**C**$OOCH_3$), 191.8 (**C**OH).

MS (FAB) m/z (rel. Int. %): 271 (M^+ + H, 100), 211 (38), 183 (27), 171 (28), 144 (11), 115 (16), 100 (11), 71 (18), 57 (13), 43 (11), 41 (17).

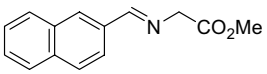
IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 2956w, 2874w, 1721s, 1665s, 1590m, 1466m, 1438m, 1345m, 1308s, 1196s, 1159s, 1100m, 1063m, 1022m, 963m, 822m, 759m, 724w.

Imine synthesis

General Procedure VIII:

Triethylamine (1.8 mmol) and anhydrous $MgSO_4$ (6.4 mmol) were added to a solution of the amine hydrochloride (1.6 mmol) in dichloromethane (10 mL). After a stirring period of 1 h the aldehyde (1.5 mmol) was added (for the synthesis of the imines **159**, **163** and **169** the reaction mixture had to be cooled to 0 °C before the aldehyde was added). The mixture was stirred for 24 h (in case of the imines **159**, **163** and **169**, 60 h at 0 °C) before the $MgSO_4$ was removed by filtration. The organic layer was washed with H_2O (3 x 5 mL), saturated $NaHCO_3$-solution (3 x 5 mL) and brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was dried at 0.8 mbar/rt. The resulting crude product, which contained 1-10 mol% of aldehyde (^{1}H NMR), was isolated in quantitative yield and used without further purification.

(*E*)-methyl 2-(naphthalene-2-ylmethyleneamino)acetate (37)



Compound **37** was prepared according to **general procedure VIII** (page 175) from 2-naphthaldehyde (5.00 g, 32.0 mmol), glycine methylester hydrochloride (4.40 g, 35.0 mmol), triethylamine (5.30 mL, 38.4 mmol), anhydrous $MgSO_4$ (15.4 g, 128 mmol) and dichloromethane as a solvent (40.0 mL). The crude product was recrystallized from hexane/dichloromethane to give a slightly yellow solid.

m.p. 88-90 °C.

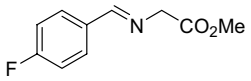
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 3.77 (s, 3H, C**H**$_3$), 4.45 (d, *J*(H,H) = 1.3 Hz, 2H, C**H**$_2$), 7.52-7.58 (m, 2H, Naph-**H**), 7.87-7.94 (m, 3H, Naph-**H**), 8.01 (dd, *J*(H,H) = 8.6 Hz, *J*(H,H) = 1.8 Hz, 1H, Naph-**H**), 8.10 (s, 1H, Naph-**H**), 8.44 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 52.5 (**C**H$_3$), 62.4 (**C**H$_2$), 124.1 (**Naph**-H), 127.1 (**Naph**-H), 128.0 (**Naph**-H), 128.4 (**Naph**-H), 129.1 (**Naph**-H), 129.2 (**Naph**-H), 131.1 (**Naph**-H), 133.6 (**Naph**-C), 134.0 (**Naph**-C), 135.5 (**Naph**-C), 165.6 (**C**H=N), 171.1 (**C**O).

MS (FAB) m/z (rel. Int. %): 228 (100, [M^+ + H]), 168 (20), 141 (16).

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 3056w, 3002w, 2952w, 2878w, 1721s, 1642m, 1424m, 1267s.

(*E*)-methyl 2-(4-fluorobenzylideneamino)acetate (128)



Compound **128** was prepared according to **general procedure VIII** (page 175) from 4-fluorobenzaldehyde (2.00 mL, 18.9 mmol), glycine methylester hydrochloride (2.60 g, 20.8 mmol), triethylamine (3.10 mL, 22.7 mmol), anhydrous $MgSO_4$ (9.80 g, 81.4 mmol) and dichloromethane as a solvent (28.0 mL). The colorless oil was used without further purification.

$C_{10}H_{10}FNO_2$ (195.19).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 3.74 (s, 3H, C**H**$_3$), 4.37 (d, *J*(H,H) = 1.2 Hz, 2H, C**H**$_2$), 7.10-7.16 (m, 2H, Ph-**H**), 7.75-7.81 (m, 2H, Ph-**H**), 8.25 (s, 1H, C**H**=N).

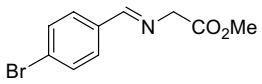
^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 52.5 (**C**H$_3$), 62.2 (**C**H$_2$), 116.2 (2C, d, *J*(C,F) = 21.9 Hz, **Ph**-H), 130.9 (2C, d, *J*(C,F) = 8.8 Hz, **Ph**-H), 132.7 (d, *J*(C,F) = 3.1 Hz, **Ph**-C), 164.2 (**C**H=N), 165.1 (d, *J*(C,F) = 250.7 Hz, **Ph**-F), 171.0 (**C**=O).

^{19}F{^{1}H} NMR (376.5 MHz, CD_2Cl_2, 300 K): δ = -109.8 (m).

MS (FAB) m/z (rel int %): 196 (M +1, 100), 136 (32), 109 (21), 89 (10), 77 (12), 57 (11), 39 (17).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3003w, 2954m, 2879m, 1746s, 1648s, 1600s, 1508s, 1435m, 1388m, 1346m, 1271s, 1228s, 1063m, 1016m, 965w, 838s.

(*E*)-methyl 2-(4-bromobenzylideneamino)acetate (129)



Compound **129** was prepared according to **general procedure VIII** (page 175) from 4-bromobenzaldehyde (2.00 g, 11.0 mmol), glycine methylester hydrochloride (1.50 g, 12.1 mmol), triethylamine (1.80 mL, 12.7 mmol), anhydrous $MgSO_4$ (5.30 g, 44.0 mmol) and dichloromethane as a solvent (15.0 mL). The colorless solid was used without further purification.

$C_{10}H_{10}BrNO_2$ (256.10).

m.p. 47-49 °C.

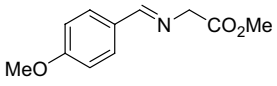
^{1}H NMR ($CDCl_3$, 400 MHz, 300 K): δ = 3.78 (s, 3H, C**H**$_3$), 4.40 (d, *J*(H,H) = 1.3, 2H, C**H**$_2$), 7.55 (d, *J*(H,H) = 8.4, 2H, Ph-**H**), 7.65 (d, *J*(H,H) = 8.6, 2H, Ph-**H**), 8.24 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR ($CDCl_3$, 80 MHz, 300 K): δ = 52.6 (**C**H$_3$), 62.3 (**C**H$_2$), 126.2 (**Ph**-Br), 130.3 (2C, **Ph**-H), 132.3 (2C, **Ph**-H), 134.9 (**Ph**-C), 164.6 (**C**H=N), 170.7 (**C**=O).

MS (FAB): *m*/*z* (rel int %): 256 (M^+, 100), 196 (21), 171 (11), 89 (12), 77 (14), 55 (19), 41 (17), 39 (14).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3477w, 3056w, 2997w, 2948w, 2884w, 1752s, 1646m, 1588w, 1484w, 1434w, 1406w, 1350w, 1197s, 1067m, 1009m, 960w, 848w, 820m, 694w.

(*E*)-methyl 2-(4-methoxybenzylideneamino)acetate (130)



Compound **130** was prepared according to **general procedure VIII** (page 175) from anisaldehyde (2.30 mL, 18.9 mmol), glycine methylester hydrochlorid (2.60 g, 20.8 mmol), triethylamine (3.10 mL, 22.7 mmol), anhydrous $MgSO_4$ (9.80 g, 81.4 mmol) and dichloromethane as a solvent (28.0 mL). Hexane was added to the crude product whereupon the product precipitated as a colorless solid which was washed several times with hexane.

$C_{11}H_{13}NO_3$ (207.23).

m.p. 68-70 °C.

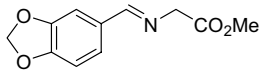
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 3.74 (s, 3H, C**H**$_3$), 3.84 (s, 3H, C**H**$_3$), 4.34 (d, *J*(H,H) = 1.3 Hz, 2H, C**H**$_2$), 6.93-6.96 (m, 2H, Ph-**H**), 7.69-7.72 (m, 2H, Ph-**H**), 8.19 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 52.4 (**C**H$_3$), 55.9 (**C**H$_3$), 62.3 (**C**H$_2$), 114.5 (2C, **Ph**-H), 129.2 (**Ph**-C), 130.5 (2C, **Ph**-H), 162.7 (**Ph**-OMe), 164.8 (**C**H=N), 171.3 (**C**=O).

MS (EI, 70 eV): m/z (rel int %): 207 (M +1, 19), 148 (93), 134 (19), 121 (100), 91 (11).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3474w, 3012w, 2962w, 2875w, 1745s, 1646s, 1600s, 1506m, 1461m, 1418w, 1353w, 1305m, 1255s, 1197s, 1156s, 1070m, 1021m, 960w, 832m.

(*E*)-methyl 2-(benzo[*d*][1,3]dioxol-5-ylmethyleneamino)acetate (131)



Compound **131** was prepared according to **general procedure VIII** (page 175) from piperonal (2.00 g, 13.3 mmol), glycine methylester hydrochloride (1.80 g, 14.7 mmol), triethylamine (2.10 mL, 15.3 mmol), anhydrous $MgSO_4$ (6.90 g, 57.2 mmol) and dichloromethane as a solvent (20.0 mL). The crude product was recrystallized from hexane/dichloromethane to give colorless needles.

$C_{11}H_{11}NO_4$ (221.21).

m.p. 84-85 °C.

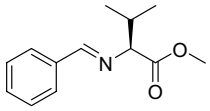
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 3.73 (s, 3H, C**H**$_3$), 4.33 (d, *J*(H,H) = 1.3 Hz, 2H, C**H**$_2$), 6.02 (s, 2H, OC**H**$_2$O), 6.85 (d, *J*(H,H) = 7.8 Hz, 1H, Ph-**H**), 7.15 (dd, *J*(H,H) = 7.8, *J*(H,H) = 1.7, 1H, Ph-**H**), 7.36 (d, *J*(H,H) = 1.5 Hz, 1H, Ph-**H**), 8.15 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 52.4 (**C**H$_3$), 62.1 (N**C**H$_2$), 102.3 (O**C**H$_2$O), 106.9 (**Ph**-H), 108.5 (**Ph**-H), 125.5 (**Ph**-H), 131.2 (**Ph**-C), 149.0 (**Ph**-C), 150.9 (**Ph**-C), 164.7 (**C**H=N), 171.2 (**C**=O).

MS (FAB) m/z (rel int %): 222 (M+1, 100), 162 (M-CO_2CH_3, 15), 135 (4), 104 (1).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3056w, 3003w, 2959w, 2919w, 2867m, 1750s, 1693w, 1645s, 1603s, 1501s, 1450s, 1417m, 1395m, 1364w, 1344w, 1263s, 1196s, 1178s, 1034s, 927s, 821m, 796m, 704m.

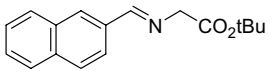
2-(Benzylidene-amino)-3-methyl-butyric acid methyl ester (133)



Compound **133** was prepared according to **general procedure VIII** (page 175) from benzaldehyde (1.2 mL, 11.4 mmol), L-valine methyl ester hydrochloride (2.00 g, 12.0 mmol), triethylamine (1.70 mL, 12.6 mmol), anhydrous $MgSO_4$ (5.50 g, 45.7 mmol) and dichloromethane as a solvent (8.00 mL). The crude product was purified by bulb-to-bulb distillation (110 °C, 10^{-1} bar) to give a colorless oil.

$C_{13}H_{17}NO_2$ (219.29).
^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 0.94 (d, *J*(H,H) = 6.8 Hz, 3H, C**H**$_3$), 0.97 (d, *J*(H,H) = 6.8 Hz, 3H, C**H**$_3$), 2.38 (ds, *J*(H,H) = 7.0 Hz, *J*(H,H) = 6.9 Hz, 1H, C**H**$(CH_3)_2$), 3.67 (d, *J*(H,H) = 7.4 Hz, 1H, NC**H**), 3.74 (s, 3H, OC**H**$_3$), 8.25 (s, 1H, C**H**=N), 7.45-7.39 (m, 3H, Ph-**H**), 7.80-7.78 (m, 2H, Ph-**H**,).
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 19.1 (CH(**C**$H_3)_2$), 19.9 (CH(**C**$H_3)_2$), 32.1 (**C**$H(CH_3)_2$), 52.3 (O**C**H_3), 80.8 (N**C**H), 128.9 (2C, **Ph**-H), 129.0 (2C, **Ph**-H), 131.4 (**Ph**-H), 136.1 (**Ph**-C), 163.7 (**C**H=N), 172.8 (**C**=O).

(*E*)-*tert*-butyl 2-(naphthalen-2-ylmethyleneamino)acetate (134)



Compound **134** was prepared according to **general procedure VIII** (page 175) from 2-naphthaldehyde (2.00 g, 12.6 mmol), glycine *tert*-butylester hydrochlorid (2.40 g, 14.3 mmol), triethylamine (2.30 mL, 16.3 mmol), anhydrous $MgSO_4$ (6.50 g, 54.0 mmol) and dichloromethane as a solvent (18.0 mL). The crude product was recrystallized from hexane to give a colorless solid.

$C_{17}H_{19}NO_2$ (269.34).
m.p. 72-74 °C.

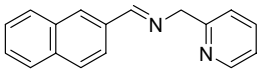
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 1.50 (s, 9H, C(C**H**$_3$)$_3$), 4.34 (d, *J*(H,H) = 1.5 Hz, 2H, C**H**$_2$), 7.51-7.58 (m, 2H, Naph-**H**), 7.87-7.94 (m, 3H, Naph-**H**), 8.02 (dd, *J*(H,H) = 8.6, *J*(H,H) = 1.5, 1H, Naph-**H**), 8.09 (s, 1H, Naph-**H**), 8.41 (s, 1H, C**H**N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 27.6 (3C, C(**C**H$_3$)$_3$), 62.5 (**C**H$_2$), 80.9 (**C**(CH$_3$)$_3$), 123.4 (**Naph**-H), 126.3 (**Naph**-H), 127.1 (**Naph**-H), 127.6 (**Naph**-H), 128.2 (**Naph**-H), 128.4 (**Naph**-H), 130.1 (**Naph**-H), 132.8 (**Naph**-C), 133.4 (**Naph**-C), 134.6 (**Naph**-C), 164.5 (**C**H=N), 169.0 (**C**=O).

MS (FAB) m/z (rel int %): 270 (M + 1, 74), 214 (100), 212 (19), 168 (40), 141 (29), 77 (11), 57 (51), 51 (12), 41 (18), 39 (16).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3062w, 2978m, 2933m, 2878m, 2832m, 1734s, 1641s, 1458m, 1437m, 1370s, 1347s, 1236s, 1160s, 1064m, 1003m, 972m, 895m, 865m, 828s, 790w, 754s.

(*E*)-*N*-(naphthalen-2-ylmethylene)(pyridine-2-yl)methanamine (135)



Compound **135** was prepared according to **general procedure VIII** (page 175) from 2-naphthaldehyde (1.00 g, 6.40 mmol), 2-picolylamine (750 µL, 7.30 mmol), anhydrous $MgSO_4$ (3.30 g, 27.5 mmol) and dichloromethane as a solvent (9.00 mL). The crude product was recrystallized from hexane/dichloromethane to give a colorless solid.

$C_{17}H_{14}N_2$ (246.31).

m.p. 75-77 °C.

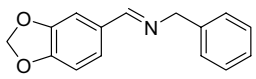
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 4.97 (d, *J*(H,H) = 1.0 Hz, 2H, C**H**$_2$), 7.18-7.21 (m, 1H, Ar-**H**), 7.47 (d, *J*(H,H) = 7.6 Hz, 1H, Ar-**H**), 7.52-7.59 (m, 2H, Ar-**H**), 7.71 (td, *J*(H,H) = 7.6, *J*(H,H) = 1.8, 1H, Ar-**H**), 7.89-7.96 (m, 3H, Ar-**H**), 8.06-8.08 (m, 1H, Ar-**H**), 8.12 (s, 1H, Ar-**H**), 8.56-8.58 (m, 1H, Ar-**H**), 8.64 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 67.4 (**C**H$_2$), 122.5 (**Ar**-H), 122.8 (**Ar**-H), 124.3 (**Ar**-H), 124.3 (**Ar**-H), 127.1 (**Ar**-H), 127.8 (**Ar**-H), 128.4 (**Ar**-H), 129.0 (**Ar**-H), 130.8 (**Ar**-H), 133.7 (**Ar**-C), 134.6 (**Ar**-C), 135.3 (**Ar**-C), 137.0 (**Ar**-H), 149.8 (**Ar**-H), 160.1 (**Ar**-C), 163.3 (**C**H=N).

MS (FAB) m/z (rel int %): 247 (M +1, 100), 141 (7), 93 (69), 77 (5), 65 (9), 51 (6), 39 (7).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448w, 3047w, 3006w, 2886w, 2867m, 1641s, 1584s, 1566m, 1474m, 1434s, 1417s, 1349m, 1324m, 1324s, 1121m, 1048s, 1002m, 901w, 864s, 828s, 747s.

(*E*)-*N*-(benzo[*d*][1,3]dioxol-5-ylmethylene)(phenyl)methanamine (136)



Compound **136** was prepared according to **general procedure VIII** (page 175) from piperonal (2.0 g, 13.3 mmol), benzylamine (1.7 mL, 15.2 mmol), anhydrous $MgSO_4$ (6.9 g, 57.2 mmol) and dichloromethane as a solvent (18 mL). The crude product was recrystallized from hexane/dichloromethane to give colorless needles.

$C_{15}H_{13}NO_2$ (239.27).

m.p. 74-75 °C.

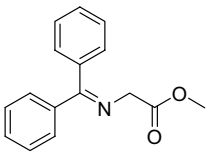
^{1}H NMR (400.1 MHz, CD_2Cl_2, 295 K): δ = 4.75 (d, *J*(H,H) = 1.0 Hz, 2H, C**H**$_2$), 6.00 (s, 2H, OC**H**$_2$O), 6.85 (d, *J*(H,H) = 7.8 Hz, 1H, Ar-**H**), 7.16 (dd, *J*(H,H) = 8.1 Hz, *J*(H,H) = 1.5 Hz, 1H, Ar-**H**), 7.29-7.23 (m, 1H, Ar-**H**), 7.32-7.36 (m, 4H, Ar-**H**), 7.39 (d, *J*(H,H) = 1.5 Hz, 1H, Ar-**H**), 8.28 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 295 K): δ = 65.3 (**C**H$_2$), 102.2 (O**C**H$_2$O), 106.9 (**Ar**-H), 108.5 (**Ar**-H), 125.0 (**Ar**-H), 127.4 (**Ar**-H), 128.5 (2C, **Ar**-H), 128.9 (2C, **Ar**-H), 131.8 (**Ar**-C), 140.4 (**Ar**-C), 148.9 (**Ar**-C), 150.5 (**Ar**-C), 161.3 (**C**H=N).

MS (FAB) m/z (rel int %): 240 (M+1, 100), 162 (3), 148 (3), 91 (80), 77 (5), 65 (3), 51 (4).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3061w, 3027m, 2911w, 2859m, 2830m, 1641s, 1602m, 1501s, 1484s, 1443s, 1385w, 1331w, 1257s, 1206w, 1121w, 1097s, 1045s, 1028s, 924s, 870m, 825m, 792w, 747m, 695s.

Methyl *N*-(diphenylmethylene)glycinate[96] (132)



Benzophenone (926 µL, 5.52 mmol) was added to a solution of glycine methyl ester hydrochloride (693 mg, 5.52 mmol) in CH_2Cl_2 (20.0 mL) and the resulting mixture was

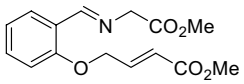
stirred for 24 h. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was diluted in diethyl ether (20 mL), washed with water (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was recrystallized from diethyl ether/hexane (1:8) to afford colorless needles.

$C_{16}H_{15}NO_2$ (253.30).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 3.75 (s, 3H, C**H$_3$**), 4.22 (s, 2H, C**H$_2$**), 7.19-7.17 (m, 2H, Ph-**H**), 7.36-7.32 (m, 2H, Ph-**H**), 7.43-7.38 (m, 1H, Ph-**H**), 7.49-7.44 (m, 3H, Ph-**H**), 7.68-7.65 (m, 2H, Ph-**H**).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 52.4 (**C**H$_3$), 56.0 (**C**H$_2$), 128.1 (2C, **Ph**-H), 128.5 (2C, **Ph**-H), 129.1 (2C, **Ph**-H), 129.2 (2C, **Ph**-H), 129.3 (**Ph**-H), 130.9 (**Ph**-C), 136.3 (**Ph**-C), 139.6 (**Ph**-C), 171.5 (**C**=N), 172.4 (**C**=O).

(*E*)-4-[2-(Methoxycarbonylmethylimino-methyl)-phenoxy]-but-2-enoic acid methyl ester (159)



Compound **159** was prepared according to **general procedure VIII** (page 175) from 4-(2-formyl-phenoxy)-but-2-enoic acid methyl ester (500 mg, 2.30 mmol), glycine methylester hydrochloride (314 mg, 2.50 mmol), triethylamine (314 µL, 2.70 mmol), anhydrous $MgSO_4$ (1.20 g, 9.80 mmol) and dichloromethane as a solvent (10.0 mL). The crude product appeared as a colorless oil and was used without further purification.

$C_{15}H_{17}NO_5$ (291.30).

R$_f$ = 0.65 (hexane : EtOAc 1:1).

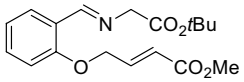
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 3.75 (s, 3H, C**H$_3$**), 3.76 (s, 3H, C**H$_3$**), 4.42 (d, *J*(H,H) = 1.2 Hz, 2H, NC**H$_2$**), 4.79 (dd, *J*(H,H) = 4.3 Hz, *J*(H,H) = 2.0 Hz, 2H, OC**H$_2$**), 6.19 (td, *J*(H,H) = 15.7 Hz, *J*(H,H) = 2.0 Hz, 1H, CH_2CH=C**H**), 6.92 (d, *J*(H,H) = 8.3 Hz, 1H, Ph-**H**), 7.04 (t, *J*(H,H) = 7.6 Hz, 1H, Ph-**H**), 7.11 (td, *J*(H,H) = 15.8 Hz, *J*(H,H) = 4.3 Hz, 1H, CH_2C**H**=CH), 7.71-7.45 (m, 1H, Ph-**H**), 8.00 (dd, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.8 Hz, 1H, Ph-**H**), 8.77 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 52.1 (**C**H_3), 52.4 (**C**H_3), 62.8 (N**C**H_2), 67.5 (O**C**H_2), 112.8 (**Ph**-H), 122.0 (**Ph**-H), 122.3 (CH=**C**HCO$_2$Me), 125.0 (**Ph**-C), 128.1 (**Ph**-H), 133.0 (**Ph**-H), 142.7 (**C**H=CHCO$_2$Me), 158.0 (**Ph**-C), 161.0 (**C**H=N), 166.7 (**C**=O), 171.2 (**C**=O).

MS (FAB) m/z (rel. Int. %): 292 (100, [M^+ + H]), 232 (17), 193 (13), 133 (16), 99 (17), 77 (14), 69 (11), 57 (20).

IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3485w, 3415w, 3004w, 2953w, 2867w, 1750s, 1720s, 1636m, 1603m, 1493m, 1450m, 1309s, 1249s, 1197s, 1173s, 1116m, 1070m, 1021m, 754m.

(*E*)-4-[2-(*tert*-Butoxycarbonylmethylimino-methyl)-phenoxy]-but-2-enoic acid methyl ester (163)



Compound **163** was prepared according to **general procedure VIII** (page 175) from 4-(2-formyl-phenoxy)-but-2-enoic acid methyl ester (400 mg, 1.48 mmol), glycine *tert*-butylester hydrochloride (273 mg, 1.63 mmol), triethylamine (248 µL, 1.78 mmol), anhydrous $MgSO_4$ (766 mg, 6.36 mmol) and dichloromethane as a solvent (10.0 mL). The crude product appeared as colorless oil and was used without further purification.

$C_{18}H_{23}NO_5$ (333.38).

R_f = 0.41 (hexane : EtOAc 2:1).

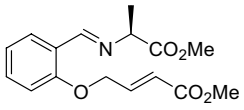
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 1.48 (s, 9H, C(C**H**$_3$)$_3$), 3.74 (s, 3H, OC**H**$_3$), 4.29 (s, 2H, NC**H**$_2$), 4.78 (dd, *J*(H,H) = 4.0 Hz, *J*(H,H) = 2.0 Hz, 2H, OC**H**$_2$), 6.18 (td, *J*(H,H) = 15.9 Hz, *J*(H,H) = 2.0 Hz, 1H, CH$_2$CH=C**H**), 6.91 (d, *J*(H,H) = 8.3 Hz, 1H, Ph-**H**), 7.02 (t, *J*(H,H) = 7.6 Hz, 1H, Ph-**H**), 7.10 (td, *J*(H,H) = 15.9 Hz, *J*(H,H) = 4.0 Hz, 1H, CH$_2$C**H**=CH), 7.38-7.43 (m, 1H, Ph-**H**), 7.99 (dd, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.5 Hz, 1H, Ph-**H**), 8.72 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 28.4 (3C, C(**C**H$_3$)$_3$), 52.1 (O**C**H$_3$), 63.6 (N**C**H$_2$), 67.5 (O**C**H$_2$), 81.5 (**C**(CH$_3$)$_3$), 112.8 (**Ph**-H), 121.9 (**Ph**-H), 122.3 (CH$_2$CH=**C**H), 125.3 (**Ph**-C), 128.1 (**Ph**-H), 132.8 (**Ph**-H), 142.8 (CH$_2$**C**H=CH), 158.0 (**Ph**O), 160.7 (**C**H=N), 166.7 (**C**=O), 170.0 (**C**=O).

MS (FAB) m/z (rel. Int. %): 334 (85, [M^+ + H]), 278 (75), 232 (16), 218 (17), 180 (18), 133 (19), 99 (27), 77 (11), 57 (100).

IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3415w, 3050w, 2978m, 2865w, 1726s, 1641m, 1600m, 1485m, 1448m, 1372m, 1284s, 1245s, 1158s, 1020m, 757m.

(*E*)-4-[2-((1-Methoxycarbonyl-ethylimino)-methyl)-phenoxy]-but-2-enoic acid methyl ester (164)



Compound **164** was prepared according to **general procedure VIII** (page 175) from 4-(2-formyl-phenoxy)-but-2-enoic acid methyl ester (500 mg, 2.30 mmol), L-alanine methyl ester hydrochloride (350 mg, 2.50 mmol), triethylamine (379 µL, 2.70 mmol), anhydrous $MgSO_4$ (1.20 g, 9.80 mmol) and dichloromethane as a solvent (20.0 mL). The crude product appeared as colorless oil and was used without further purification.

$C_{16}H_{19}NO_5$ (305.33).

R_f = 0.65 (hexane : EtOAc 1:1).

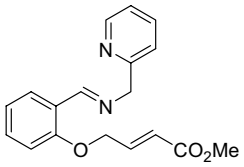
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 1.48 (d, *J*(H,H) = 6.8 Hz, 3H, CH**C**H_3), 3.72 (s, 3H, O**C**H_3), 3.74 (s, 3H, O**C**H_3), 4.17 (q, *J*(H,H) = 6.8 Hz, 1H, N**C**H), 4.78 (dd, *J*(H,H) = 4.0 Hz, *J*(H,H) = 2.0 Hz, 2H, O**C**H_2), 6.18 (td, *J*(H,H) = 15.9 Hz, *J*(H,H) = 2.0 Hz, 1H, CH_2CH=**C**H), 6.90 (d, *J*(H,H) = 8.4 Hz, 1H, Ph-**H**), 7.02 (t, *J*(H,H) = 7.6 Hz, 1H, Ph-**H**), 7.10 (td, *J*(H,H) = 15.9 Hz, *J*(H,H) = 4.0 Hz, 1H, CH_2**C**H=CH), 7.38-7.43 (m, 1H, Ph-**H**), 7.97 (dd, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.8 Hz, 1H, Ph-**H**), 8.77 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 19.9 (CH**C**H_3), 52.1 (O**C**H_3), 52.5 (O**C**H_3), 67.5 (**C**HCH_3), 68.8 (O**C**H_2), 112.8 (**Ph**-H), 121.9 (**Ph**-H), 121.9 (CH_2CH=**C**H), 125.2 (**Ph**-C), 128.2 (**Ph**-H), 132.9 (**Ph**-H), 142.8 (CH_2**C**H=CH), 158.0 (**Ph**O), 158.7 (**C**H=N), 166.7 (**C**=O), 173.6 (**C**=O).

MS (FAB) m/z (rel. Int. %): 306 (100, [M^+ + H]), 246 (21), 207 (12), 148 (18), 132 (14), 99 (14), 77 (18).

IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3415w, 3050w, 2978m, 2865w, 1726s, 1641m, 1600m, 1485m, 1448m, 1372m, 1284s, 1245s, 1158s, 1020m, 757m.

(*E*)-4-[2-((Pyridin-2-ylmethylimino)-methyl)-phenoxy]-but-2-enoic acid methyl ester (155)



Compound **155** was prepared according to **general procedure VIII** (page 175) from 4-(2-formyl-phenoxy)-but-2-enoic acid methyl ester (650 mg, 3.00 mmol), 2-picolylamin (332 µL, 3.30 mmol), anhydrous $MgSO_4$ (1.50 g, 12.7 mmol) and dichloromethane as a solvent (10.0 mL). The crude product appeared as slightly yellow oil and was used without further purification.

$C_{18}H_{18}N_2O_3$ (310.35).

R_f = 0.72 (Hx : EtOAc 1:1).

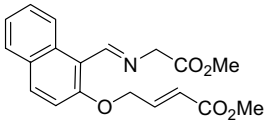
^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 3.74 (s, 3H, C**H**$_3$), 4.78 (s, 2H, NC**H**$_2$), 4.93 (s, 2H, OC**H**$_2$), 6.20 (dt, *J*(H,H) = 15.9 Hz, *J*(H,H) = 2.0 Hz, 1H, CH_2CH=C**H**), 6.92 (d, *J*(H,H) = 8.3 Hz, 1H, Ar-**H**), 7.03 (t, *J*(H,H) = 7.5 Hz, 1H, Ar-**H**), 7.11 (dt, *J*(H,H) = 15.8 Hz, *J*(H,H) = 4.1 Hz, 1H, CH_2C**H**=CH), 7.18 (dd, *J*(H,H) = 7.0 Hz, *J*(H,H) = 5.2 Hz, 1H, Ar-**H**), 7.40 (dd, *J*(H,H) = 7.3 Hz, *J*(H,H) = 1.8 Hz, 2H, Ar-**H**), 7.68 (td, *J*(H,H) = 7.7 Hz, *J*(H,H) = 1.8 Hz, 1H, Ar-**H**), 8.03 (d, *J*(H,H) = 4.6 Hz, 1H, Ar-**H**), 8.55 (d, *J*(H,H) = 4.6 Hz, 1H, Ar-**H**), 8.93 (s, 1H, C**H**=N).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 52.1 (**C**H$_3$), 67.5 (**C**H$_2$), 67.7 (**C**H$_2$), 112.8 (**Ar**-H), 121.9 (**Ar**-H), 122.2 (CH_2CH=**C**H), 122.4 (**Ar**-H), 122.7 (**Ar**-H), 125.5 (**Ar**-C), 128.0 (**Ar**-H), 132.5 (**Ar**-H), 136.9 (**Ar**-H), 142.8 (CH_2**C**H=CH), 149.7 (**Ar**-H), 157.9 (**Ar**-C), 158.7 (**C**H=N), 160.2 (**Ar**-C), 166.7 (**C**=O).

MS (FAB) m/z (rel. Int. %): 311 (100, [M^+ + H]), 93 (41), 92 (11).

IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3388m, 3008m, 2949m, 2893m, 1722s, 1636s, 1599s, 1487s, 1435s, 1375s, 1307s, 1246s, 1173s, 1113s, 1045s, 1020s, 966m, 838w, 756s.

(*E*)-Methyl 4-(1-((*E*)-(2-methoxy-2-oxoethylimino)methyl)naphthalene-2-yloxy)but-2-enoate (169)

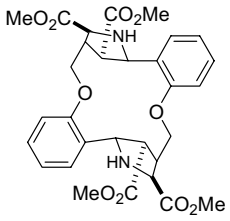


Compound **169** was prepared according to **general procedure VIII** (page 175) from (*E*)-methyl 4-(1-formylnaphthalen-2-yloxy)but-2-enoate (250 mg, 0.92 mmol), glycine methylester hydrochloride (126 mg, 1.00 mmol), triethylamine (154 µL, 1.11 mmol), 4Å molecular sieves (1.20 g) and dichloromethane as a solvent (10.0 mL). The crude product appeared as slightly yellow oil and was used without further purification.

$C_{19}H_{19}NO_5$ (341.36).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 3.75 (s, 3H, C**H**$_3$), 3.81 (s, 3H, C**H**$_3$), 4.55 (d, *J*(H,H) = 1.2 Hz, 2H, NC**H**$_2$), 4.92 (dd, *J*(H,H) = 4.3 Hz, *J*(H,H) = 2.0 Hz, 2H, OC**H**$_2$), 6.23 (td, *J*(H,H) = 15.9 Hz, *J*(H,H) = 2.0 Hz, 1H, CH_2CH=C**H**), 7.11-8.11 (m, 7H, Naph-**H** & CH_2C**H**=CH), 8.77 (s, 1H, C**H**=N);

Analytical datas of the dimer of 4-[2-(Methoxycarbonylmethylimino-methyl)-phenoxy]-but-2-enoic acid methyl ester (160)



$C_{30}H_{34}N_2O_{10}$ (582.22).

R$_f$ = 0.15 (hexane : EtOAc 5:1).

m.p. 321-323 °C.

^{1}H NMR (500 MHz, CD_2Cl_2, 295 K): δ = 3.01 (m, 2H, CH_2C**H**), 3.14 (s, 6H, OC**H**$_3$), 3.58 (dd, *J*(H,H) = 6.6 Hz, *J*(H,H) = 3.5 Hz, 2H, NHCH(Ph)C**H**), 3.83 (s, 6H, OC**H**$_3$), 3.91 (d, *J*(H,H) = 7.3 Hz, 2H, NHC**H**CO_2Me), 4.12 (dd, *J*(H,H) = 9.3 Hz, *J*(H,H) = 3.5 Hz, 2H, C**H**$_2$), 4.47 (dd, *J*(H,H) = 9.5 Hz, *J*(H,H) = 1.0 Hz, 2H, C**H**$_2$), 5.06 (bd, *J*(H,H) = 6.4 Hz, 2H, NHC**H**Ph), 6.94 (dd, *J*(H,H) = 8.2 Hz, *J*(H,H) = 0.9 Hz, 2H, Ph-**H**), 6.97 (td, *J*(H,H) = 7.5 Hz, *J*(H,H) = 0.8 Hz, 2H, Ph-**H**), 7.18 (dd, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.4 Hz, 2H, Ph-**H**), 7.28 (ddd, *J*(H,H) = 8.0 Hz, *J*(H,H) = 7.4 Hz, *J*(H,H) = 1.6 Hz, 2H, Ph-**H**).(NH not visible)

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 48.1 (2C, CH_2**C**H), 51.7 (2C, O**C**H$_3$), 52.7 (2C, O**C**H$_3$), 52.8 (2C, NHCH(Ph)**C**H), 61.3 (2C, NH**C**HPh), 63.7 (2C, NH**C**HCO_2Me), 68.5

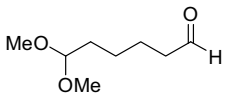
(2C, **C**H_2), 111.0 (2C, **Ph**-H), 121.2 (2C, **Ph**-H), 125.7 (2C, **Ph**-H), 126.3 (2C, **Ph**-H), 129.1 (2C, **Ph**-H), 156.1 (2C, **Ph**-H), 173.5 (2C, **C**O), 174.3 (2C, **C**O).

MS (FAB) m/z (rel. Int. %): 583 (100, [M^+ + H]), 581 (10), 198 (12), 172 (12),133 (10), 132 (14), 99 (18), 77 (12), 59 (15).

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 3324w, 2952m, 2883w, 1735s, 1604m, 1499s, 1456s, 1436s, 1380m, 1285s, 1246s, 1170s, 1124s, 1066m, 1015m, 958m, 912m, 753s, 678w.

EA % found (calcd): C: 61.60 (61.85), H: 5.87 (5.88), N: 4.81 (4.81).

6,6-Dimethoxy-hexanal (172)



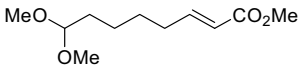
Ozone was bubbled through a solution of cyclohexene (7.60 mL, 75.0 mmol) in dichloromethane (250 mL) and methanol (50.0 mL) at -78 °C till the solution turned blue. Afterwards nitrogen was passed through the solution until the blue color was discharged. The cold bath was removed and *p*-toluenesulfonic acid (1.21 g, 6.4 mmol) was added. The solution was allowed to warm to rt as it stirred under an atmosphere of nitrogen for 90 min. Thereupon anhydrous sodium bicarbonate (2.15 g, 25.6 mmol) was added and the mixture was stirred for 15 min, before dimethyl sulfide (12.0 mL, 163 mmol) was added. After being stirred for 12 h, the heterogenous mixture was concentrated to approximately 50 mL under reduced pressure. Dichloromethane (100 mL) was added and the mixture was washed with water (75 mL). The aqueous layer was extracted with dichloromethane (2 x 100 mL), and the combined organic layers were washed with water (100 mL). After extracting the aqueous layer with dichloromethane (100 mL), the organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc : Hx 1 : 1, $\mathbf{R}_f$ = 0.38) to afford **172** (8.00 g, 66%) as a colorless oil.

$C_8H_{16}O_3$ (160.21).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 1.34-1.42 (m, 2H, C**H**$_2$), 1.59-1.69 (m, 4H, C**H**$_2$), 2.21 (dt, *J*(H,H) = 7.3 Hz, *J*(H,H) = 1.5 Hz, 2H, C**H**$_2$), 3.31 (s, 6H, OC**H**$_3$), 4.35 (t, J(H,H)= 5.8 Hz, 1H, C**H**), 9.76 (t, *J*(H,H) = 1.5 Hz, 1H, C**H**O).

^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 22.0 (**C**H_2), 24.3 (**C**H_2), 32.4 (**C**H_2), 44.0 (**C**H_2), 52.9 (2C, O**C**H_3), 104.4 (**C**H), 202.6 (**C**O).
IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3428w, 2945s, 2830s, 2721s, 1725s, 1458s, 1387s, 1191s, 1166s, 1128s, 1057s, 969s, 915m, 811w, 738w.

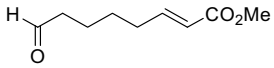
(*E*)-8,8-Dimethoxy-oct-2-enoic acid methyl ester (173)



6,6-dimethoxy-hexanal (1.66 g, 10.4 mmol) was added dropwise to a solution of (triphenylphosphoranyliden)-2-propanon (3.10 g, 9.40 mmol) in dichloromethane (35.0 mL). The resulting solution was stirred overnight before the solvent was removed under reduced pressure. The residue was diluted with diethyl ether and filtered to remove the precipitated triphenylphosphine oxide. The crude product was purified by column chromatography (Hx : EtOAc 5 : 1, $\mathbf{R}_f$ = 0.38) to give **173** as a colorless oil (1.50 g, 67%).

$C_{11}H_{20}O_4$ (216.27).
^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 1.34-1.40 (m, 2H, C**H**$_2$), 1.44-1.52 (m, 2H, C**H**$_2$), 1.57-1.62 (m, 2H, C**H**$_2$*)*, 2.21 (qd, *J*(H,H) = 7.3 Hz, *J*(H,H) = 1.5 Hz, 2H, C**H**$_2$), 3.31 (s, 6H, OC**H**$_3$), 3.72 (s, 3H, CO_2C**H**$_3$), 4.34 (t, *J*(H,H)= 5.8 Hz, 1H, C**H**), 5.82 (td, *J*(H,H) = 15.6 Hz, *J*(H,H) = 1.5 Hz, 1H, CH_2CH=C**H**), 6.95 (td, *J*(H,H) = 15.6 Hz, *J*(H,H) = 7.1 Hz, 1H, CH_2C**H**=CH).
^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 300 K): δ = 24.3 (**C**H_2), 28.0 (**C**H_2), 32.3 (**C**H_2), 32.4 (**C**H_2), 51.5 (CO_2**C**H_3), 52.8 (2C, O**C**H_3), 104.5 (**C**H), 121.2 (CH_2CH=**C**H), 149.5 (CH_2**C**H=CH), 167.3 (**C**O).
IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3432w, 2945s, 2830s, 2676w, 1725s, 1656s, 1440s, 1272s, 1125s, 957s, 844w, 716w.

(*E*)-8-Oxo-oct-2-enoic acid methyl ester (174)

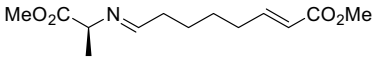


A 2M HCl-solution (7.00 mL) was added to a solution of (*E*)-8,8-dimethoxy-oct-2-enoic acid methyl ester (1.00 g, 4.60 mmol) in THF (10.0 mL). After stirring for 8 hours at rt, the reaction mixture was extracted with diethyl ether (3 x 25 mL). The organic phases were combined, washed with an aqueous $NaHCO_3$-solution (3 x 5 mL), brine (2 x 3 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **174** as a colorless oil (682 mg, 87%).(Analytical data in accordance to that reported[82]).

$C_9H_{14}O_3$ (170.21).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 1.46-1.54 (m, 2H, C**H**$_2$), 1.62-1.70 (m, 2H, C**H**$_2$), 2.23 (qd, *J*(H,H) = 7.1 Hz, *J*(H,H) = 1.5 Hz, 2H, C**H**$_2$), 2.45 (dt, *J*(H,H) = 7.3 Hz, *J*(H,H) = 1.5 Hz, 2H, C**H**$_2$), 3.72 (s, 3H, CO_2C**H**$_3$), 5.83 (td, *J*(H,H) = 15.7 Hz, *J*(H,H) = 1.5 Hz, 1H, CH_2CH=C**H**), 6.94 (td, *J*(H,H) = 15.7 Hz, *J*(H,H) = 6.8 Hz, 1H, CH_2C**H**=CH), 9.76 (d, *J*(H,H) = 1.5, 1H, C**H**O).

(*E*)-Methyl 8-((*S*)-1-Methoxy-1-oxopropan-2-ylimino)oct-2-enoat (175)



A concentrated aqueous ammonia solution (1.5 mL) was added to a solution of L-alanine methyl ester hydrochloride (110 mg, 1.07 mmol) in anhydrous dichloromethane (10 mL). The mixture was shaken for 5 min before the organic layer was separated and dried over $MgSO_4$. The solvent was removed under reduced pressure to isolate the free amine.

A mixture of 8-oxo-oct-2-enoic acid methyl ester (200 mg, 1.18 mmol), the free amine and anhydrous $MgSO_4$ (610 mg, 5.07 mmol) in anhydrous dichloromethane (5 mL) was stirred for 48 h at rt. The reaction mixture was filtered and the solvent was removed under reduced pressure to afford **175** as a colorless solid which was used without further purification in the following step (8 mol% of aldehyde were detected by ^{1}H NMR spectroscopy as the only impurity).

$C_{13}H_{21}NO_4$ (255.31).

^{1}H NMR (400.1 MHz, $CDCl_3$, 300 K): δ = 1.34 (d, *J*(H,H) = 6.8 Hz, 3H, CHC**H**$_3$), 1.48-1.58 (m, 4H, C**H**$_2$), 2.20-2.30 (m, 4H, C**H**$_2$), 3.67 (s, 3H, CO_2C**H**$_3$), 3.68 (s, 3H, CO_2C**H**$_3$), 3.86 (q, *J*(H,H) = 6.8 Hz, 1H, C**H**CH_3), 5.82 (td, *J*(H,H) = 15.6 Hz, *J*(H,H) = 1.5 Hz, 1H,

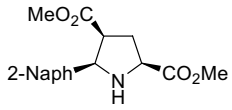
CH_2CH=C**H**), 6.93 (td, *J*(H,H) = 15.7 Hz, *J*(H,H) = 6.8 Hz, 1H, CH_2C**H**=CH), 7.67 (t, *J*(H,H) = 4.8, 1H, C**H**=N).

13.4.2 Asymmetric Ag(I)-Catalyzed [3+2] Cycloadditions

General Procedure IX:

A suspension of AgOAc (3 mol%) and the ligand (3.3 mol%) in degassed toluene was stirred for 10 h. The resulting solution was cooled to 0 °C before the substrate(s) were added (concentration of the imine 0.05 M). After stirring for 5-12 h the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica.

(+)-Dimethyl 5-(naphthalen-2-yl)pyrrolidine-2,4-dicarboxylate (38a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{18}H_{19}NO_4$ (313.35).

colorless oil. $\mathbf{R}_f$ = 0.26 (Et_2O : pentane 3:1).

$[\alpha]_D^{20}$ = +17.3° (c = 0.610, $CHCl_3$. 62% *ee*).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 295 K): δ = 2.37-2.49 (m, 2H, C**H**$_2$), 2.85 (br s, 1H, N**H**), 3.11 (s, 3H, OC**H**$_3$), 3.39 (q, *J*(H,H) = 7.5 Hz, 1H, C**H**CO_2CH_3), 3.81 (s, 3H, OC**H**$_3$), 4.01 (t, *J*(H,H) = 8.3 Hz, 1H, NHC**H**CO_2CH_3), 4.67 (d, *J*(H,H) = 7.8 Hz, 1H, NHC**H**), 7.41-7.50 (m, 3H, Naph-**H**), 7.79-7.85 (m, 4H, Naph-**H**).

^{13}C{^{1}H} NMR (100.8 MHz, CD_2Cl_2, 295 K): δ = 33.8 (**C**H_2), 50.1 (**C**HCO_2CH_3), 51.6 (O**C**H_3), 52.6 (O**C**H_3), 60.4 (NH**C**HCO_2CH_3), 66.3 (NH**C**H), 125.8 (**Naph**-H), 125.9 (**Naph**-H), 126.4 (**Naph**-H), 126.6 (**Naph**-H), 128.1 (**Naph**-H), 128.1 (**Naph**-H), 128.4 (**Naph**-H), 133.4 (**Naph**-C), 133.7 (**Naph**-C), 137.7 (**Naph**-C), 173.6 (CH**C**O_2CH_3), 174.3 (NHCH**C**O_2CH_3).

MS (FAB) m/z (rel. Int. %): 314 (100, [M^+ + H]), 254 (19), 227 (16), 194 (15), 167 (13).

IR (NaCl): $\tilde{\upsilon}$ [cm^{-1}] = 3446w, 3053w, 2995w, 2951m, 2886w, 1736s, 1600w, 1508w, 1438s, 1374m, 1207s, 1169s, 1126m, 1036w, 823m, 750m.

EA % found (calcd): C: 68.80 (68.99), H: 6.10 (6.11), N: 4.47 (4.47).

HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (80 : 20), 0.5 ml/min, 25 °C, t_R = 41 min, **72 min**, $\lambda_{local\ max}$ 225 nm, 275 nm.

Analytical data of **38b**.

$C_{18}H_{19}NO_4$ (313.35).

colorless oil. $\mathbf{R}_f$ = 0.26 (Et_2O : pentane 3:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 295 K): δ = 2.41 (ddd, *J*(H,H) = 13.1 Hz, *J*(H,H) = 8.7 Hz, *J*(H,H) = 5.7 Hz, 1H, C**H**$_2$), 2.52 (ddd, *J*(H,H) = 13.1 Hz, *J*(H,H) = 8.7 Hz, *J*(H,H) = 8.3 Hz, 1H, C**H**$_2$), 3.00 (q, *J*(H,H) = 8.5 Hz, 1H, C(4)**H**CO_2CH_3), 3.61 (s, 3H, OC**H**$_3$), 3.78 (s, 3H, OC**H**$_3$), 4.08 (dd, *J*(H,H) = 8.8 Hz, *J*(H,H) = 5.8 Hz, 1H, C(2)**H**CO_2CH_3), 4.55 (d, *J*(H,H) = 8.4 Hz, 1H, NHC**H**), 7.44-7.61 (m, 3H, Naph-**H**), 7.81-8.00 (m, 4H, Naph-**H**). (NH not visible).

HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (80 : 20), 0.5 ml/min, 25 °C, t_R = 27 min, **31 min**, $\lambda_{local\ max}$ 225 nm, 275 nm.

Analytical data of **38c**.

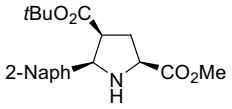
$C_{18}H_{19}NO_4$ (313.35).

colorless oil. $\mathbf{R}_f$ = 0.26 (Et_2O : pentane 3:1).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 295 K): δ = 2.17 (ddd, *J*(H,H) = 12.6 Hz, *J*(H,H) = 10.2 Hz, *J*(H,H) = 9.5 Hz, 1H, C**H**$_2$), 2.53 (ddd, *J*(H,H) = 12.6 Hz, *J*(H,H) = 7.9 Hz, *J*(H,H) = 6.3 Hz, 1H, C**H**$_2$), 2.85 (br s, 1H, N**H**), 3.43 (ddd, *J*(H,H) = 9.3 Hz, *J*(H,H) = 8.8 Hz, *J*(H,H) = 7.8 Hz, 1H, C(3)**H**CO_2CH_3), 3.67 (s, 3H, OC**H**$_3$), 3.72 (s, 3H, OC**H**$_3$), 4.15 (t, *J*(H,H) = 8.8 Hz, 1H, C(2)**H**CO_2CH_3), 4.36 (dd, *J*(H,H) = 10.2 Hz, *J*(H,H) = 6.3 Hz, 1H, NHC**H**), ~7.40-~8.00 (7H, Naph-**H**).

HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (80 : 20), 0.5 ml/min, 25 °C, t_R = 43.2 min, 61.3 min, $\lambda_{measured}$ 225 nm, 275 nm.

(+)-4-*tert*-Butyl 2-methyl 5-(naphthalen-2-yl)pyrrolidine-2,4-dicarboxylate (149a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{21}H_{25}NO_4$ (355.18).

colorless solid. $\mathbf{R}_f$ = 0.24 (Et_2O : pentane 3:1).

m.p. 120–122 °C.

$[\alpha]_D^{20}$ = +13.0° (c = 0.190, $CHCl_3$. 43% *ee*).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 0.90 (s, 9H, C(C**H**$_3$)$_3$), 2.37-2.55 (m, 2H, C**H**$_2$), 3.36 (dt, *J*(H,H) = 7.5 Hz, *J*(H,H) = 5.6 Hz, 1H, C**H**CO$_2$C(C**H**$_3$)$_3$), 3.84 (s, 3H, OC**H**$_3$), 4.05 (t, *J*(H,H) = 8.3 Hz, 1H, NHC**H**CO$_2$CH$_3$), 4.66 (d, *J*(H,H) = 7.6 Hz, 1H, NHC**H**), 7.44-7.48 (m, 3H, Naph-**H**), 7.78-7.83 (m, 4H, Naph-**H**).(NH not visible).

^{13}C{^{1}H} NMR (100.8 MHz, CD_2Cl_2, 300 K): δ = 27.8 (3C, C(C**H**$_3$)$_3$), 34.5 (**C**H$_2$), 50.5 (**C**HCO$_2$CH$_3$), 52.8 (O**C**H$_3$), 60.3 (NH**C**HCO$_2$CH$_3$), 66.2 (NH**C**H), 81 2 (O**C**(CH$_3$)$_3$), 126.0 (2C, **Naph**-H), 126.2 (**Naph**-H), 126.5 (**Naph**-H), 127.9 (**Naph**-H), 128.1 (**Naph**-H), 128.3 (**Naph**-H), 133.2 (**Naph**-C), 133.6 (**Naph**-C), 136.7 (**Naph**-C), 172.2 (CH**C**O$_2$CH$_3$), 173.9 (NHCH**C**O$_2$CH$_3$).

MS (FAB) m/z (rel int): 356 (M + 1, 66), 300 (100), 240 (16), 227 (16), 222 (12), 194 (21), 179 (12), 167 (23), 57 (73), 41 (30).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3427w, 3275w, 3056w, 2976m, 2946m, 1742s, 1703s, 1436m, 1368m, 1309w, 1208m, 1153s, 1110m, 1031w, 965w, 930w, 888w, 856w, 828w, 749m.

EA % found (calcd): C: 70.57 (70.96), H: 7.11 (7.09), N: 3.94 (3.95).

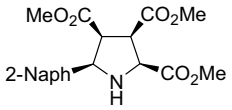
HPLC: Daicel Chiralcel AS (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (90 : 10), 1.0 ml/min, 20 °C, t_R = **7.6 min**, 13.1 min, $\lambda_{local\ max}$ 220 nm, 254 nm.

Analytical data of **149b**.

$C_{21}H_{25}NO_4$ (355.18).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 1.34 (s, 9H, C(C**H**$_3$)$_3$), 2.35 (ddd, *J*(H,H) = 12.9 Hz, *J*(H,H) = 8.7 Hz, *J*(H,H) = 5.8 Hz, 1H, C**H**$_2$), 2.49 (ddd, *J*(H,H) = 12.8 Hz, *J*(H,H) = 8.8 Hz, *J*(H,H) = 8.6 Hz, 1H, C**H**$_2$), 3.36 (app q, *J*(H,H) = 8.4 Hz, 1H, C**H**CO$_2$C(C**H**$_3$)$_3$), 3.77 (s, 3H, OC**H**$_3$), 4.05 (t, *J*(H,H) = 8.4 Hz, 1H, NHC**H**CO$_2$CH$_3$), 4.48 (d, *J*(H,H) = 8.3 Hz, 1H, NHC**H**), 7.44-7.53 (m, 3H, Naph-**H**), 7.81-7.93 (m, 4H, Naph-**H**).(NH not visible).

(+)-Trimethyl 5-(naphthalen-2-yl)pyrrolidine-2,3,4-tricarboxylate (150a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{20}H_{21}NO_6$ (371.39).

colorless solid. $\mathbf{R}_f$ = 0.10 (Et_2O : pentane 3:1).

m.p. 123-126 °C.

$[\alpha]_D^{20}$ = +25.8° (c = 0.610, $CHCl_3$. 60% *ee*).

^{1}H NMR (CD_2Cl_2, 500.13 MHz, 295 K): δ = 3.13 (s, 3H, $CO_2C\mathbf{H}_3$), 3.41 (br t, *J*(H,H) = 10.4 Hz, 1H, N**H**), 3.64 (s, 3H, $CO_2C\mathbf{H}_3$), 3.68 (dd, *J*(H,H) = 8.2 Hz, *J*(H,H) = 6.6 Hz, 1H, C(4)**H**CO_2Me), 3.78 (s, 3H, $CO_2C\mathbf{H}_3$), 3.79 (dd, *J*(H,H) = 9.2 Hz, *J*(H,H) = 8.2 Hz, 1H, C(3)**H**CO_2Me), 4.18 (t, *J*(H,H) = 9.2 Hz, 1H, C(2)**H**CO_2Me), 4.58 (dd, *J*(H,H) = 10.9 Hz, *J*(H,H) = 6.7 Hz, 1H, C(5)**H**CO_2Me), 7.43 (dd, *J*(H,H)=8.6 Hz, *J*(H,H)=1.8 Hz, 1H, Naph-**H**), 7.46-7.50 (m, 2H, Naph-**H**), 7.81-7.86 (m, 4H, Naph-**H**).

^{13}C{^{1}H} NMR (CD_2Cl_2, 125.0 MHz, 295 K): δ = 51.7 (O**C**H_3), 51.9 (**C**(3)), 52.5 (O**C**H_3), 52.7 (O**C**H_3), 53.0 (**C**(4)), 62.4 (**C**(2)), 65.8 (**C**(5)), 125.4 (**Naph**-H), 125.9 (**Naph**-H), 126.5 (**Naph**-H), 126.8 (**Naph**-H), 128.1 (**Naph**-H), 128.3 (**Naph**-H), 128.4 (**Naph**-H), 133.3 (**Naph**-C), 133.7 (**Naph**-H), 135.6 (**Naph**-H), 171.2 (**C**O), 171.5 (**C**O), 171.7 (**C**O).

MS (FAB) m/z (rel int): 372 (M + 1, 100), 312 (14), 252 (10), 227 (27), 167 (14), 59 (9).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3451w, 3289w, 3053w, 2998w, 2951m, 1743s, 1436s, 1348m, 1301m, 1207s, 1109m, 1051m, 956m, 860m, 826m, 742w.

EA % found (calcd): C: 64.68 (64.68), H: 5.70 (5.70), N: 3.80 (3.77).

HPLC: Daicel Chiralcel AS (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (70 : 30), 0.5 ml/min, 20 °C, t_R = **22.9** min, 52.7 min, $\lambda_{local\ max}$ 224 nm, 266 nm.

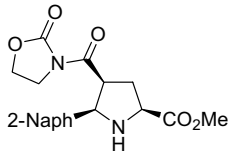
Analytical data of **150b**.

$C_{20}H_{21}NO_6$ (371.39).

^{1}H NMR (CD_2Cl_2, 500.13 MHz, 295 K): δ = 2.73 (br s, 1H, N**H**), 3.34 (dd, *J*(H,H) = 8.8 Hz, *J*(H,H) = 7.6 Hz, 1H, C(4)**H**CO_2Me), 3.62 (s, 3H, $CO_2C\mathbf{H}_3$), 3.64 (dd, *J*(H,H) = 9.1 Hz, *J*(H,H) = 6.1 Hz, 1H, C(3)**H**CO_2Me), 3.70 (s, 3H, $CO_2C\mathbf{H}_3$), 3.80 (s, 3H, $CO_2C\mathbf{H}_3$), 4.39 (d, *J*(H,H) = 6.3 Hz, 1H, C(2)**H**CO_2Me), 4.80 (d, *J*(H,H) = 7.8 Hz, 1H, C(5)**H**CO_2Me),), 7.46-

7.49 (m, 2H, Naph-**H**),7.57 (dd, *J*(H,H) = 8.6 Hz, *J*(H,H) = 1.8 Hz, 1H, Naph-**H**), 7.82-7.91 (m, 4H, Naph-**H**).

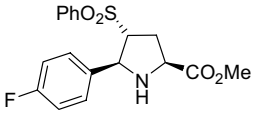
(2*S,4*S**,5*R**)-Methyl 5-(naphthalen-2-yl)-4-(2-oxooxazolidine-3-carbonyl)pyrrolidine-2-carboxylate (151b)**



The synthesis was performed according to **general procedure IX** (page 190).

$C_{20}H_{20}N_2O_5$ (368.39).
colorless solid. $\mathbf{R}_f$ = 0.04 (EtOAc : Hx 1:2).
m.p. 128-130 °C.
^{1}H NMR (500.1 MHz, CD_2Cl_2, 300 K): δ = 2.36-2.42 (m, 1H, C**H**$_{2(py)}$), 2.54-2.60 (m, 1H, C**H**$_{2(py)}$), 2.78 (br s, 1H, N**H**), 2.87-2.92 (m, 1H, C**H**$_{2(ox)}$), 3.21 (q, *J*(H,H) = 8.5 Hz, 1H, C**H**$_{2(ox)}$), 3.50-3.56 (m, 1H, C**H**$_{2(ox)}$), 3.81 (s, 3H, OC**H**$_3$), 3.89-3.93 (m, 1H, C**H**$_{2(ox)}$), 4.00 (t, *J*(H,H) = 8.5 Hz, 1H, C**H**CO_2Me), 4.73-4.78 (m, 1H, C**H**C(O)N), 4.81 (d, *J*(H,H) = 8.5 Hz, 1H, Naph-C**H**), 7.41 (dd, *J*(H,H) = 8.5 Hz, *J*(H,H) = 2.0 Hz, 1H, Naph-**H**), 7.45-7.49 (m, 2H, Naph-**H**), 7.77-7.84 (m, 4H, Naph-**H**).
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 32.6 (**C**H$_{2(Py)}$), 42.3 (**C**H$_{2(Ox)}$), 47.9 (**C**HC(O)N), 52.0 (O**C**H$_3$), 59.9 (**C**HCO$_2$Me), 61.7 (**C**H$_{2\ (Ox)}$), 65.6 (Naph-**C**H), 125.4 (**Naph**-H), 125.6 (**Naph**-H), 126.0 (**Naph**-H), 126.3 (**Naph**-H), 127.5 (**Naph**-H), 127.5 (**Naph**-H), 127.8 (**Naph**-H), 132.9 (**Naph**-C) 136.9 (2C, **Naph**-C), 153.1 (O**C**(O)N), 172.5 (CH**C**(O)N), 173.6 (**C**O).
MS (FAB) m/z (rel int %): 369 (M + H, 100), 309 (10), 282 (14), 227 (11), 194 (13), 167 (10).
IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3451w, 3056w, 2950w, 2911m, 1769s, 1745s, 1681m, 1477w, 1436w, 1396m, 1272m, 1204s, 1103m, 1040m, 925w, 860w, 809m, 761m.
EA % found (calcd): C: 65.10 (65.21), H: 5.47 (5.47), N: 7.54 (7.60).
HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : EtOH (85 : 15), 0.5 ml/min, 25 °C, t_R = **36.3** min, 82.4 min, $\lambda_{local\ max}$ 225 nm, 275 nm.

(+)-Methyl 5-(4-fluorophenyl)-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (153b)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{18}H_{18}FNO_4S$ (363.40).

colorless solid. $\mathbf{R}_f$ = 0.18 (EtOAc : Hx 1 : 2).

m.p. 83-85 °C.

$[\alpha]_D^{20}$ = +29.1° (c = 0.650, $CHCl_3$, 88% *ee*).

^{1}H NMR (CD_2Cl_2, 500.1 MHz, 295 K): δ = 2.28-2.36 (m, 1H, C**H**$_2$), 2.53 (br s, 1H, N**H**), 2.63 (ddd, *J*(H,H) = 14.0, *J*(H,H) = 7.6, *J*(H,H) = 4.8, 1H, C**H**$_2$), 3.58-3.62 (m, 1H, C**H**SO_2Ph), 3.73 (s, 3H, OC**H**$_3$), 4.10 (t, *J*(H;H) = 8.1 Hz, 1H, C**H**CO_2Me), 4.66 (d, *J*(H,H) = 5.8 Hz, 1H, *p*FPhC**H**), 6.90-6.94 (m, 2H, *p*FPh-**H**), 7.20-7.22 (m, 2H, *p*FPh-**H**), 7.49-7.53 (m, 2H, Ph-**H**), 7.61-7.65 (m, 1H, Ph-**H**), 7.78-7.80 (m, 2H, Ph-**H**).

^{13}C{^{1}H} NMR (CD_2Cl_2, 125.8 MHz, 295 K): δ = 31.5 (**C**H$_2$), 52.7 (O**C**H$_3$), 59.7 (**C**HCO_2Me), 62.5 (**C**HPhF), 70.5 (**C**HSO_2Ph), 115.7 (d, *J*(C,F) = 21.6 Hz, 2C, *p*F**Ph**-H), 129.0 (2C, **Ph**-H), 129.3 (d, *J*(C,F) = 8.2 Hz, 2C, *p*F**Ph**-H), 129.9 (2C, **Ph**-H), 134.5 (**Ph**-H), 137.9 (d, *J*(C,F) = 3.4 Hz, *p*F**Ph**$_{(ipso)}$-C), 138.6 (**Ph**-S), 162.7 (d, *J*(C,F) = 245.3 Hz, **Ph**-F), 173.6 (**C**=O).

^{19}F{^{1}H} NMR (376.5 MHz, CD_2Cl_2, 300 K): δ = -117.5 (m).

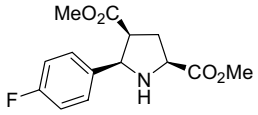
MS (FAB) m/z (rel int %): 364 (M + H, 100), 333 (12), 221 (25), 162 (92), 136 (42),120 (17), 107 (32), 105 (13), 91 (31), 89 (46), 77 (58), 71 (11), 69 (16), 65 (31), 63 (29), 57 (45), 55 (27), 51 (38), 43 (31), 41 (43), 39 (71).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3350m, 3053w, 2961w, 2870w, 1744s, 1601w, 1507m, 1448m, 1379m, 1297s, 1218s, 1144s, 1088m, 1018m, 846m, 741m, 686m, 597s.

EA % found (calcd): C: 59.54 (59.49), H: 4.95 (4.99), N: 3.93 (3.85).

HPLC: Daicel Chiralcel AS (0.46 cm x 25 cm), *n*-Heptan : iPrOH (60 : 40), 0.8 ml/min, 25 °C, t_R = 20.2 min, **29.1** min, $\lambda_{local\ max}$ 208 nm, 265 nm.

(+)-Dimethyl 5-(4-fluorophenyl)pyrrolidine-2,4-dicarboxylate (137a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{14}H_{16}FNO_4$ (281.23).

colorless oil. $\mathbf{R}_f$ = 0.18 (EtOAc : Hx 1 : 2).

$[\alpha]_D^{20}$ = +25.1° (c = 0.890, $CHCl_3$, 65% *ee*).

^{1}H NMR (CD_2Cl_2, 500.1 MHz, 295 K): δ = 2.31-2.40 (m, 2H, C**H**$_2$), 2.68 (br s, 1H, N**H**), 3.22 (s, 3H, OC**H**$_3$), 3.25-3.31 (m, 1H, C**H**CO$_2$Me), 3.78 (s, 3H, OC**H**$_3$), 3.94 (t, *J*(H,H) = 8.2, 1H, NHC**H**CO$_2$Me), 4.66 (d, *J*(H,H) = 8.1, 1H, FPhC**H**), 6.98-7.03 (m, 2H, Ph-**H**), 7.30-7.34 (m, 2H, Ph-**H**).

^{13}C{^{1}H} NMR (CD_2Cl_2, 125.8 MHz, 295 K): δ = 33.3 (**C**H$_2$), 50.0 (**C**HCO$_2$Me), 51.6 (O**C**H$_3$), 52.6 (O**C**H$_3$), 60.2 (NH**C**HCO$_2$Me), 65.2 (*p*FPh**C**H), 115.3 (d, *J*(C,F) = 21.1, 2C, *p*F**Ph**-H), 129.2 (d, *J*(C,F) = 8.2, 2C, *p*F**Ph**-H), 136.3 (d, *J*(C,F) = 3.4, *p*F**Ph**$_{(ipso)}$-C), 162.7 (d, *J*(C,F) = 244.8, **Ph**-F),173.3 (**C**=O), 174.3 (**C**=O).

^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -118.0 (m).

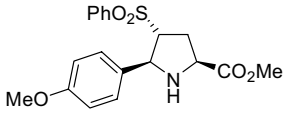
MS (FAB) m/z (rel int %): 282 (M + H, 100), 222 (32), 162 (12), 137 (20),107 (10), 91 (11), 77 (18), 65 (12), 57 (21), 55(12), 51 (15), 43 (13), 41 (20), 39 (26).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3352m, 3055w, 2997m, 2954s, 2893w, 1737s, 1605m, 1511s, 1440s, 1377s, 1214s, 1166s, 1116m, 1036m, 938m, 842s.

EA % found (calcd): C: 59.41 (59.78), H: 5.73 (5.73), N: 5.38 (4.98).

HPLC: Daicel Chiralcel OB-H (0.46 cm x 25 cm), *n*-Heptan : iPrOH (95 : 5), 0.5 ml/min, 25 °C, t_R = 57.0 min, **66.8** min, $\lambda_{local\ max}$ 207 nm, 265 nm.

(+)-Methyl 5-(4-methoxyphenyl)-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (154b)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{19}H_{21}NO_5S$ (375.44).

colorless oil. $\mathbf{R}_f$ = 0.11 (EtOAc : Hx 1 : 2).

$[\alpha]_D^{20}$ = +16.0° (c = 0.660, $CHCl_3$, 81% *ee*).

^{1}H NMR (CD_2Cl_2, 500.1 MHz, 300 K): δ = 2.31 (ddd, *J*(H,H) = 13.9, *J*(H,H) = 9.3, *J*(H,H) = 8.5, 1H, C**H**$_2$), 2.47 (br s, 1H, N**H**), 2.64 (ddd, *J*(H,H) = 13.9, *J*(H,H) = 7.6, *J*(H,H) = 4.9, 1H, C**H**$_2$), 3.60-3.65 (m, 1H, C**H**SO_2Ph), 3.72 (s, 3H, OC**H**$_3$), 3.75 (s, 3H, OC**H**$_3$), 3.78 (s, 3H, OC**H**$_3$), 4.05 (t, *J*(H,H) = 8.0, 1H, NHC**H**CO_2Me), 4.59 (d, *J*(H,H) = 6.3, 1H, *p*MeOPhC**H**), 6.73-6.76 (m, 2H, *p*MeOPh-**H**), 7.10-7.14 (m, 2H, *p*MeOPh-**H**), 7.47-7.52 (m, 2H, Ph-**H**), 7.59-7.64 (m, 1H, Ph-**H**), 7.77-7.80 (m, 2H, Ph-**H**).

^{13}C{^{1}H} NMR (CD_2Cl_2, 125.8 MHz, 300 K): δ = 31.9 (**C**H$_2$), 52.7 (O**C**H$_3$), 55.7 (OCH$_3$), 59.6 (**C**HCO$_2$Me), 63.0 (**C**HPhOMe), 70.3 (**C**HSO_2Ph), 114.3 (2C, *p*MeO**Ph**-H), 128.7 (2C, *p*MeO**Ph**-H), 130.0 (2C, **Ph**-H), 129.8 (2C, **Ph**-H), 133.6 (**Ph**-C), 134.4 (**Ph**-H), 138.7 (**Ph**-C), 159.7 (**Ph**-C), 173.6 (**C**=O).

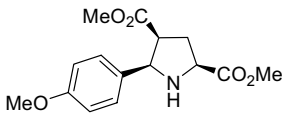
MS (FAB) m/z (rel int %): 376 (M + H, 100), 333 (10), 233 (41), 207 (11), 174 (63), 147 (37), 137 (28), 120 (11), 107 (17), 91 (17), 89 (19), 77 (25), 68 (14), 65 (18), 63 (12), 57 (10), 51 (16), 43 (13), 41 (17), 39 (29).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3343w, 3062w, 3001w, 2953m, 2840w, 1737s, 1611m, 1586w, 1513s, 1445s, 1374m, 1297s, 1246s, 1218s, 1144s, 1086s, 1029s, 832s, 758m, 723m, 691m, 597s.

EA % found (calcd): C: 60.33 (60.78), H: 5.26 (5.64), N: 3.43 (3.73).

HPLC: Daicel Chiralcel AS (0.46 cm x 25 cm), *n*-Heptan : iPrOH (60 : 40), 0.8 ml/min, 20 °C, t_R = 31.4 min, **39.9** min, $\lambda_{local\ max}$ 218 nm, 267 nm.

(2S*,4S*,5R*)-Dimethyl 5-(4-methoxyphenyl)pyrrolidine-2,4-dicarboxylate (139a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{15}H_{19}NO_5$ (293.32).

colorless oil. $\mathbf{R}_f$ = 0.08 (EtOAc : Hx 1 : 2).

^{1}H NMR (CD_2Cl_2, 500.1 MHz, 295 K): δ = 2.30-2.40 (m, 2H, C**H**$_2$), 2.57 (br s, 1H, N**H**), 3.22-3.28 (m, 1H, C**H**CO_2CH_3), 3.23 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.92 (t, *J*(H,H) = 8.2 Hz, 1H, NHC**H**CO_2CH_3), 4.45 (d, *J*(H,H) = 7.8 Hz, 1H, *p*MeOPhC**H**),

6.82-6.85 (d, *J*(H,H) = 8.7 Hz, 2H, *p*MeOPh-**H**), 7.20-7.24 (d, *J*(H,H) = 8.7 Hz, 2H, *p*MeOPh-**H**).

^{13}C{^{1}H} NMR (CD_2Cl_2, 125.8 MHz, 300 K): δ = 33.6 (**C**H_2), 50.1 (**C**HCO_2Me), 51.6 (O**C**H_3), 52.6 (O**C**H_3), 55.7 (O**C**H_3), 60.2 (NH**C**HCO_2CH_3), 65.6 (*p*MeOPh**C**H), 113.9 (2C, *p*MeO**Ph**-H), 128.5 (2C, *p*MeO**Ph**-H), 132.1 (*p*MeO**Ph**$_{(ipso)}$CH), 159.6 (*p*MeO**Ph**), 173.6 (**C**=O), 174.4 (**C**=O).

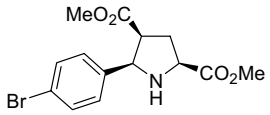
MS (+EI) m/z (rel int %): 293 (M +, 5), 234 (26), 207 (83), 202 (17), 175 (29), 147 (100), 132 (14).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3350w, 3054w, 2998w, 2952m, 2840w, 1737s, 1612m, 1513s, 1440s, 1377m, 1248s, 1207s, 1175s, 1114m, 1034m, 937w, 836m.

EA % found (calcd): C: 61.02 (61.42), H: 6.40 (6.53), N: 4.72 (4.78).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan : iPrOH (80 : 20), 0.5 ml/min, 25 °C, t_R = **28.6** min, 45.5 min, $\lambda_{local\ max}$ 207 nm, 227 nm.

(+)-Dimethyl 5-(4-bromophenyl)pyrrolidine-2,4-dicarboxylate (138a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{14}H_{16}BrNO_4$ (342.19).

colorless oil. $\mathbf{R}_f$ = 0.15 (Et_2O : Pe 3 : 2).

$[\alpha]_D^{20}$ = +22.6° (c = 0.660, $CHCl_3$, 50% *ee*).

^{1}H NMR (CD_2Cl_2, 400.1 MHz, 300 K): δ = 2.30-2.42 (m, 2H, C**H**$_2$), 2.77 (br s, 1H, N**H**), 3.27 (s, 3H, OC**H**$_3$), 3.31 (q, *J*(H,H) = 7.1, 1H, C**H**CO_2Me), 3.82 (s, 3H, OC**H**$_3$), 3.98 (t, *J*(H,H) = 8.1, 1H, NHC**H**CO_2Me), 4.50 (d, *J*(H,H) = 7.8, 1H, *p*BrPh-C**H**), 7.21-7.25 (m, 2H, Ar-**H**), 7.42-7.46 (m, 2H, Ar-**H**).

^{13}C{^{1}H} NMR (CD_2Cl_2, 125.8 MHz, 300 K): δ = 33.5 (**C**H_2), 49.9 (**C**HCO_2Me), 51.8 (O**C**H_3), 52.8 (O**C**H_3), 60.2 (*p*BrPh-**C**H), 65.5 (NH**C**HCO_2Me), 121.9 (*p*Br**Ph**), 129.0 (2C, *p*Br**Ph**-H), 131.7 (2C, *p*Br**Ph**-H), 138.8 (*p*Br**Ph**$_{(ipso)}$-C), 173.1 (**C**=O), 174.1 (**C**=O).

MS (FAB): *m*/*z* (rel int %) = 342 (M^+, 100, ^{79}Br), 282 (29, ^{79}Br), 222 (10, ^{79}Br), 88 (10).

IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3370w, 2994w, 2951w, 2889w, 2884w, 1738s, 1591w, 1487w, 1438m, 1375w, 1207s, 1169s, 1076w, 1010m, 936w, 831w.

EA % found (calcd): C: 49.08 (49.14), H: 4.68 (4.71), N: 4.20 (4.09).

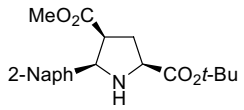
HPLC: Daicel Chiralcel AS (0.46 cm x 25 cm), *n*-Heptan : iPrOH (50 : 50), 0.5 ml/min, 20 °C, t_R = **11.4** min, 18.9 min, $\lambda_{local\ max}$ 222 nm, 260 nm.

Analytical data of **138b**.

$C_{14}H_{16}BrNO_4$ (342.19).

^{1}H NMR (CD_2Cl_2, 400.1 MHz, 300 K): δ = 1.99-2.07 (m, 1H, C**H**$_2$), 2.38-2.48 (m, 1H, C**H**$_2$), 3.37 (app q, *J*(H,H) = 7.8 Hz, 1H, C**H**CO_2Me), 3.65 (s, 3H, OC**H**$_3$), 3.69 (s, 3H, OC**H**$_3$), 4.10 (d, *J*(H,H) = 8.5 Hz, 1H, *p*BrPh-C**H**), 4.18 (dd, *J*(H,H) = 10.1 Hz, *J*(H,H) = 6.3 Hz, 1H, NHC**H**CO_2Me), 7.35 (d, *J*(H,H) = 8.6 Hz, 2H, Ar-**H**), 7.45-7.48 (m, 2H, Ar-**H**).(NH not visible)

(+)-2-*tert*-Butyl 4-methyl 5-(naphthalen-2-yl)pyrrolidine-2,4-dicarboxylate (143a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{21}H_{25}NO_4$ (355.43).

colorless solid. $\mathbf{R}_f$ = 0.45 (Et_2O : Pe 3 : 1).

m.p. 75-77 °C.

$[\alpha]_D^{20}$ = +4.5° (c = 0.670, $CHCl_3$, 45% *ee*).

^{1}H NMR (500.13 MHz, CD_2Cl_2, 295 K): δ = 1.53 (s, 9H, C(C**H**$_3$)$_3$), 2.30-2.43 (m, 2H, C**H**$_2$), 2.82(br s, 1H, N**H**), 3.12 (s, 3H, OC**H**$_3$), 3.38 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H) = 6.4 Hz, 1H, C**H**CO_2Me), 3.88 (t, *J*(H,H) = 8.3 Hz, 1H, NHC**H**CO_2Me), 4.64 (d, *J*(H,H) = 7.8 Hz, 1H, C**H**Naph), 7.42 (dd, *J*(H,H) = 8.4 Hz, *J*(H,H) = 6.6 Hz 1H, Naph-**H**), 7.44-7.49 (m, 2H, Naph-**H**), 7.78-7.84 (m, 4H, Naph-**H**).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 295 K): δ = 28.4 (3C, C(**C**H$_3$)$_3$), 34.1 (**C**H$_2$), 50.3 (**C**HCO_2Me), 51.5 (O**C**H$_3$), 61.3 (**C**HCO_2*t*Bu), 66.4 (**C**HNaph), 81.8 (**C**(CH$_3$)$_3$), 125.9 (**Naph**-H), 125.9 (**Naph**-H), 126.4 (**Naph**-H), 126.6 (**Naph**-H), 128.1 (**Naph**-H), 128.1 (**Naph**-H), 128.4 (**Naph**-H), 133.4 (**Naph**-C), 133.7 (**Naph**-C), 138.0 (**Naph**-C), 173.0 (**C**O), 173.2 (**C**O).

MS (FAB) m/z (rel int): 356 (M + 1, 76), 300 (100), 254 (71), 222 (13), 194 (21), 167 (12), 57 (55), 41 (23).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3431w, 3281w, 3053w, 2975m, 2853m, 1728s, 1441m, 1369m, 1296m, 1210s, 1160s, 1105m, 1040m, 945m, 893w, 856m, 825m, 742m.

EA % found (calcd): C: 71.04 (70.96), H: 7.01 (7.09), N: 4.04 (3.94).

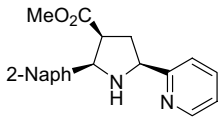
HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : iPrOH (80 : 20), 0.5 ml/min, 20 °C, t_R = **34.4** min, 47.6 min, $\lambda_{local\ max}$ 224 nm, 275 nm.

Analytical data of **143b**.

$C_{21}H_{25}NO_4$ (355.43).

^{1}H NMR (500.13 MHz, CD_2Cl_2, 295 K): δ = 1.51 (s, 9H, C(C**H**$_3$)$_3$), 2.32-2.39 (m, 1H, C**H**$_2$), 2.45-2.53 (m, 1H, C**H**$_2$), 2.51 (br s, 1H, N**H**), 2.97 (app q, *J*(H,H) = 8.8 Hz, 1H, C**H**CO_2Me), 3.61 (s, 3H, OC**H**$_3$), 3.88 (dd, *J*(H,H) = 8.8 Hz, *J*(H,H) = 5.3 Hz, 1H, NHC**H**CO_2Me), 4.51 (d, *J*(H,H) = 8.6 Hz, 1H, C**H**Naph), 7.46-7.49 (m, 2H, Naph-**H**), 7.59 (dd, *J*(H,H) = 8.6 Hz, *J*(H,H) = 1.8 Hz 1H, Naph-**H**),7.82-7.88 (m, 4H, Naph-**H**).

Methyl 2-(naphthalen-2-yl)-5-(pyridin-2-yl)pyrrolidine-3-carboxylate (144a, 144b)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{21}H_{20}N_2O_2$ (332.40).

colorless oil. $\mathbf{R}_f$ = 0.13 (Hx : EtOAc 2 : 1, 8% Et_3N).

144a:

^{1}H NMR (500.1 MHz, CD_2Cl_2, 300 K): δ = 2.31-2.37 (m, 1H, C**H**$_2$), 2.50-2.55 (m, 1H, C**H**$_2$), 3.04 (s, 3H, OC**H**$_3$), 3.51-3.56 (m, 1H, C**H**CO_2Me), 4.48 (dd, *J*(H,H) = 9.6 Hz, *J*(H,H)= 7.5 Hz, 1H, C**H**Py), 4.84 (d, *J*(H,H) = 8.9 Hz, 1H, C**H**Naph), 7.23 (ddd, *J*(H,H) = 7.4 Hz, *J*(H,H) = 4.8 Hz, *J*(H,H) = 1.3 Hz, 1H, Py-**H**), 7.44-7.49 (m, 2H, Naph-**H**), 7.55 (dd, *J*(H,H) = 8.5 Hz, *J*(H,H) = 1.8 Hz, 1H, Naph-**H**), 7.69 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.0 Hz, 1H, Py-**H**), 7.75 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H)= 1.8 Hz, 1H, Py-**H**), 7.80 (d, *J*(H,H) = 8.6 Hz, 1H, Naph-**H**), 7.82-7.85 (m, 2H, Naph-**H**), 7.92 (s, 1H, Naph-**H**), 8.58 (ddd, *J*(H,H) = 4.8 Hz, *J*(H,H) = 1.8 Hz, *J*(H,H) = 0.9 Hz, 1H, Py-**H**).

$^{13}C\{^1H\}$ NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 36.6 (**C**H_2), 50.0 (**C**HCO_2Me), 50.8 (O**C**H_3), 63.5 (**C**HPy), 65.3 (**C**HNaph), 121.3 (**Py**-H), 122.2 (**Py**-H), 125.6 (**Naph**-H), 125.8 (**Naph**-H), 125.8 (**Naph**-H), 125.9 (**Naph**-H), 127.3 (**Naph**-H), 127.5 (**Naph**-H), 127.8 (**Naph**-H), 132.8 (**Naph**-C), 133.1 (**Naph**-C), 136.5 (**Py**-H), 138.4 (**Naph**-C), 148.9 (**Py**-H), 162.2 (**Py**-C), 173.4 (**C**O).

MS (FAB) m/z (rel int): 333 (M + 1, 100), 246 (22), 230 (11), 178 (5), 141 (5), 118 (6), 108 (12), 80 (6).

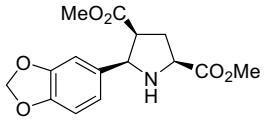
IR (NaCl) : $\tilde{\upsilon}$ [cm^{-1}] = 3328w, 3265w, 3054w, 3011w, 2948m, 2848m, 1951w, 1731s, 1633w, 1592s, 1507w, 1435m, 1368m, 1314m, 1296m, 1168s, 1086m, 1041m, 945m, 893w, 858m, 819m, 753m.

144b:

^1H NMR (500.1 MHz, CD_2Cl_2, 300 K): δ = 2.31-2.38 (m, 1H, C**H**$_2$), 2.48-2.55 (m, 1H, C**H**$_2$), 3.22 (s, 3H, OC**H**$_3$), 3.52-3.59 (m, 1H, C**H**CO_2Me), 4.48 (dd, *J*(H,H) = 10.0 Hz, *J*(H,H)= 6.8 Hz, 1H, C**H**Py), 4.77 (d, *J*(H,H) = 9.1 Hz, 1H, C**H**Naph), 7.18 (ddd, *J*(H,H) = 7.5 Hz, *J*(H,H) = 4.8 Hz, *J*(H,H) = 1.3 Hz, 1H, Py-**H**), 7.45-7.55 (m, 3H, Naph-**H**), 7.69 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.8 Hz, 1H, Py-**H**), 7.76 (dd, *J*(H,H) = 8.3 Hz, *J*(H,H)= 1.5 Hz, 1H, Py-**H**), 7.84-7.89 (m, 3H, Naph-**H**), 7.92 (s, 1H, Naph-**H**), 7.89 (br s, 1H, Naph-**H**), 8.51-8.53 (m, 1H, Py-**H**).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan : iPrOH (92 : 8), 0.5 ml/min, 30 °C, *endo* (**144a**) t_R = **51.7** min, 76.6 min/ *exo* (**144b**) t_R = **42.1** min, 69.7 min, $\lambda_{local\ max}$ 225 nm, 265 nm.

(+)-Dimethyl 5-(benzo[d][1,3]dioxol-5-yl)pyrrolidine-2,4-dicarboxylate (140a)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{15}H_{17}NO_6$ (307.30).

colorless solid. $\mathbf{R}_f$ = 0.21 (Hx : EtOAc 1 : 1).

m.p. 65-68 °C.

$[\alpha]_D^{20}$ = +16.1° (c = 0.670, $CHCl_3$, 47% *ee*).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 300 K): δ = 2.33 (m, 2H, C**H**$_2$), 2.60 (br s, 1H, N**H**), 3.24 (q, *J*(H,H) = 7.5 Hz, 1H, C**H**CO_2Me), 3.29 (s, 3H, OC**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 3.91 (t, *J*(H,H) = 8.3 Hz, 1H, NHC**H**CO_2Me), 4.43 (d, *J*(H,H) = 8.0 Hz, 1H, C**H**Ph), 5.93 (s, 2H, OC**H**$_2$O), 6.73 (d, *J*(H,H) = 8.0 Hz, 1H, Ph-**H**), 6.77 (dd, *J*(H,H) = 8.0 Hz, *J*(H,H) = 2.0 Hz, 1H, Ph-**H**), 6.84 (d, *J*(H,H) = 1.5 Hz, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2, 300 K): δ = 32.8 (**C**H_2), 49.5 (**C**HCO_2Me), 51.1 (O**C**H_3), 52.0 (O**C**H_3), 59.6 (NH**C**HCO_2Me), 65.1 (**C**HPh), 101.2 (OC**H**$_2$O), 107.4 (**Ph**-H), 107.6 (**Ph**-H), 120.1 (**Ph**-H), 133.8 (**Ph**-C), 146.8 (**Ph**-C), 147.5 (**Ph**-C), 172.8 (**C**O), 173.8 (**C**O).

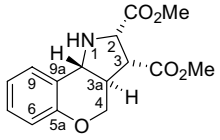
MS (FAB) m/z (rel int): 308 (M + 1, 100), 248 (17), 221 (31), 216 (10), 188 (10), 161 (14).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3435w, 3282w, 3050w, 2956m, 2891m, 1733s, 1612m, 1493s, 1439s, 1359m, 1289m, 1240s, 1206s, 1172s, 1106m, 1032m, 926m, 880w, 814m.

EA % found (calcd): C: 58.74 (58.63), H: 5.50 (5.58), N: 4.61 (4.56).

HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : iPrOH (80 : 20), 0.5 ml/min, 25 °C, t_R = 37.2 min, **49.9** min, $\lambda_{local\ max}$ 206 nm, 286 nm.

(2*S*,3*R*,3a*R*,9b*R*)-1,2,3,3a,4,9b-Hexahydro-5-oxa-1-aza-cyclopenta[a]naphthalene-2,3-dicarboxylic acid dimethyl ester (161)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{15}H_{17}NO_5$ (291.30).

white solid. $\mathbf{R}_f$ = 0.29 (Hx : EtOAc 1 : 1).

m.p. 132-134 °C.

$[\alpha]_D^{20}$ = +19.5° (c = 0.930, $CHCl_3$, 96% *ee*).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 2.34 (qd, *J*(H,H) = 11.5 Hz, *J*(H,H) = 4.3 Hz, 1H, **H**-3a), 2.55 (br s, 1H, **H**-1), 3.08 (dd, *J*(H,H) = 11.9 Hz, *J*(H,H) = 10.0 Hz, 1H, **H**-3), 3.67 (s, 3H, C(3)CO_2C**H**$_3$), 3.69 (s, 3H, C(2)CO_2C**H**$_3$), 3.77 (d, *J*(H,H) = 11.2 Hz, 1H, **H**-9b), 4.18 (dd, *J*(H,H) = 11.5 Hz, *J*(H,H) = 10.1 Hz, 1H, **H**-4), 4.38 (d, *J*(H,H) = 10.1 Hz, 1H, **H**-2), 4.57 (dd, J(H,H) = 10.1 Hz, *J*(H,H) = 4.3 Hz, 1H, **H**-4), 6.81 (dd, *J*(H,H) = 7.1 Hz, *J*(H,H) =

1.0 Hz, *J*(H,H) = 1.4 Hz, 1H, **H**-6), 6.89 (td, *J*(H,H) = 6.3 Hz, *J*(H,H) = 1.1 Hz, 1H, **H**-8), 7.13–7.17 (m, 1H, **H**-7), 7.25 (dd, *J*(H,H) = 4.7 Hz, *J*(H,H) = 1.5 Hz, 1H, **H**-9).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 47.0 (**C**-3a), 50.3 (**C**-3), 52.7 (C(3)CO_2**C**H_3), 52.9 (C(2)CO_2**C**H_3), 60.6 (**C**-9b), 64.6 (**C**-2), 69.8 (**C**-4), 116.4 (**C**-6), 120.7 (**C**-8), 125.1 (**C**-9), 125.3 (**C**-9a), 129.1 (**C**-7), 153.7 (**C**-5a), 172.3 (C(3)**C**O), 172.3 (C(2)**C**O).

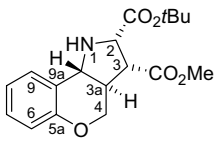
MS (FAB) m/z (rel. Int. %): 292 (100, [M^+ + H]), 290 (28), 232 (32).

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 3301m, 2988w, 2946m, 1732s, 1622m, 1599m, 1512m, 1471m, 1433m, 1386m, 1370m, 1270s, 1226s, 1208s, 1171m, 1132s, 1109m, 1038m, 1024m, 973m, 902m, 880m,828m, 785m, 754m, 645w, 517w, 443w.

EA % found (calcd): C: 61.92 (61.85), H: 5.83 (5.88), N: 4.71 (4.81).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (90 : 10), 0.5 ml/min, 25 °C, t_R = **35** min, 48 min, $\lambda_{local\ max}$ 205 nm, 277 nm.

(2*S*,3*R*,3a*R*,9b*R*)-Hexahydro-5-oxa-1-aza-cyclopenta[a]naphthalene-2,3-dicarboxylic acid 2-*tert*-butyl ester 3-methyl ester (165)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{18}H_{23}NO_5$ (333.38).

white solid. $\mathbf{R}_f$ = 0.52 (Hx : EtOAc 4 : 1).

m.p. 98-100 °C.

$[\alpha]_D^{20}$ = +18.1° (c = 0.800, $CHCl_3$, 99% *ee*).

^{1}H NMR (500.0 MHz, CD_2Cl_2, 295 K): δ = 1.43 (s, 9H, C(C**H**$_3$)$_3$), 2.33 (qd, *J*(H,H) = 11.6 Hz, *J*(H,H) = 4.3 Hz, 1H, **H**-3a), 2.49 (bs, 1H, **H**-1), 3.02 (dd, *J*(H,H) = 11.6 Hz, *J*(H,H) = 10.4 Hz, 1H, **H**-3), 3.70 (s, 3H, OC**H**$_3$), 3.71-3.75 (m, 1H, **H**-9b), 4.15 (dd, *J*(H,H) = 11.6 Hz, *J*(H,H) = 10.4 Hz, 1H, **H**-4), 4.24 (d, *J*(H,H) = 9.1 Hz, 1H, **H**-2), 4.55 (dd, *J*(H,H) = 10.1 Hz, *J*(H,H) = 4.3 Hz, 1H, **H**-4), 6.80 (d, *J*(H,H) = 8.1 Hz, 1H, **H**-6), 6.88 (t, *J*(H,H) = 7.6 Hz, 1H, **H**-8), 7.15 (t, *J*(H,H) = 7.6 Hz, 1H, **H**-7), 7.26 (d, *J*(H,H) = 7.3 Hz, 1H, **H**-9).

$^{13}C\{^1H\}$ NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 28.2 (3C, C(**C**H_3)$_3$), 47.3 (**C**-3a), 50.4 (**C**-3), 52.5 (O**C**H_3), 60.4 (**C**-9b), 64.8 (**C**-2), 69.9 (**C**-4), 82.8 (**C**$(CH_3)_3$), 116.4 (**C**-6), 120.6 (**C**-8), 125.1 (**C**-9), 125.5 (**C**-9a), 129.0 (**C**-7), 153.7 (**C**-5a), 170.8 (C(2)**C**O), 172.4 (C(3)**C**O).

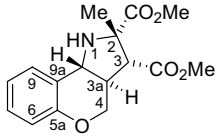
MS (FAB) m/z (rel. Int. %): 334 (60, $[M^+ + H]$), 278 (100), 232 (64), 172 (12), 131 (9), 57 (62), 41 (22).

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 3378w, 3259w, 2970w, 1735s, 1648w, 1577w, 1486w, 1451m, 1382m, 1314m, 1288m, 1212s, 1172m, 1095w, 1059w, 913w, 842w,822w, 763m.

EA % found (calcd): C: 64.86 (64.85), H: 6.92 (6.95), N: 4.22 (4.20).

HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (90 : 10), 0.5 ml/min, 20 °C, t_R = **33 min**, 52 min, λ_{max} 205 nm, 276 nm.

(2*S*,3*R*,3a*R*,9b*R*)-9b-Methyl-1,2,3,3a,4,9b-hexahydro-5-oxa-1-aza-cyclopenta[a]naphthalene-2,3-dicarboxylic acid dimethyl ester (166)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{16}H_{19}NO_5$ (305.33).

white solid. $\mathbf{R}_f$ = 0.38 (Hx : EtOAc 5 : 1).

m.p. 137-139 °C.

$[\alpha]_D^{20}$ = +12.0° (c = 0.980, $CHCl_3$, 96% *ee*).

^1H NMR (500.0 MHz, CD_2Cl_2, 295 K): δ = 1.66 (s, 3H, C(2)C**H**$_3$), 2.48 (dq, *J*(H,H) = 11.6 Hz, *J*(H,H) = 4.3 Hz, 1H, **H**-3a), 2.65 (d, *J*(H,H) = 12.1 Hz, 1H, **H**-3), 2.77 (s, 1H, **H**-1), 3.65 (s, 3H, C(2)CO_2C**H**$_3$), 3.67 (s, 3H, C(3)CO_2C**H**$_3$), 3.90 (d, *J*(H,H) = 11.1 Hz, 1H, **H**-9b), 4.14 (dd, *J*(H,H) = 11.4 Hz, *J*(H,H) = 10.1 Hz, 1H, **H**-4), 4.55 (dd, *J*(H,H) = 10.1 Hz, *J*(H,H) = 4.3 Hz, 1H, **H**-4), 6.80 (d, *J*(H,H) = 8.1 Hz, 1H, **H**-6), 6.87 (t, *J*(H,H) = 6.8 Hz, 1H, **H**-8), 7.12-7.20 (m, 2H, **H**-7, **H**-9).

$^{13}C\{^1H\}$ NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 27.4 (C(2)**C**H_3), 47.0 (**C**-3a), 52.6 (C(3)CO_2**C**H_3), 53.1 (C(2)CO_2**C**H_3), 58.5 (**C**-3), 58.9 (**C**-9b), 69.9 (**C**-4), 70.6 (**C**-2), 116.4 (**C**-6), 120.6 (**C**-8), 125.1 (**C**-9), 125.6 (**C**-9a), 128.9 (**C**-7), 153.8 (**C**-5a), 172.1 (C(3)**C**O), 174.3 (C(2)**C**O).

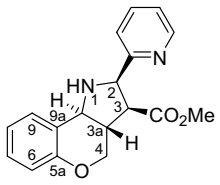
MS (FAB) m/z (rel. Int. %): 306 (100, [M^+ + H]), 246 (62), 214 (6), 186 (8), 173 (6), 131 (8), 102 (27), 42 (7).

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 3445s, 3326w, 2986w, 2889w, 1727s, 1608w, 1576w, 1488m, 1439m, 1375w, 1326w, 1212s, 1170m, 1097w, 1037w, 989m, 916w, 869w,831w, 770m.

EA % found (calcd): C: 63.05 (62.94), H: 6.21 (6.27), N: 4.64 (4.59).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (90 : 10), 0.5 ml/min, 25 °C, t_R = **27 min**, 58 min, $\lambda_{local\ max}$ 205 nm, 275 nm.

(2*R*,3*S*,3a*S*,9b*S*)-2-Pyridin-2-yl-1,2,3,3a,4,9b-hexahydro-5-oxa-1-aza-cyclopenta[a]naphthalene-3-carboxylic acid methyl ester (156)



The synthesis was performed according to **general procedure IX** (page 190).

$C_{18}H_{18}N_2O_3$ (310.35).

white solid. $\mathbf{R}_f$ = 0.10 (Hx : EtOAc 1 : 1).

m.p. 92-94 °C.

$[\alpha]_D^{20}$ = -30.1° (c = 0.560, $CHCl_3$, 83% *ee*).

^{1}H NMR (500.0 MHz, CD_2Cl_2, 295 K): δ = 2.60 (dqd, *J*(H,H) = 11.7 Hz, *J*(H,H) = 4.4 Hz, *J*(H,H) = 0.3 Hz, 1H, **H**-3a), 3.17 (dd, *J*(H,H) = 11.8 Hz, *J*(H,H) = 10.2 Hz, 1H, **H**-3), 3.21 (s, 3H, C(3)$CO_2C\mathbf{H}_3$), 3.90 (dt, *J*(H,H) = 11.2 Hz, *J*(H,H) = 1.1 Hz, 1H, **H**-9b), 4.17 (dd, *J*(H,H) = 11.7 Hz, *J*(H,H) = 9.9 Hz, 1H, **H**-4), 4.54 (dd, *J*(H,H) = 9.9 Hz, *J*(H,H) = 4.3 Hz, 1H, **H**-4), 4.99 (d, *J*(H,H) = 10.1 Hz, 1H, **H**-2), 6.83 (dd, *J*(H,H) = 8.2 Hz, *J*(H,H) = 1.1 Hz, 1H, **H**-6), 6.90 (td, *J*(H,H) = 7.4 Hz, *J*(H,H) = 1.2 Hz, 1H, **H**-8), 7.16 (dddd, *J*(H,H) = 8.3 Hz, *J*(H,H) = 7.5 Hz, *J*(H,H) = 1.8 Hz, *J* (H,H) = 0.8 Hz, 1H, **H**-7), 7.17 (ddd, *J*(H,H) = 7.5 Hz, *J*(H,H) = 4.8 Hz, *J*(H,H) = 1.2 Hz, 1H, **Py**(5)), 7.32 (dddd, *J*(H,H) = 7.5 Hz, *J*(H,H) = 1.7 Hz, *J*(H,H) = 1.2 Hz, *J* (H,H) = 0.5 Hz, 1H, **H**-9), 7.33 (dt, *J*(H,H) = 7.8 Hz, *J*(H,H) = 1.1 Hz, 1H, **Py**(3)), 7.65 (td, *J*(H,H) = 7.6 Hz, *J*(H,H) = 1.8 Hz, 1H, **Py**(4)), 8.46 (ddd, *J*(H,H) = 4.8 Hz, *J*(H,H) = 1.7 Hz, *J*(H,H) = 1.0 Hz, 1H, **Py**(6)) (NH not visible).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 45.3 (**C**-3a), 51.5 (C(3)$CO_2\mathbf{C}H_3$), 52.5 (**C**-3), 60.3 (**C**-9b), 66.8 (**C**-2), 70.1 (**C**-4), 116.2 (**C**-6), 120.3 (**C**-8), 123.0 (**Py**(5)), 123.8

(**Py**(3)), 125.1 (**C**-9), 126.0 (**C**-9a), 128.7 (**C**-7), 136.5 (**Py**(4)), 149.2 (**Py**(6)), 153.8 (**C**-5a), 159.0 (**Py**(2)), 171.6 (C(3)**C**O).

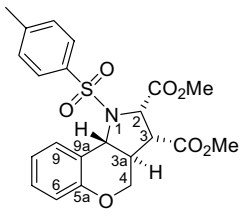
MS (FAB) m/z (rel. Int. %): 311 (100, [M^+ + H]), 310 (22), 309 (25), 290 (28), 232 (32), 131 (13), 108 (36), 107 (42), 89 (11), 78 (11), 77 (19), 73 (12), 57 (12), 55 (12), 51 (13), 43 (14), 41 (14), 39 (15).

IR (KBr): $\tilde{\upsilon}$ [cm^{-1}] = 3433w, 2947m, 2925m, 2868m, 2400w, 1723s, 1594m, 1571m, 1484m, 1455s, 1426s, 1374m, 1314m, 1254m, 1201s, 1171s, 1135m, 1082m, 1032m, 982s, 931m, 881m, 812m, 750s, 677w, 632w.

EA % found (calcd): C: 69.68 (69.66), H: 5.91 (5.85), N: 8.97 (9.03).

HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (90 : 10), 0.5 ml/min, 25 °C, t_R = 49 min, **99 min**, $\lambda_{local\ max}$ 205 nm, 263 nm.

(2*S*,3*R*,3a*R*,9b*R*)-1-(Toluene-4-sulfonyl)-1,2,3,3a,4,9b-hexahydro-5-oxa-1-aza-cyclopent-[a]naphthalene-2,3-dicarboxylic acid dimethyl ester (162)



Triethylamine (115 µL, 0.83 mmol) was added to a solution of p-toluenesufonyl chloride (159 mg, 0.83 mmol) and 1,2,3,3a,4,9b-hexahydro-5-oxa-1-aza-cyclopenta[a]naphthalene-2,3-dicarboxylic acid dimethyl ester (157 mg, 0.54 mmol) in dichloromethane (20.0 mL). The reaction mixture was heated to reflux for 20 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc : Hx 1 : 1, $\mathbf{R}_f$ = 0.35) on silica to give a colorless solid (200 mg, 83%). Crystals suitable for X-ray analysis were obtained from ethyl acetate/pentane.

$C_{22}H_{23}NO_7S$ (445.49).

Colorless solid.

m.p. 178-180 °C.

$[\alpha]_D^{20}$ = +107.3° (c =0.780, $CHCl_3$, 97% *ee*).

^{1}H NMR (400.1 MHz, CD_2Cl_2, 295 K): δ = 2.43 (dd, *J*(H,H) = 12.6 Hz, *J*(H,H)= 7.8 Hz, 1H, **H**-3), 2.47 (s, 3H, C**H**$_3$), 3.01 (dq, *J*(H,H) = 12.0 Hz, *J*(H,H) = 5.2 Hz 1H, **H**-3a), 3.60 (s, 3H,

C(2)$CO_2C\mathbf{H}_3$), 3.63 (s, 3H, C(3)$CO_2C\mathbf{H}_3$), 4.05 (dd, *J*(H,H) = 12.0 Hz, *J*(H,H) = 9.7 Hz, 1H, **H**-4), 4.32 (d, *J*(H,H) = 11.0 Hz, 1H, **H**-9b), 4.56 (dd, *J*(H,H) = 9.6 Hz, *J*(H,H) = 5.2 Hz, 1H, **H**-4), 4.75 (d, *J*(H,H) = 7.9 Hz, 1H, **H**-2), 6.82 (dd, *J*(H,H) = 8.1 Hz, *J*(H,H) = 1.1 Hz, 1H, **H**-6), 6.95 (dt, *J*(H,H) = 7.5 Hz, *J*(H,H) = 1.0 Hz, 1H, **H**-8), 7.17-7.21 (m, 1H, **H**-7), 7.43 (d, *J*(H,H) = 8.0 Hz, 2H, $Ph_{(Tos)}$-**H**), 7.69 (dt, *J*(H,H) = 7.7 Hz, *J*(H,H) = 1.3 Hz, 1H, **H**-9), 7.82 (d, *J*(H,H) = 8.3 Hz, 2H, $Ph_{(Tos)}$-**H**).

$^{13}C\{^1H\}$ NMR (100.6 MHz, CD_2Cl_2, 295 K): δ = 22.0 (**C**H_3), 43.5 (**C**-3a), 47.3 (**C**-3), 52.9 (C(3)$CO_2\mathbf{C}H_3$), 53.2 (C(2)$CO_2\mathbf{C}H_3$), 63.1 (**C**-9b), 65.6 (**C**-2), 70.1 (**C**-4), 116.5 (**C**-6), 120.8 (**C**-8), 125.7 (**C**-9), 126.9 (**C**-9a), 128.9 (2C, $\mathbf{Ph}_{(Tos)}$-H), 129.2 (**C**-7), 130.8 (2C, $\mathbf{Ph}_{(Tos)}$-H), 133.1 ($\mathbf{Ph}_{(q)(Tos)}$), 145.9 ($\mathbf{Ph}_{(q)(Tos)}$), 153.8 (**C**-5a), 169.1 (C(3)**C**O), 169.9 (C(2)**C**O).

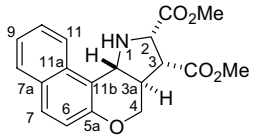
MS (FAB) m/z (rel int %): 446 (M + H, 100), 386 (51), 290 (60), 230 (63), 172 (13), 132 (11), 91 (70), 77 (23), 63 (16), 57 (15), 51 (23), 41 (19).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3449m, 3057w, 2956m, 1743s, 1607w, 1484m, 1454m, 1359s, 1326m, 1213s, 1167s, 1032m, 823m, 759m, 667s, 591w, 547w.

EA % found (calcd): C: 59.55 (59.32), H: 5.22 (5.20), N: 3.14 (3.14).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (90 : 10), 0.5 mL/min., 25 °C, t_R = 43 min, 47 min, $\lambda_{local\ max}$ 204 nm, 224 nm.

(2*S,3*R**,3a*R**,11c*R**)-1,2,3,3a,4,11c-hexahydro-5-oxa-1-aza-cyclopenta[c]phenanthrene-2,3-dicarboxylic acid dimethyl ester (170a)**



The synthesis was performed according to **general procedure IX** (page 190).

$C_{19}H_{19}NO_5$ (341.13).

colorless solid. $\mathbf{R}_f$ = 0.15 (Hx : EtOAc 2 : 1).

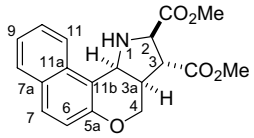
^1H NMR (500.1 MHz, CD_2Cl_2, 300 K): δ = 2.55 (dq, *J*(H,H) = 11.7 Hz, *J*(H,H) = 3.8 Hz, 1H, **H**-3a), 2.59 (bd, *J*(H,H) ≈ 11 Hz, 1H, **H**-1), 3.12 (dd, *J*(H,H) = 11.7 Hz, *J*(H,H) = 10.8 Hz, 1H, **H**-3), 3.70 (s, 3H, C(3)$CO_2C\mathbf{H}_3$), 3.71 (s, 3H, C(2)$CO_2C\mathbf{H}_3$), 4.08 (bt, *J*(H,H) = 11.5 Hz, 1H, **H**-11c), 4.22 (dd, *J*(H,H) = 11.7 Hz, *J*(H,H) = 10.2 Hz, 1H, **H**-4), 4.45 (bt, *J*(H,H) = 9.5 Hz, 1H, **H**-2), 4.57 (dd, *J*(H,H) = 10.2 Hz, *J*(H,H) = 3.7 Hz, 1H, **H**-4), 7.04 (d, *J*(H,H) = 9.1

Hz, 1H, **H**-6), 7.32 (m, 1H, **H**-9), 7.44 (m, 1H, **H**-10), 7.67 (bd, *J*(H,H) = 8.8 Hz, 1H, **H**-7), 7.74 (bd, *J*(H,H) = 8.1 Hz, 1H, **H**-8), 8.75 (bd, *J*(H,H) = 8.8 Hz, 1H, **H**-11).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 300 K): δ = 49.0 (**C**-3a), 49.2 (**C**-3), 52.5 (C(3)CO_2**C**H_3), 52.8 (C(2)CO_2**C**H_3), 60.2 (**C**-11c), 64.0 (**C**-3a), 68.5 (**C**-4), 115.9 (**C**-11b), 118.7 (**C**-6), 123.7 (**C**-9), 126.1 (**C**-11), 126.4 (**C**-10), 128.3 (**C**-8), 129.3 (**C**-7a), 129.7 (**C**-7), 132.8 (**C**-11a), 152.3 (**C**-5a), 172.4 (C(3)**C**O_2CH_3), 172.5 (C(2)**C**O_2CH_3).

HPLC: Daicel Chiralcel AD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (90 : 10), 0.5 ml/min, 25 °C, t_R = **41 min**, 49 min, $\lambda_{local\ max}$ 231 nm, 276 nm.

(2*R,3*R**,3a*R**,11c*S**)-1,2,3,3a,4,11c-hexahydro-5-oxa-1-aza-cyclopenta[c]phenanthrene-2,3-dicarboxylic acid dimethyl ester (170b)**



$C_{19}H_{19}NO_5$ (341.13).

m.p. 80–83 °C.

R_f = 0.17 (Hx : EtOAc 5:1).

^{1}H NMR (500.0 MHz, CD_2Cl_2, 295 K): δ = 2.60 (br s, 1H, **H**-1), 2.84 (dddd, *J*(H,H) = 11.2 Hz, *J*(H,H) = 6.1 Hz, *J*(H,H) = 4.9 Hz, *J*(H,H) = 3.5 Hz, 1H, **H**-3a), 2.86 (dd, *J*(H,H) = 6.6 Hz, *J*(H,H) = 3.5 Hz, 1H, **H**-3), 3.67 (s, 3H, C(3)CO_2C**H**$_3$), 3.79 (t, *J*(H,H) = 10.7 Hz, 1H, **H**-4), 3.79 (s, 3H, C(2)CO_2C**H**$_3$), 4.20-4.25 (m, 1H, **H**-3), 4.28 (d, *J*(H,H) = 6.4 Hz, 1H, **H**-2), 4.63 (d, *J*(H,H) = 5.8 Hz, 1H, **H**-11c), 7.07 (d, *J*(H,H) = 8.9 Hz, 1H, **H**-6), 7.37 (ddd, *J*(H,H) = 8.1 Hz, *J*(H,H) = 6.9 Hz, *J*(H,H) = 1.2 Hz, 1H, **H**-9), 7.53 (ddd, *J*(H,H) = 8.5 Hz, *J*(H,H) = 6.9 Hz, *J*(H,H) = 1.4 Hz, 1H, **H**-10), 7.70 (dq, *J*(H,H) = 8.9 Hz, *J*(H,H) = 0.5 Hz, 1H, **H**-7), 7.77 (ddt, *J*(H,H) = 8.1 Hz, *J*(H,H) = 1.4 Hz, *J*(H,H) = 0.7 Hz, 1H, **H**-8), 8.20 (dq, *J*(H,H) = 8.5 Hz, *J*(H,H) = 0.9 Hz, 1H, **H**-11).

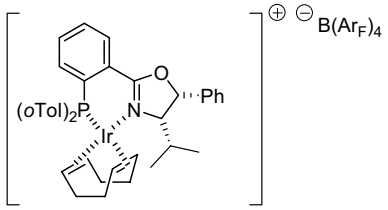
^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 42.0 (**C**-3a), 50.9 (**C**-3), 52.7 (C(3)CO_2**C**H_3), 52.8 (C(2)CO_2**C**H_3), 54.3 (**C**-11c), 62.8 (**C**-2), 65.2 (**C**-4), 114.6 (**C**-11b), 118.8 (**C**-6), 123.9 (**C**-11), 124.1 (**C**-9), 127.1 (**C**-10), 128.5 (**C**-8), 129.7 (**C**-7a), 129.8 (**C**-7), 133.8 (**C**-11a), 152.8 (**C**-5a), 173.2 (C(3)**C**O_2CH_3), 173.5 (C(2)**C**O_2CH_3);

MS (FAB) m/z (rel. Int. %): 342 (M+1,100), 341 (22), 340 (10), 282 (30), 182 (27), 181 (12).

13.5 Asymmetric Hydrogenation of Olefines and Imines

13.5.1 Preparation of Ir(I)-PHOX Complexes

(4*S*,5*R*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5-phenyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (196)



General Procedure X:

A solution of the (4*S*,5*R*)-2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5-phenyl-4,5-dihydrooxazole (70.0 mg, 0.15 mmol) in dichloromethane (3.00 mL) was added to a solution of $[Ir(COD)Cl]_2$ (49.0 mg, 0.07 mmol) in dichloromethane (3.00 mL). The reaction mixture was heated to reflux for 2 h before $NaB(Ar_F)_4$ (203 mg, 0.23 mmol) was added at rt followed by H_2O (6.00 mL). The resulting two-phase mixture was stirred vigorously for 10 min. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 6 mL). The combined organic extracts were washed with H_2O (6 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (Diethyl ether : DCM 4 : 1) on silica to afford the pure complex **196** as a red solid (200 mg, 81%).

$C_{72}H_{56}NOPF_{24}BIr$ (1641.18).

m.p. 86-89 °C.

$[\alpha]_D^{20}$ = -161.5° (c = 0.390, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = 0.06 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 0.25 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 1.12 (br s, 1H, C**H**$_{2(COD)}$), 1.27 (br s, 1H, C**H**$_{2(COD)}$), 1.60 (br s, 1H, C**H**(CH$_3$)$_2$), 1.66-1.75 (m, 2H, C**H**$_{2(COD)}$), 1.88-1.98 (m, 2H, C**H**$_{2(COD)}$), 2.04-2.17 (m, 2H, C**H**$_{2(COD)}$), 2.15 (s, 3H, *o*Tol-C**H**$_3$), 2.40 (br s, 3H, *o*Tol-C**H**$_3$), 2.66 (br s, 1H, C**H**$_{(COD)}$), 3.15 (br s, 1H, C**H**$_{(COD)}$), 3.98 (dd, *J*(H,H) = 8.9 Hz, *J*(H,H) = 2.7 Hz, 1H, NC**H**), 4.42-4.48 (m, 1H, C**H**$_{(COD)}$), 4.66 (br s, 1H, C**H**$_{(COD)}$), 5.36 (d, *J*(H,H) = 8.9 Hz, 1H, OC**H**), 6.61 (dd, *J*(H,P) = 12.0 Hz, *J*(H,H) = 7.9 Hz, 1H, Ar-**H**), 6.81-6.86 (m, 2H, Ar-**H**), 6.92-6.98

(m, 5H, Ar-**H**), 7.00-7.04 (m, 2H, Ar-**H**), 7.06-7.12 (m, 5H, Ar-**H**), 7.13-7.17 (m, 1H, Ar-**H**), 7.64 (br s, 4H, $B(Ar_F)_4$-**H**), 7.95 (ddd, *J*(H,P) = 8.1 Hz, *J*(H,H) = 4.3 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 8.19 (br s, 8H, $B(Ar_F)_4$-**H**).

$^{13}C\{^1H\}$ NMR (125.8 MHz, toluene-d_8, 340 K): δ = 17.3 ($CH(\mathbf{C}H_3)_2$), 17.5 ($CH(\mathbf{C}H_3)_2$), 24.2 (d, *J*(C,P) = 6.2 Hz, *o*Tol-$\mathbf{C}H_3$), 25.1 (d, *J*(C,P) = 6.1 Hz, *o*Tol-$\mathbf{C}H_3$), 26.0 (d, *J*(C,P) = 1.9 Hz, $\mathbf{C}H_{2(COD)}$), 28.4 ($\mathbf{C}H_{2(COD)}$), 31.8 ($\mathbf{C}H(CH_3)_2$), 32.9 ($\mathbf{C}H_{2(COD)}$), 35.6 (d, *J*(C,P) = 4.8 Hz, $\mathbf{C}H_{2(COD)}$), 67.3 ($\mathbf{C}H_{(COD)}$), 67.6 ($\mathbf{C}H_{(COD)}$), 74.0 (N**C**H), 86.5 (O**C**H), 90.2 (d, *J*(C,P) = 13.9 Hz, $\mathbf{C}H_{(COD)}$), 94.8 (d, *J*(C,P) = 10.6 Hz, $\mathbf{C}H_{(COD)}$), 118.1 (sept, *J*(C,F) = 3.8 Hz, 4C, $B(Ar_F)_4$-H), 120.5 (d, *J*(C,P) = 53.2 Hz, ***o*Tol**$_{(ipso)}$-P), 125.5 (q, *J*(C,F)= 272.6 Hz, 8C, $\mathbf{C}F_3$), 126.3 (2C, **Ar**-H), 127.3 (d, *J*(C,P)= 11.0 Hz, **Ar**-H), 127.4 (d, *J*(C,P)= 10.1 Hz, **Ar**-H), 129.6 (2C, Ar-H), 130.2 (d, *J*(C,P) = 48.5 Hz, **oTol**$_{(ipso)}$-P), 130.2 (qq, *J*(C,F) = 31.7 Hz, *J*(C,B) = 2.9 Hz, 8C, **Ar**-CF_3), 131.6 (**Ar**-H), 132.5 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.8 (d, *J*(C,P) = 2.3 Hz, **Ar**-H), 132.9 (**Ar**-H), 133.0 (**Ar**-H), 133.1 (d, *J*(C,P) = 1.4 Hz, **Ar**-H), 133.3 (d, *J*(C,P) = 8.1 Hz, **Ar**-H), 133.6 (d, *J*(C,P) = 6.7 Hz, **Ar**-H), 134.0 (d, *J*(C,P) = 9.6 Hz, **Ar**-H), 134.3 (d, *J*(C,P) = 8.2 Hz, **Ar**-H), 135.8 (**Ar**-H), 135.8 (br s, 8C, $B(Ar_F)_4$-H), 141.8 (d, *J*(C,P) = 9.6 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 143.7 (d, *J*(C,P) = 9.6 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 162.9 (q, J(C,B) = 49.9 Hz, 4C, **C**-B), 164.5 (d, *J*(C,P) = 6.2 Hz, **C**=N). (Three quaternary C-atoms are not visible).

$^{31}P\{^1H\}$ NMR (202.5 MHz, toluene-d_8, 300 K): δ = 12.7.

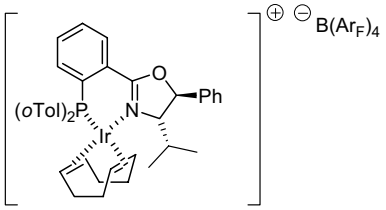
$^{19}F\{^1H\}$ NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.4 (m).

+ESIMS, CH_2Cl_2, m/e: 778 ($[M - B(Ar_F)_4]^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3449w, 3066w, 2966m, 2926m, 2889w, 1607m, 1456w, 1356s, 1279s, 1127s, 965w, 890m, 839w, 805w, 750w, 713m, 676m.

EA % found (calcd): C: 52.84 (52.69), H: 3.41 (3.44), N: 1.07 (0.85).

(4*S*,5*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Di*o*-t*o*lylphosphino)phenyl)-4-isopropyl-5-phenyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (195)



Complex **195** was prepared according to **general procedure X** (page 209) from (4*S*,5*R*)-2-(2-(Dio-t*o*lylphosphino)phenyl)-4-isopropyl-5-phenyl-4,5-dihydrooxazole (100 mg, 0.21 mmol), $[Ir(COD)Cl]_2$ (70.0 mg, 0.10 mmol), $NaB(Ar_F)_4$ (327 mg, 0.33 mmol) and dichloromethane as

a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **195** (290 mg, 84%) was isolated as a red solid.

$C_{72}H_{56}NOPF_{24}BIr$ (1641.18).

m.p. 80–83 °C.

$[\alpha]_D^{20}$ = -151.8° (c = 0.400, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = -0.01 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 0.68 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 0.97-1.05 (m, 1H, C**H**$_{2(COD)}$), 1.06-1.14 (m, 1H, C**H**$_{2(COD)}$), 1.56-1.63 (m, 2H, C**H**$_{2(COD)}$), 1.77-1.87 (m, 2H, C**H**$_{2(COD)}$), 1.95-2.06 (m, 3H, CH$_{2(COD)}$ & C**H**(CH$_3$)$_2$)), 2.12 (s, 3H, *o*Tol-C**H**$_3$), 2.37 (br s, 3H, *o*Tol-C**H**$_3$), 2.58 (br s, 1H, C**H**$_{(COD)}$), 3.10 (br s, 1H, C**H**$_{(COD)}$), 3.75 (app t, *J*(H,H) = 3.2 1H, NC**H**), 4.19-4.25 (m, 1H, C**H**$_{(COD)}$), 4.32 (br s, 1H, C**H**$_{(COD)}$), 5.04 (d, *J*(H,H) = 3.8 Hz, 1H, OC**H**), 6.61 (dd, *J*(H,P) = 12.8 Hz, *J*(H,H) = 7.9 Hz, 1H, Ar-**H**), 6.83-6.86 (m, 1H, Ar-**H**), 6.87-6.93 (m, 3H, Ar-**H**), 6.95-7.02 (m, 4H, Ar-**H**), 7.05-7.19 (m, 7H, Ar-**H**), 7.65 (br s, 4H, B(Ar$_F$)$_4$-**H**), 7.93 (dd, *J*(H,P) = 7.9 Hz, *J*(H,H) = 7.9 Hz, 1H, Ar-**H**), 8.19 (br s, 8H, B(Ar$_F$)$_4$-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, toluene-d_8, 340 K): δ = 13.7 (CH(**C**H$_3$)$_2$), 18.2 (CH(**C**H$_3$)$_2$), 24.3 (d, *J*(C,P) = 6.2 Hz, *o*Tol-**C**H$_3$), 25.0 (d, *J*(C,P) = 6.1 Hz, *o*Tol-**C**H$_3$), 26.0 (d, *J*(C,P) = 1.9 Hz, **C**H$_{2(COD)}$), 28.3 (d, *J*(C,P) = 3.8 Hz, **C**H$_{2(COD)}$), 32.9 (d, *J*(C,P)= 1.0 Hz, **C**H$_{2(COD)}$), 33.0 (**C**H(CH$_3$)$_2$), 35.6 (d, *J*(C,P) = 5.2 Hz, **C**H$_{2(COD)}$), 67.3 (2C, **C**H$_{(COD)}$), 79.3 (N**C**H), 81.6 (O**C**H), 89.2 (d, *J*(C,P) = 13.9 Hz, **C**H$_{(COD)}$), 95.1 (d, *J*(C,P) = 10.0 Hz, **C**H$_{(COD)}$), 118.1 (sept, *J*(C,F) = 3.8 Hz, 4C, B(Ar$_F$)$_4$-H), 120.4 (d, *J*(C,P) = 59.0 Hz, ***o*Tol**$_{(ipso)}$-P), 124.7 (2C, **Ar**-H), 125.5 (q, *J*(C,F) = 272.6 Hz, 8C, **C**F$_3$), 127.3 (d, *J*(C,P) = 11.5 Hz, **Ar**-H), 127.4 (d, *J*(C,P) = 10.0 Hz, **Ar**-H), 129.7 (d, *J*(C,P) = 65.0 Hz, ***o*Tol**$_{(ipso)}$-P), 130.1 (2C, **Ar**-H), 130.2 (qq, *J*(C,F) = 31.1 Hz, *J*(C,B) = 2.8 Hz, 8C, **Ar**-CF$_3$), 130.3 (**Ar**-H), 132.5 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.8 (**Ar**-H), 132.9 (**Ar**-H), 132.9 (**Ar**-H), 133.2 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 133.3 (d, *J*(C,P) = 8.6 Hz, **Ar**-H), 133.4 (d, *J*(C,P) = 6.7 Hz, **Ar**-H), 133.8 (d, *J*(C,P) = 7.6 Hz, **Ar**-H), 134.0 (d, *J*(C,P) = 10.0 Hz, **Ar**-H), 135.6 (**Ar**-H), 135.8 (br s, 8C, B(Ar$_F$)$_4$-H), 138.4 (OCH-**Ph**$_{(ipso)}$), 141.8 (d, *J*(C,P) = 9.1 Hz, ***o*Tol**$_{(ortho)}$-CH$_3$), 143.8 (d, *J*(C,P) = 9.1 Hz, ***o*Tol**$_{(ortho)}$-CH$_3$), 162.9 (q, J(C,B) =49.9 Hz, 4C, **C**-B), 163.8 (d, *J*(C,P) = 6.7 Hz, **C**=N).(two quaternary C-atoms are not visible).

^{31}P{^{1}H} NMR (202.5 MHz, toluene-d_8, 300 K): δ = 13.4.

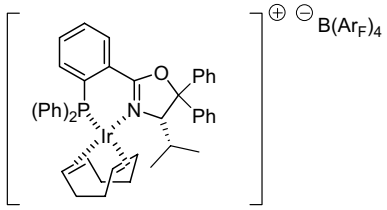
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.5 (m).

+ESIMS, CH_2Cl_2, m/e: 778 ([M - B(Ar$_F$)$_4$]$^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448w, 3066w, 2966m, 2926m, 1607m, 1457w, 1355s, 1279s, 1127s, 965w, 890m, 839w, 805w, 749w, 714m, 677m.

EA % found (calcd): C: 52.71 (52.69), H: 3.59 (3.44), N: 0.95 (0.85).

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Diphenylphosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl-phenyl]borate (193)



Complex **193** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Diphenylphosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (100 mg, 0.19 mmol), $[Ir(COD)Cl]_2$ (64.0 mg, 0.10 mmol), $NaB(Ar_F)_4$ (263 mg, 0.30 mmol) and dichloromethane as a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **193** (230 mg, 72%) was isolated as a red solid.

$C_{76}H_{56}NOPF_{24}BIr$ (1689.22).

m.p. 85–88 °C.

$[\alpha]_D^{20}$ = -104.0° (c = 0.170, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = -0.09 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 0.94 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 1.34-1.42 (m, 1H, C**H**$_{2(COD)}$), 1.62-1.70 (m, 1H, C**H**$_{2(COD)}$), 1.84-1.90 (m, 1H, C**H**$_{2(COD)}$), 2.01 (ds, *J*(H,P) = 6.9 Hz, *J*(H,H) = 2.1 Hz, 1H, C**H**(CH$_3$)$_2$)), 2.03-2.13 (m, 2H, C**H**$_{2(COD)}$), 2.22 (dd, *J*(H,P) = 15.6 Hz, *J*(H,H) = 8.4 Hz, 1H, C**H**$_{2(COD)}$), 2.47 (dd, *J*(H,P) = 15.6 Hz, *J*(H,H) = 7.4 Hz, 1H, **CH$_2$**$_{(COD)}$), 2.57-2.65 (m, 1H, C**H**$_{2(COD)}$), 2.89-2.94 (m, 1H, C**H**$_{(COD)}$), 3.44-3.47 (m, 1H, C**H**$_{(COD)}$), 4.36 (br s, 1H, C**H**$_{(COD)}$), 4.89 (d, *J*(H,H) = 2.2 Hz, 1H, NC**H**), 5.04-5.09 (m, 1H, C**H**$_{(COD)}$), 7.06-7.10 (m, 2H, Ph-**H**), 7.26-7.27 (m, 1H, Ph-**H**), 7.31-7.35 (m, 2H, Ph-**H**), 7.37-7.41 (m, 1H, Ph-**H**), 7.42-7.63 (m, 15H, Ph-**H**), 7.56 (br s, 4H, B(Ar$_F$)$_4$-**H**), 7.72 (br s, 8H, B(Ar$_F$)$_4$-**H**), 7.72 (tt, *J*(H,P) = 7.6 Hz, *J*(H,H)=1.1 Hz, 1H, Ph-**H**), 7.90 (tt, *J*(H,P) = 7.8 Hz, *J*(H,H) = 1.4 Hz, 1H, Ph-**H**), 8.72 (ddd, *J*(H,P) = 8.1 Hz, *J*(H,H) = 4.1 Hz, *J*(H,H) = 1.1 Hz, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 15.0 (CH(**C**H$_3$)$_2$), 20.2 (CH(**C**H$_3$)$_2$), 26.5 (d, *J*(C,P) = 1.9 Hz, **C**H$_{2(COD)}$), 27.7 (d, *J*(C,P) = 1.9 Hz, **C**H$_{2(COD)}$), 31.1 (**C**H(CH$_3$)$_2$), 32.9 (d, *J*(C,P) = 1.4 Hz, **C**H$_{2(COD)}$), 37.1 (d, *J*(C,P) = 4.8 Hz, **C**H$_{2(COD)}$), 63.9 (**C**H$_{(COD)}$), 64.3

(**C**H$_{(COD)}$), 78.9 (N**C**H), 94.3 (d, *J*(C,P) = 13.4 Hz, **C**H$_{(COD)}$), 94.5 (O**C**), 99.1 (d, *J*(C,P) = 10.6 Hz, **C**H$_{(COD)}$), 118.0 (sept, *J*(C,F) = 3.8 Hz, 4C, B(Ar$_F$)$_4$-H), 123.4 (d, *J*(C,P) = 57.6 Hz, **Ph**$_{(ipso)}$-P), 124.3 (2C, **Ph**-H), 125.4 (q, *J*(C,F) = 272.2 Hz, 8C, **C**F$_3$), 126.2 (2C, **Ph**-H), 128.9 (**Ph**-H), 129.2 (2C, **Ph**-H), 129.3 (**Ph**-H), 129.4 (**Ph**-H), 129.4 (d, *J*(C,P) = 47.0 Hz, **Ph**$_{(ortho)}$-P), 129.4 (qq, *J*(C,F) = 31.7 Hz, *J*(C,B) = 2.9 Hz, 8C, **Ar**-CF$_3$), 129.7 (d, *J*(C,P) = 13.0 Hz, **Ph**$_{(ipso)}$-CN), 129.8 (**Ph**-H), 129.9 (2C, **Ph**-H), 130.1 (d, *J*(C,P) = 52.3 Hz, **Ph**$_{(ipso)}$-P), 130.2 (**Ph**-H), 130.3 (**Ph**-H), 132.5 (d, *J*(C,P) = 2.4 Hz, **Ph**-H), 133.2 (d, *J*(C,P) = 2.4 Hz, **Ph**-H), 133.3 (d, *J*(C,P) = 1.9 Hz, **Ph**-H), 133.8 (**Ph**-H), 133.9 (**Ph**-H), 134.6 (d, *J*(C,P) = 8.2 Hz, **Ph**-H), 135.0 (d, *J*(C,P) = 7.2 Hz, **Ph**-H), 135.3 (br s, 8C, B(Ar$_F$)$_4$-H), 135.3 (**Ph**-H), 135.5 (d, *J*(C,P)= 1.4 Hz, **Ph**-H), 136.0 (d, *J*(C,P) = 1.4 Hz, **Ph**-H), 137.0 (C(**Ph**$_{(ipso)}$)$_2$), 143.6 (C(**Ph**$_{(ipso)}$)$_2$), 162.3 (q, J(C,B) = 49.9 Hz, 4C, **C**-B), 163.0 (d, *J*(C,P) = 6.7 Hz, **C**=N).

^{31}P{^{1}H} NMR (202.5 MHz, CD_2Cl_2, 295 K): δ = 16.1.

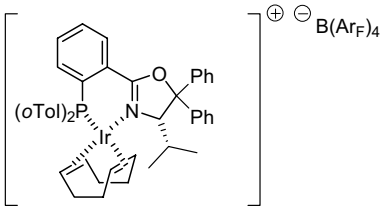
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.5 (m).

MS (FAB) m/z (rel int %): 826 ([M – B(Ar$_F$)$_4$]$^+$, 100), 542 (10), 453 (14), 375 (22), 305 (30), 300 (16), 178 (12), 165 (28), 105 (46), 91 (38), 79 (14), 65 (22).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3066w, 2966m, 1610m, 1567m, 1483m, 1450w, 1438m, 1355s, 1278s, 1127s, 1000m, 980w, 929w, 886m, 839w, 745w, 712m, 698m.

EA % found (calcd): C: 54.13 (54.04), H: 3.51 (3.34), N: 1.00 (0.83).

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl-phenyl]borate (194)



Complex **194** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (300 mg, 0.57 mmol), [Ir(COD)Cl]$_2$ (195 mg, 0.29 mmol), NaB(Ar$_F$)$_4$ (789 mg, 0.89 mmol) and dichloromethane as a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **194** (730 mg, 75%) was isolated as a red solid.

$C_{78}H_{60}NOPF_{24}BIr$ (1717.28).

m.p. 82–84 °C.

$[\alpha]_D^{20}$ = -181.5° (c = 0.830, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = -0.11 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.64 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 0.96-1.01 (m, 1H, C**H**$_{2(COD)}$), 1.19-1.23 (m, 1H, C**H**$_{2(COD)}$), 1.48-1.52 (m, 1H, C**H**$_{2(COD)}$), 1.68-1.76 (m, 3H, C**H**$_{2(COD)}$), 1.82-1.90 (m, 2H, $CH_{2(COD)}$ & C**H**(CH$_3$)$_2$)), 1.99 (br s, 3H, *o*Tol-C**H**$_3$), 2.05-2.12 (m, 1H, C**H**$_{2(COD)}$), 2.46 (br s, 3H, *o*Tol-C**H**$_3$), 2.56 (br s, 1H, C**H**$_{(COD)}$), 3.18 (br s, 1H, C**H**$_{(COD)}$), 4.13 (br s, 1H, C**H**$_{(COD)}$), 4.54 (br s, 1H, C**H**$_{(COD)}$), 4.64 (d, *J*(H,H) = 2.1 Hz, 1H, NC**H**), 6.63 (ddd, *J*(H,P) = 12.5 Hz, *J*(H,H) =7.9 Hz, *J*(H,H) = 1.0 Hz, 1H, Ar-**H**), 6.77-6.80 (m, 1H, Ph-**H**), 6.81-6.84 (m ,1H, Ar-**H**), 6.92-7.14 (m, 15H, Ar-**H**), 7.18-7.21 (m, 1H, Ar-**H**), 7.25-7.27 (m, 2H, Ar-**H**), 7.65 (br s, 4H, B(Ar$_F$)$_4$-**H**), 8.23 (br s, 8H, B(Ar$_F$)$_4$-**H**), 8.26 (ddd, *J*(H,P) = 7.9 Hz, *J*(H,H) = 7.9 Hz, *J*(H,H) = 1.0 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, toluene-d_8, 340 K): δ = 15.4 (CH(**C**H$_3$)$_2$), 19.3 (CH(**C**H$_3$)$_2$), 24.3 (d, *J*(C,P) = 6.1 Hz, *o*Tol-**C**H$_3$), 25.1 (d, *J*(C,P) = 6.1 Hz, *o*Tol-**C**H$_3$), 25.7 (d, *J*(C,P) = 2.3 Hz, **C**H$_{2(COD)}$), 28.1 (**C**H$_{2(COD)}$), 31.2 (**C**H(CH$_3$)$_2$), 32.8 (**C**H$_{2(COD)}$), 35.7 (d, *J*(C,P) = 5.2 Hz, **C**H$_{2(COD)}$), 67.5 (**C**H$_{(COD)}$), 67.5 (**C**H$_{(COD)}$), 78.9 (N**C**H), 89.6 (d, *J*(C,P) = 14.6 Hz, **C**H$_{(COD)}$), 94.7 (O**C**), 95.9 (d, *J*(C,P) = 9.9 Hz, **C**H$_{(COD)}$), 118.1 (sept, *J*(C,F)= 3.9 Hz, 4C, B(Ar$_F$)$_4$-H), 120.2 (d, *J*(C,P) = 54.0 Hz, ***o*Tol**$_{(ipso)}$-P), 124.1 (2C, **Ar**-H), 125.4 (q, *J*(C,F)= 273.0 Hz, 8C, **C**F$_3$), 125.5 (**Ar**-H), 126.1 (2C, **Ar**-H), 127.3 (d, *J*(C,P) = 5.0 Hz, **Ar**-H), 127.4 (d, *J*(C,P) = 5.0 Hz, **Ar**-H), 128.3 (**Ar**-H), 128.4 (d, *J*(C,P) = 12.8 Hz, **Ar**$_{(ipso)}$-CN), 128.8 (**Ar**-H), 128.9 (**Ar**-H), 129.3 (**Ar**-H), 129.6 (**Ar**-H), 129.6 (d, *J*(C,P) = 37.0 Hz, **Ar**$_{(ortho)}$-P), 130.1 (qq, *J*(C,F) = 31.2 Hz, *J*(C,B) = 2.9 Hz, 8C, **Ar**-CF$_3$), 130.2 (d, *J*(C,P) = 48.0 Hz, ***o*Tol**$_{(ipso)}$-P), 132.6 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.7 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.8 (**Ar**-H), 132.9 (**Ar**-H), 132.9 (**Ar**-H), 133.2 (d, *J*(C,P) = 8.2 Hz, **Ar**-H), 133.7 (d, *J*(C,P) = 6.2 Hz, **Ar**-H), 133.9 (d, *J*(C,P) = 4.8 Hz, **Ar**-H), 133.9 (d, *J*(C,P) = 2.4 Hz, **Ar**-H), 135.7 (br s, 8C, B(Ar$_F$)$_4$-H), 135.9 (**Ar**-H), 136.8 (C(**Ph**$_{(ipso)}$)$_2$), 141.7 (d, *J*(C,P) = 9.3 Hz, ***o*Tol**$_{(ortho)}$-CH$_3$), 143.4 (C(**Ph**$_{(ipso)}$)$_2$), 143.5 (d, *J*(C,P) = 10.0 Hz, ***o*Tol**$_{(ortho)}$-CH$_3$), 162.7 (d, *J*(C,P) = 5.8 Hz, **C**=N), 162.8 (q, J(C,B) = 50.0 Hz, 4C, **C**-B).

^{31}P{^{1}H} NMR (202.5 MHz, toluene-d_8, 300 K): δ = 13.0.

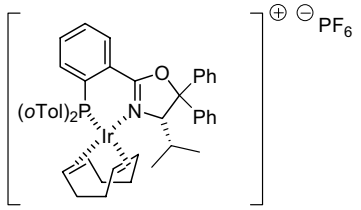
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = - 64.6 (m).

MS (FAB) m/z (rel int %): 854 ([M – B(Ar$_F$)$_4$]$^+$, 100), 745 (11), 479 (14), 401 (20), 387 (17), 313 (22), 178 (15), 165 (20), 105 (30), 91 (25), 77 (33), 63 (13), 55 (17), 51 (19), 43 (19), 41 (25), 39 (28).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3449s, 3066w, 2966m, 2931m, 1655m, 1612m, 1458w, 1356s, 1279s, 1128s, 889m, 751w, 709w, 676w.

EA % found (calcd): C: 54.47 (54.55), H: 3.48 (3.52), N: 0.90 (0.82).

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole}iridium(I)]-hexafluorophosphate (219)



Complex **219** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-diphenyl-4,5-dihydrooxazole (300 mg, 0.57 mmol), $[Ir(COD)Cl]_2$ (195 mg, 0.29 mmol) and dichloromethane as a solvent (6.00 mL). Anion exchange was achieved by washing the reaction solution twice with an aqueous solution of NH_4PF_6 (0.4M, two 11 mL portions). The organic layer was washed with water and dried over Na_2SO_4. Crystals suitable for X-ray analysis were obtained from diethyl ether/pentane.

$C_{46}H_{48}NOP_2F_6Ir$ (999.27).

m.p. 275 °C (decomposition).

$[\alpha]_D^{20}$ = -402.5° (c = 0.400, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_3CN, 300 K): δ = -0.25 (br s, 3H, CH(C**H**$_3$)$_2$), 0.99 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 1.39 (br s, 1H, C**H**$_{2(COD)}$), 1.59 (br s, 1H, C**H**$_{2(COD)}$), 1.89-1.94 (m, 2H, C**H**$_{2(COD)}$), 2.06 (m, 3H, 2 x C**H**$_{2(COD)}$ & C**H**(CH$_3$)$_2$)), 2.31 (s, 3H, *o*Tol-C**H**$_3$), 2.34 (br s, 1H, C**H**$_{2(COD)}$), 2.43 (br s, 1H, C**H**$_{2(COD)}$), 2.74 (br s, 3H, *o*Tol-C**H**$_3$), 3.06 (br s, 1H, C**H**$_{(COD)}$), 3.37 (br s, 1H, C**H**$_{(COD)}$), 4.10 (br s, 1H, C**H**$_{(COD)}$), 4.95 (br s, 1H, C**H**$_{(COD)}$), 5.04 (br s, 1H, NC**H**), 6.81 (ddd, *J*(H,P) = 12.8 Hz, *J*(H,H) =7.9 Hz, *J*(H,H) = 1.2 Hz, 1H, Ar-**H**), 7.19-7.29 (m, 3H, Ar-**H**), 7.33-7.38 (m, 4H, Ar-**H**), 7.41-7.50 (m, 7H, Ar-**H**), 7.54-7.56 (m, 2H, Ar-**H**), 7.74-7.80 (m, 3H, Ar-**H**), 7.92-7.95 (m, 1H, Ar-**H**), 8.85 (br s, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_3CN, 300 K): δ = 14.6 (CH(**C**H$_3$)$_2$), 20.1 (CH(**C**H$_3$)$_2$), 25.0 (*o*Tol-**C**H$_3$), 26.0 (*o*Tol-**C**H$_3$), 26.0 (**C**H$_{2(COD)}$), 28.3 (**C**H$_{2(COD)}$), 31.0 (**C**H(CH$_3$)$_2$), 33.6 (**C**H$_{2(COD)}$), 36.4 (**C**H$_{2(COD)}$), 67.8 (**C**H$_{(COD)}$), 67.8 (**C**H$_{(COD)}$), 79.2 (N**C**H), 89.6 (d, *J*(C,P) = 14.9 Hz, **C**H$_{(COD)}$), 94.9 (O**C**), 97.1 (d, *J*(C,P) = 10.1 Hz, **C**H$_{(COD)}$), 125.1 (2C, **Ar**-H), 126.7 (2C, **Ar**-H), 127.9 (d, *J*(C,P) = 10.0 Hz, **Ar**-H), 128.0 (d, *J*(C,P) = 10.0 Hz, **Ar**-H), 128.6 (**Ar**$_{(q)}$), 129.0 (**Ar**-H), 129.5 (2C, **Ar**-H), 129.9 (**Ar**-H), 130.2 (2C, **Ar**-H), 132.9 (**Ar**-H),

133.3-133.7 (5C, **Ar**-H), 134.7 (**Ar**-H), 134.7 (**Ar**-H), 135.3 (**Ar**-H), 135.4 (**Ar**-H), 136.9 (br s, $\mathbf{Ar}_{(q)}$), 138.3 ($\mathbf{Ar}_{(q)}$), 142.8 (br s, $\mathbf{Ar}_{(q)}$), 144.5 ($\mathbf{Ar}_{(q)}$), 144.6 ($\mathbf{Ar}_{(q)}$), 144.9 ($\mathbf{Ar}_{(q)}$), 163.3 (d, *J*(C,P) = 6.2 Hz, **C**=N). (One quaternary C-atom is not visible).

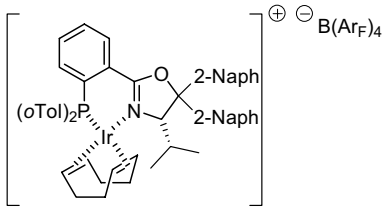
^{31}P{^{1}H} NMR (202.5 MHz, CD_3CN, 300 K): δ = 5.8 (s), -147.6 (sept, *J*(P,F) = 705 Hz).

^{19}F{^{1}H} NMR (376.5 MHz, CD_3CN, 300 K): δ = -74.0 (d, *J*(F,P) = 707 Hz).

+ESIMS, CH_2Cl_2, m/e: 854 ($[M - PF_6]^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448m, 3058w, 2963m, 2941m, 2916m, 2883m, 2840m, 1600s, 1582m, 1566m, 1477m, 1450s, 1358s, 1283m, 1256m, 1235m, 1126s, 985m, 839m, 761s, 710s, 679w.

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-di(naphthalen-2-yl)-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]-borate (197)



Complex **197** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-di(naphthalen-2-yl)-4,5-dihydrooxazole (143 mg, 0.22 mmol), $[Ir(COD)Cl]_2$ (73.0 mg, 0.11 mmol), $NaB(Ar_F)_4$ (302 mg, 0.34 mmol) and dichloromethane as a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **197** (340 mg, 85%) was isolated as a red solid.

$C_{86}H_{64}NOPF_{24}BIr$ (1817.29).

m.p. 110-114 °C.

$[\alpha]_D^{20}$ = -220.0° (c = 0.460, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = 0.02 (d, *J*(H,H) = 6.9 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 0.72 (d, *J*(H,H) = 7.0 Hz, 3H, $CH(C\mathbf{H}_3)_2$), 0.92-1.00 (m, 1H, $C\mathbf{H}_{2(COD)}$), 1.27 (br s, 1H, $C\mathbf{H}_{2(COD)}$), 1.39-1.47 (m, 1H, $C\mathbf{H}_{2(COD)}$), 1.48-1.54 (m, 1H, $C\mathbf{H}_{2(COD)}$), 1.55-1.62 (m, 1H, $C\mathbf{H}_{2(COD)}$), 1.78-1.84 (m, 1H, $C\mathbf{H}_{2(COD)}$), 1.85-1.90 (m, 1H, $C\mathbf{H}_{2(COD)}$), 1.98 (br s, 3H, *o*Tol-$C\mathbf{H}_3$), 2.00 (ds, *J*(H,H) = 7.1 Hz, *J*(H,H) = 2.1 Hz, 1H, $C\mathbf{H}(CH_3)_2$), 2.05-2.12 (m, 1H, $C\mathbf{H}_{2(COD)}$), 2.45 (br s, 3H, *o*Tol-$C\mathbf{H}_3$), 2.56 (br s, 1H, $C\mathbf{H}_{(COD)}$), 3.26 (br s, 1H, $C\mathbf{H}_{(COD)}$), 4.45 (br s, 1H, $C\mathbf{H}_{(COD)}$), 4.76 (quint, *J*(H,H) = *J*(H,P) = 7.1 Hz, 1H, $C\mathbf{H}_{(COD)}$), 5.06 (d, *J*(H,H) = 2.1 Hz, 1H, NC**H**),

6.64 (dd, *J*(H,P) = 12.5 Hz, *J*(H,H) = 7.9 Hz, 1H, Ar-**H**), 6.82-6.85 (m, 2H, Ar-**H**), 6.94-7.00 (m, 3H, Ar-**H**), 7.00-7.05 (m, 2H, Ar-**H**), 7.13-7.29 (m, 8H, Ar-**H**), 7.47-7.54 (m, 5H, Ar-**H**), 7.58-7.59 (m, 1H, Ar-**H**), 7.62-7.64 (m, 1H, Ar-**H**),7.64 (br s, 4H, $B(Ar_F)_4$-**H**), 7.94 (d, *J*(H,H) = 1.6 Hz, 1H, Ar-**H**), 7.96 (d, *J*(H,H) = 1.6 Hz, 1H, Ar-**H**), 8.21 (br s, 8H, $B(Ar_F)_4$-**H**), 8.45 (dd, *J*(H,H) = 7.9 Hz, *J*(H,P) = 4.1 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, toluene-d_8, 340 K): δ = 15.9 ($CH(\mathbf{C}H_3)_2$), 19.5 ($CH(\mathbf{C}H_3)_2$), 24.4 (d, *J*(C,P) = 6.2 Hz, *o*Tol-$\mathbf{C}H_3$), 25.1 (d, *J*(C,P) = 5.8 Hz, *o*Tol-$\mathbf{C}H_3$), 25.1 (d, *J*(C,P) = 2.4 Hz, $\mathbf{C}H_{2(COD)}$), 28.2 ($\mathbf{C}H_{2(COD)}$), 31.7 ($\mathbf{C}H(CH_3)_2$), 32.7 ($\mathbf{C}H_{2(COD)}$), 35.7 (d, *J*(C,P) = 5.3 Hz, $\mathbf{C}H_{2(COD)}$), 67.8 (2C, $\mathbf{C}H_{(COD)}$), 78.4 (N**C**H), 89.4 (d, *J*(C,P) = 14.9 Hz, $\mathbf{C}H_{(COD)}$), 95.5 (O**C**), 95.8 (d, *J*(C,P) = 9.6 Hz, $\mathbf{C}H_{(COD)}$), 118.1 (sept, *J*(C,F) = 3.8 Hz, 4C, $B(Ar_F)_4$-H), 120.4 (d, *J*(C,P) = 53.8 Hz, ***o*Tol**$_{(ipso)}$-P), 122.5 (**Ar**-H), 123.4 (**Ar**-H), 123.9 (**Ar**-H), 125.5 (**Ar**-H), 125.5 (q, *J*(C,F) = 272.6 Hz, 8C, $\mathbf{C}F_3$), 127.4 (**Ar**-H), 127.5 (**Ar**-H), 127.7 (**Ar**-H), 127.8 (**Ar**-H), 128.1 (**Ar**-H), 128.1 (**Ar**-H), 128.2 (**Ar**-H), 128.3 (**Ar**-H), 128.3 (**Ar**-H), 128.5 (**Ar**-H), 129.1 (**Ar**-H), 129.9 (d, *J*(C,P) = 50.9 Hz, **Ar**$_{(ortho)}$-P), 130.2 (qq, *J*(C,F) = 31.7 Hz, *J*(C,B) = 2.9 Hz, 8C, **Ar**-CF_3), 130.2 (d, *J*(C,P) = 47.5 Hz, ***o*Tol**$_{(ipso)}$-P), 130.4 (**Ar**-H), 132.7 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.8 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.9 (**Ar**-H), 132.9 (**Ar**-H), 133.1 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 133.4 (d, *J*(C,P) = 8.6 Hz, **Ar**-H), 133.5 (2C, Naph-C), 133.8 (d, *J*(C,P) = 6.7 Hz, **Ar**-H), 134.0 (d, *J*(C,P) = 8.2 Hz, **Ar**-H), 134.0 (2C, Naph-C), 134.1 (d, *J*(C,P) = 10.1 Hz, **Ar**-H), 135.8 (br s, 8C, $B(Ar_F)_4$-H), 136.1 (**Ar**-H), 137.4 (C(**Naph**$_{(ipso)}$)$_2$), 140.1 (C(**Naph**$_{(ipso)}$)$_2$), 141.8 (d, *J*(C,P) = 9.6 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 143.6 (d, *J*(C,P) = 10.0 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 163.0 (q, J(C,B) = 49.9 Hz, 4C, **C**-B), 163.1 (d, *J*(C,P) = 5.8 Hz, **C**=N). (One quaternary C-atom is not visible).

^{31}P{^{1}H} NMR (202.5 MHz, toluene-d_8, 300 K): δ = 13.3.

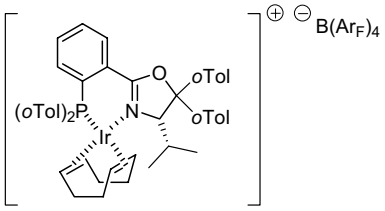
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.3 (m).

+ESIMS, CH_2Cl_2, m/e: 954 ([M - $B(Ar_F)_4$]$^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448w, 3062w, 2966m, 2926m, 2888w, 1606m, 1454w, 1355s, 1278s, 1127s, 965w, 890m, 838w, 813w, 748w, 712m, 676m.

EA % found (calcd): C: 56.90 (56.84), H: 3.58 (3.55), N: 0.86 (0.77).

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Dio-tolylphosphino)phenyl)-4-isopropyl-5,5-di*o*-tolyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (198)



Complex **198** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-4-isopropyl-5,5-di*o*-tolyl-4,5-dihydrooxazole (150 mg, 0.26 mmol), $[Ir(COD)Cl]_2$ (87.0 mg, 0.10 mmol), $NaB(Ar_F)_4$ (356 mg, 0.40 mmol) and dichloromethane as a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **198** (350 mg, 77%) was isolated as a red solid.

$C_{80}H_{64}NOPF_{24}BIr$ (1745.33).

m.p. 94–96 °C.

$[\alpha]_D^{20}$ = -274.3° (c = 0.740, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = -0.13 (d, *J*(H,H) = 6.8 Hz, 3H, CH(C**H**$_3$)$_2$), 0.92 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 1.02-1.09 (m, 1H, C**H**$_{2(COD)}$), 1.29 (br s, 1H, C**H**$_{2(COD)}$), 1.55-1.61 (m, 2H, C**H**$_{2(COD)}$ & C**H**(CH$_3$)$_2$), 1.59 (s, 3H, *o*Tol-C**H**$_3$), 1.75-1.88 (m, 3H, C**H**$_{2(COD)}$), 1.90-1.98 (m, 1H, C**H**$_{2(COD)}$), 2.05 (br s, 3H, *o*Tol-C**H**$_3$), 2.08 (s, 3H, *o*Tol-C**H**$_3$), 2.11-2.18 (m, 1H, C**H**$_{2(COD)}$), 2.32 (br s, 3H, *o*Tol-C**H**$_3$), 2.52 (br s, 1H, C**H**$_{(COD)}$), 3.53 (br s, 1H, C**H**$_{(COD)}$), 4.73 (br s, 1H, C**H**$_{(COD)}$), 5.34 (br s, 2H, C**H**$_{(COD)}$ & NC**H**), 6.60 (ddd, *J*(H,P) = 12.1 Hz, *J*(H,H) = 7.9 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 6.72 (br d, *J*(H,H) = 1.7 Hz, 1H, Ar-**H**), 6.81-7.09 (m, 15H, Ar-**H**), 7.39-7.47 (m, 1H, Ar-**H**), 7.48 (br d, *J*(H,H) = 1.9 Hz, 1H, Ar-**H**), 7.64 (br s, 4H, B(Ar$_F$)$_4$-**H**), 7.92 (ddd, *J*(H,P) = 7.9 Hz, *J*(H,H) = 4.1 Hz, *J*(H,H) = 1.5 Hz, 1H, Ar-**H**), 8.22 (br s, 8H, B(Ar$_F$)$_4$-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, toluene-d_8, 340 K): δ = 15.0 (CH(**C**H$_3$)$_2$), 21.4 (CH(**C**H$_3$)$_2$), 21.8 (*o*Tol-**C**H$_3$), 22.2 (*o*Tol-**C**H$_3$), 24.3 (d, *J*(C,P) = 6.2 Hz, *o*Tol-**C**H$_3$), 24.8 (d, *J*(C,P) = 6.2 Hz, *o*Tol-**C**H$_3$), 25.5 (d, *J*(C,P) = 2.4 Hz, **C**H$_{2(COD)}$), 28.0 (**C**H$_{2(COD)}$), 31.3 (**C**H(CH$_3$)$_2$), 33.6 (**C**H$_{2(COD)}$), 36.0 (**C**H$_{2(COD)}$), 67.9 (**C**H$_{(COD)}$), 68.5 (**C**H$_{(COD)}$), 74.9 (N**C**H), 86.7 (d, *J*(C,P) = 15.8 Hz, **C**H$_{(COD)}$), 94.9 (d, *J*(C,P) = 9.1 Hz, **C**H$_{(COD)}$), 97.1 (O**C**), 118.3 (sept, *J*(C,F) = 3.8 Hz, 4C, B(Ar$_F$)$_4$-H), 120.6 (d, *J*(C,P) = 53.8 Hz, ***o*Tol**$_{(ipso)}$-P), 125.1 (**Ar**-H), 125.3 (Ar-H), 125.4 (q, *J*(C,F) = 272.6 Hz, 8C, **C**F$_3$), 125.7 (**Ar**-H), 127.4 (d, *J*(C,P) = 5.8 Hz, **Ar**-H), 127.5 (d, *J*(C,P) = 5.8 Hz, **Ar**-H), 128.3 (**Ar**-H), 128.5 (**Ar**-H), 129.3 (**Ar**-H), 129.6 (**Ar**-H), 130.1

(qq, *J*(C,F) = 31.2 Hz, *J*(C,B) =2.9 Hz, 8C, **Ar**-CF_3), 130.5 (**Ar**-H), 132.3 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.7 (**Ar**-H), 132.7 (**Ar**-H), 132.8 (**Ar**-H), 133.0 (**Ar**-H), 133.3 (d, *J*(C,P) = 7.2 Hz, **Ar**-H), 133.3 (d, *J*(C,P) = 7.2 Hz, **Ar**-H), 133.9 (d, *J*(C,P) = 10.0 Hz, **Ar**-H), 133.9 (d, *J*(C,P) = 8.1 Hz, **Ar**-H), 134.9 (***o*Tol**$_{(ortho)}$-CH_3), 134.9 (***o*Tol**$_{(ortho)}$-CH_3), 135.1 (**Ar**-H), 135.7 (br s, 8C, B(Ar_F)$_4$-H), 138.9 (2C, C(***o*Tol**$_{(ipso)}$)$_2$), 142.1 (d, *J*(C,P) = 9.1 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 143.4 (d, *J*(C,P) = 9.6 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 162.5 (d, *J*(C,P) = 5.8 Hz, **C**=N), 162.8 (q, J(C,B)=50.0 Hz, 4C, **C**-B). (Three quaternary C-atoms are not visible).

^{31}P{^{1}H} NMR (202.5 MHz, toluene-d_8, 340 K): δ = 13.1.

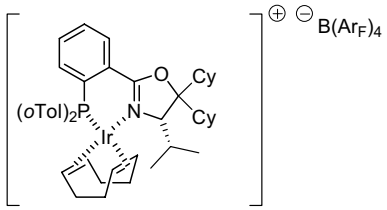
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.4 (m).

MS (FAB) m/z (rel int %): 882 ([M – B(Ar_F)$_4$]$^+$, 100), 772 (16), 401 (23), 387 (19), 313 (27), 165 (21), 105 (30), 91 (31), 77 (36), 63 (20), 57 (14), 51 (27), 39 (36).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3450m, 3067w, 2966m, 2932m, 1610m, 1459w, 1355s, 1278s, 1128s, 891m, 753m, 713m, 676m.

EA % found (calcd): C: 54.95 (55.05), H: 3.71 (3.70), N: 1.00 (0.80).

(*S*)-[(η^4-1,5-cyclooctadien)-{5,5-dicyclohexyl-2-(2-(di*o*-tolylphosphino)phenyl)-4-iso-propyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (192)



Complex **192** was prepared according to **general procedure X** (page 209) from (*S*)-5,5-dicyclohexyl-2-(2-(di*o*-tolylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole (55.0 mg, 0.10 mmol), $[Ir(COD)Cl]_2$ (34.0 mg, 0.05 mmol), NaB(Ar_F)$_4$ (141 mg, 0.16 mmol) and dichloromethane as a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **192** (140 mg, 81%) was isolated as a red solid.

$C_{78}H_{72}NOPF_{24}BIr$ (1729.38).

m.p. 76-79 °C.

$[\alpha]_D^{20}$ = -166.8° (c = 0.320, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = 0.40 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 0.86 (d, *J*(H,H) = 6.9 Hz, 3H, CH(C**H**$_3$)$_2$), 0.92-0.99 (m, 1H, C**H**$_{2(COD)}$), 0.99-1.72 (m, 10H,

C**H**$_{2(cy)}$), 1.19-1.26 (m, 1H, C**H**$_{2(COD)}$), 1.38-1.41 (m, 1H, C**H**$_{2(cy)}$), 1.48-1.50 (m, 1H, C**H**$_{2(cy)}$), 1.50-1.76 (m, 13H, 8 x C**H**$_{2(cy)}$ & 2 x C**H**$_{(cy)}$ &C**H**$(CH_3)_2$ & 2 x C**H**$_{2(COD)}$), 1.79-1.89 (m, 2H, C**H**$_{2(COD)}$), 2.07-2.15 (m, 2H, C**H**$_{2(COD)}$), 2.13 (s, 3H, *o*Tol-C**H**$_3$), 2.39 (s, 3H, *o*Tol-C**H**$_3$), 2.69 (br s, 1H, C**H**$_{(COD)}$), 3.45 (br s, 1H, C**H**$_{(COD)}$), 3.98 (d, *J*(H,H) = 3.3 Hz, 1H, NC**H**), 4.39-4.45 (m, 1H, C**H**$_{(COD)}$), 4.97 (br s, 1H, C**H**$_{(COD)}$), 6.67 (ddd, *J*(H,H) = 12.5 Hz, *J*(H,H) = 7.9 Hz, *J*(H,H) = 1.1 Hz, 1H, Ar-**H**), 6.78-6.81 (m, 1H, Ar-**H**), 6.84-6.87 (m, 1H, Ar-**H**), 6.91 (tt, *J*(H,H) = 7.8 Hz, *J*(H,H)= 1.1 Hz, 1H, Ar-**H**), 6.96-7.09 (m, 7H, Ar-**H**), 7.66 (br s, 4H, B$(Ar_F)_4$-**H**), 7.94 (ddd, *J*(H,H) = 8.1 Hz, *J*(H,H) = 4.3 Hz, *J*(H,H) = 1.3 Hz, 1H, Ar-**H**), 8.19 (br s, 8H, B$(Ar_F)_4$-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, toluene-d_8, 340 K): δ = 17.9 (CH(**C**$H_3)_2$), 20.8 (CH(**C**$H_3)_2$), 23.6 (d, *J*(C,P) = 6.2 Hz, *o*Tol-**C**H_3), 24.2 (d, *J*(C,P) = 6.7 Hz, *o*Tol-**C**H_3), 24.9 (d, *J*(C,P) = 2.9 Hz, C**H**$_{2(COD)}$), 26.0 (**C**$H_{2(Cy)}$), 26.1 (**C**$H_{2(Cy)}$), 26.6 (3C, **C**$H_{2(Cy)}$), 27.0 (**C**$H_{2(Cy)}$), 27.5 (d, *J*(C,P) = 1.5 Hz, **C**$H_{2(COD)}$), 28.3 (**C**$H_{2(Cy)}$), 28.9 (**C**$H_{2(Cy)}$), 29.1 (**C**H$(CH_3)_2$), 29.1 (**C**$H_{2(Cy)}$), 30.0 (**C**$H_{2(Cy)}$), 32.9 (C**H**$_{2(COD)}$), 35.3 (d, *J*(C,P) = 5.3 Hz, C**H**$_{2(COD)}$), 42.6 ($CH_{(Cy)}$), 45.8 ($CH_{(Cy)}$), 66.8 (C**H**$_{(COD)}$), 67.6 (C**H**$_{(COD)}$), 75.1 (N**C**H), 85.9 (C**H**$_{(COD)}$), 92.9 (d, *J*(C,P) = 9.6 Hz, C**H**$_{(COD)}$), 96.5 (O**C**), 117.4 (sept, *J*(C,F)= 3.8 Hz, 4C, B$(Ar_F)_4$-H), 119.9 (d, *J*(C,P) = 52.8 Hz, ***o*Tol**$_{(ipso)}$-P), 124.8 (q, *J*(C,F) = 272.6 Hz, 8C, **C**F_3), 126.7 (d, *J*(C,P) = 10.1 Hz, **Ar**-H), 126.7 (d, *J*(C,P) = 10.1 Hz, **Ar**-H), 128.7 (**Ar**$_{(ipso)}$-CN), 129.3 (d, *J*(C,P) = 49.0 Hz, **Ar**$_{(ortho)}$-P), 129.5 (qq, *J*(C,F) = 31.7 Hz, *J*(C,B) = 2.9 Hz, 8C **Ar**-CF_3), 129.6 (d, *J*(C,P) = 48.0 Hz, ***o*Tol**$_{(ipso)}$-P), 131.8 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.0 (d, *J*(C,P) = 2.4 Hz, **Ar**-H), 132.2 (**Ar**-H), 132.2 (**Ar**-H), 132.3 (**Ar**-H), 132.5 (**Ar**-H), 132.6 (**Ar**-H), 132.8 (d, *J*(C,P) = 8.2 Hz, **Ar**-H), 133.4 (d, *J*(C,P) = 9.6 Hz, **Ar**-H), 134.9 (**Ar**-H), 135.1 (br s, 8C, B$(Ar_F)_4$-H), 141.4 (d, *J*(C,P) = 9.1 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 142.7 (d, *J*(C,P) = 10.6 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 162.3 (q, J(C,B) = 49.9 Hz, 4C, Ar-B), 162.3 (d, *J*(C,P) = 5.8 Hz, **C**=N).

^{31}P{^{1}H} NMR (202.5 MHz, toluene-d_8, 340 K): δ = 13.7.

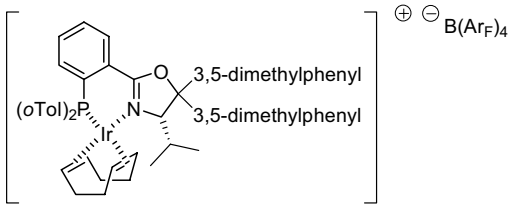
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.6 (m).

+ESIMS, CH_2Cl_2, m/e: 886 ($[M - B(Ar_F)_4]^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3447w, 3066w, 2933m, 2855m, 1609m, 1453w, 1356s, 1279s, 1127s, 978w, 888m, 838w, 750w, 713m, 676m.

EA % found (calcd): C: 54.25 (54.17), H: 4.21 (4.20), N: 0.84 (0.81).

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-bis(3,5-dimethyl-phenyl)-4-isopropyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (199)



Complex **199** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-bis(3,5-dimethylphenyl)-4-isopropyl-4,5-dihydrooxazole (210 mg, 0.33 mmol), $[Ir(COD)Cl]_2$ (110 mg, 0.16 mmol), $NaB(Ar_F)_4$ (453 mg, 0.51 mmol) and dichloromethane as a solvent (6 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **199** (450 mg, 77%) was isolated as a red solid.

$C_{82}H_{68}NOPF_{24}BIr$ (1773.39).

m.p. 90-93 °C.

$[\alpha]_D^{20}$ = -181.1° (c = 0.500, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = 0.04 (d, *J*(H,H) = 6.9 Hz, 3H, CH(C**H**$_3$)$_2$), 0.70 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 1.01-1.07 (m, 1H, C**H**$_{2(COD)}$), 1.23-1.32 (m, 1H, C**H**$_{2(COD)}$), 1.51-1.58 (m, 1H, C**H**$_{2(COD)}$), 1.74-1.82 (m, 3H, C**H**$_{2(COD)}$), 1.86-1.91 (m, 1H, C**H**$_{2(COD)}$), 1.96-2.02 (m, 1H, C**H**(CH$_3$)$_2$), 2.00 (s, 3H, *o*Tol-C**H**$_3$), 2.03 (s, 6H, 3,5-dimethylphenyl-C**H**$_3$), 2.06 (s, 6H, 3,5-dimethylphenyl-C**H**$_3$), 2.11-2.16 (m, 1H, C**H**$_{2(COD)}$), 2.43 (s, 3H, *o*Tol-C**H**$_3$), 2.58 (br s, 1H, C**H**$_{(COD)}$), 3.22 (br s, 1H, C**H**$_{(COD)}$), 4.50 (br s, 1H, C**H**$_{(COD)}$), 4.68-4.74 (br s, 1H, C**H**$_{(COD)}$), 4.85 (d, *J*(H,H) = 2.2 Hz, 1H, NC**H**), 6.61-6.65 (m, 2H, Ar-**H**), 6.71 (br s, 1H, Ar-**H**), 6.81-6.95 (m, 2H, Ar-**H**), 6.95-6.98 (m, 5H, Ar-**H**), 7.00-7.05 (m, 2H, Ar-**H**), 7.06-7.07 (m, 1H, Ar-**H**), 7.10-7.13 (m, 3H, Ar-**H**), 7.17-7.21 (m, 1H, Ar-H), 7.66 (br s, 4H, B(Ar$_F$)$_4$-**H**), 8.20 (br s, 8H, B(Ar$_F$)$_4$-**H**), 8.40 (d, *J*(H,H) = 8.0 Hz, *J*(H,H) = 4.1 Hz, *J*(H,H) = 1.1 Hz, 1H, Ar-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, toluene-d_8, 340 K): δ = 15.9 (CH(**C**H$_3$)$_2$), 19.4 (CH(**C**H$_3$)$_2$), 21.2 (2C, 3,5-dimethylphenyl-**C**H$_3$), 21.2 (2C, 3,5-dimethylphenyl-**C**H$_3$), 24.5 (d, *J*(C,P) = 6.2 Hz, *o*Tol-**C**H$_3$), 25.2 (d, *J*(C,P) = 6.7 Hz, *o*Tol-**C**H$_3$), 26.0 (d, *J*(C,P) = 2.4 Hz, C**H**$_{2(COD)}$), 28.5 (C**H**$_{2(COD)}$), 31.6 (C**H**(CH$_3$)$_2$), 33.0 (C**H**$_{2(COD)}$), 35.9 (d, *J*(C,P) = 5.0 Hz, C**H**$_{2(COD)}$), 67.5 (C**H**$_{(COD)}$), 67.6 (C**H**$_{(COD)}$), 78.7 (N**C**H), 89.9 (d, *J*(C,P) = 14.9 Hz, C**H**$_{(COD)}$), 95.6 (O**C**), 95.9 (d, *J*(C,P) = 9.6 Hz, C**H**$_{(COD)}$), 118.3 (sept, *J*(C,F) = 4.0 Hz, 4C, B(Ar$_F$)$_4$-H), 120.6 (d, *J*(C,P)

= 53.0 Hz, ***o*Tol**$_{(ipso)}$-P), 122.6 (2C, **3,5-dimethylphenyl**-H), 124.6 (2C, **3,5-dimethylphenyl**-H), 125.7 (q, *J*(C,F) = 273 Hz, 8C, **C**F_3), 127.5 (**Ar**-H), 127.6 (**Ar**-H), 129.0 (**Ar**$_{(ipso)}$-CN), 130.0 (d, *J*(C,P) = 54.7 Hz, **Ar**-P), 130.4 (qq, *J*(C,F) = 31.7 Hz, *J*(C,B) = 2.9 Hz, 8C **Ar**-CF_3), 130.8 (**Ar**-H), 131.5 (**Ar**-H), 132.8 - 134.2 (9C, **Ar**-H), 135.9 (br s, 8C, B(Ar_F)$_4$-H), 136.2 (**Ar**-H), 139.0 (2C, **3,5-dimethylphenyl**$_{(meta)}$-CH_3), 139.8 (2C, **3,5-dimethylphenyl**$_{(meta)}$-CH_3), 142.0 (d, *J*(C,P) = 9.6 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 143.8 (d, *J*(C,P) = 10.1 Hz, ***o*Tol**$_{(ortho)}$-CH_3), 143.8 (2C, C(**3,5-dimethylphenyl**$_{(ipso)}$)$_2$), 163.1 (q, J(C,B) = 50.0 Hz, 4C, Ar-B), 163.3 (d, *J*(C,P) = 5.8 Hz, **C**=N). (One quaternary C-atom is not visible).

^{31}P{^{1}H} NMR (202.5 MHz, toluene-d_8, 340 K): δ = 13.2.

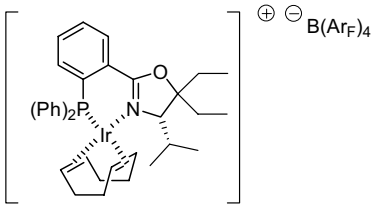
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.2 (m).

+ESIMS, CH_2Cl_2, m/e: 910 ([M - B(Ar_F)$_4$]$^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3452w, 3056w, 2963m, 2927m, 1603m, 1459w, 1356s, 1278s, 1128s, 889m, 840w, 805w, 749w, 712m, 677m.

EA % found (calcd): C: 55.56 (55.54), H: 3.71 (3.86), N: 1.00 (0.79).

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Diphenylphosphino)phenyl)-5,5-diethyl-4-isopropyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (190)



Complex **190** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Diphenylphosphino)phenyl)-5,5-diethyl-4-isopropyl-4,5-dihydrooxazole (100 mg, 0.23 mmol), $[Ir(COD)Cl]_2$ (78.0 mg, 0.12 mmol), NaB(Ar_F)$_4$ (322 mg, 0.36 mmol) and dichloromethane as a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **190** (250 mg, 68%) was isolated as a red solid.

$C_{68}H_{56}NOPF_{24}BIr$ (1593.13).

m.p. 60-64 °C.

$[\alpha]_D^{20}$ = -110.0° (c = 0.230, $CHCl_3$).

^{1}H NMR (500.1 MHz, CD_2Cl_2, 295 K): δ = 0.31 (br s, 3H, CH(C**H**$_3$)$_2$), 0.83 (br s, 3H, CH(C**H**$_3$)$_2$), 0.97 (t, *J*(H,H) = 7.6 Hz, 3H, CH_2C**H**$_3$), 1.03 (t, *J*(H,H) = 7.4 Hz, 3H, CH_2C**H**$_3$), 1.43-1.51 (m, 1H, C**H**$_{2(COD)}$), 1.62 (dq, *J*(H,H) = 14.8 Hz, *J*(H,H) = 7.6 Hz, 1H, C**H**$_2$$CH_3$),

1.66-1.73 (m, 1H, C**H**$_{2(COD)}$), 1.82 (dq, *J*(H,H) = 14.7 Hz, *J*(H,H) = 7.4 Hz, 1H, C**H**$_2$CH$_3$), 1.92-2.04 (m, 4H, C**H**$_{2(COD)}$ & 2 x C**H**$_2$CH$_3$ & C**H**(CH$_3$)$_2$), 2.07-2.13 (m, 1H, C**H**$_{2(COD)}$), 2.44-2.67 (m, 4H, C**H**$_{2(COD)}$), 2.96-3.01 (m, 1H, C**H**$_{(COD)}$), 3.40-3.42 (m, 1H, C**H**$_{(COD)}$), 3.76 (d, *J*(H,H) = 1.8 Hz, 1H, NC**H**), 4.92 (br s, 1H, C**H**$_{(COD)}$), 4.99-5.04 (m, 1H, C**H**$_{(COD)}$), 7.08-7.12 (m, 2H, Ph-**H**), 7.38-7.42 (m, 1H, Ph-**H**), 7.43-7.46 (m, 2H, Ph-**H**), 7.49-7.65 (m, 7H, Ph-**H**), 7.56 (br s, 4H, B(Ar$_F$)$_4$-**H**), 7.69-7.74 (m, 1H, Ph-**H**), 7.73 (br s, 8H, B(Ar$_F$)$_4$-**H**), 8.27 (dddd, *J*(H,H) = 8.0 Hz, *J*(H,H) = 4.3 Hz, *J*(H,H) = 1.5 Hz, *J*(H,H) = 0.5 Hz, 1H, Ph-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, CD_2Cl_2, 295 K): δ = 7.9 (CH_2**C**H$_3$), 9.1 (CH_2**C**H$_3$), 16.8 (CH(**C**H$_3$)$_2$), 19.7 (CH(**C**H$_3$)$_2$), 22.3 (**C**H$_2$CH$_3$), 26.9 (d, *J*(C,P) = 1.4 Hz, **C**H$_{2(COD)}$), 28.7 (**C**H$_2$CH$_3$), 28.9 (d, *J*(C,P) = 1.4 Hz, **C**H$_{2(COD)}$), 31.3 (**C**H(CH$_3$)$_2$), 33.3 (d, *J*(C,P) = 1.4 Hz, **C**H$_{2(COD)}$), 37.1 (d, *J*(C,P) = 5.2 Hz, **C**H$_{2(COD)}$), 63.6 (**C**H$_{(COD)}$), 63.9 (**C**H$_{(COD)}$), 75.8 (N**C**H), 94.5 (d, *J*(C,P) = 13.4 Hz, **C**H$_{(COD)}$), 94.5 (O**C**), 98.1 (d, *J*(C,P) = 11.0 Hz, **C**H$_{(COD)}$), 118.0 (sept, *J*(C,F) = 3.8 Hz, 4C, B(Ar$_F$)$_4$-H), 123.6 (d, *J*(C,P) = 58.1 Hz, **Ph**$_{(ipso)}$-P), 125.2 (q, *J*(C,F) = 272.2 Hz, 8C, **C**F$_3$), 128.8 (d, *J*(C,P) = 48.0 Hz, **Ph**$_{(ortho)}$-P), 129.2 (**Ph**-H), 129.3 (**Ph**-H), 129.4 (qq, *J*(C,F) = 31.2 Hz, *J*(C,B) = 2.9 Hz, 8C **Ar**-CF$_3$), 130.2 (**Ar**-CN), 130.3 (d, *J*(C,P) = 52.8 Hz, **Ph**$_{(ipso)}$-P), 130.3 (**Ph**-H), 130.3 (**Ph**-H), 132.4 (d, *J*(C,P) = 2.4 Hz, **Ph**-H), 132.9 (d, *J*(C,P) = 1.9 Hz, **Ph**-H), 133.2 (d, *J*(C,P) = 2.4 Hz, **Ph**-H), 133.9 (**Ph**-H), 133.9 (**Ph**-H), 134.4 (**Ph**-H), 134.5 (d, *J*(C,P) = 1.9 Hz, **Ph**-H), 135.4 (br s, 8C, B(Ar$_F$)$_4$-H), 135.5 (**Ph**-H), 135.5 (**Ph**-H), 135.6 (d, *J*(C,P) = 1.9 Hz, **Ph**-H), 162.3 (q, *J*(C,B) = 49.9 Hz, 4C, **C**-B), 163.6 (d, *J*(C,P) = 6.7 Hz, **C**=N).

^{31}P{^{1}H} NMR (202.5 MHz, CD_2Cl_2, 295 K): δ = 15.6.

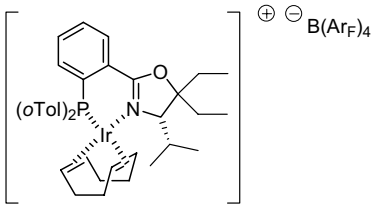
^{19}F{^{1}H} NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.3 (m).

+ESIMS, CH_2Cl_2, m/e: 730 ([M - B(Ar$_F$)$_4$]$^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3448w, 3067w, 2974w, 2890w, 1607w, 1565w, 1463w, 1437w, 1356s, 1279s, 1127s, 891m, 839w, 744w, 710m, 677m.

EA % found (calcd): C: 51.09 (51.27), H: 3.64 (3.54), N: 0.89 (0.88).

(*S*)-[(η^4-1,5-cyclooctadien)-{2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-diethyl-4-isopropyl-4,5-dihydrooxazole}iridium(I)]-tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate (191)



Complex **191** was prepared according to **general procedure X** (page 209) from (*S*)-2-(2-(Di*o*-tolylphosphino)phenyl)-5,5-diethyl-4-isopropyl-4,5-dihydrooxazole (100 mg, 0.22 mmol), $[Ir(COD)Cl]_2$ (73.0 mg, 0.11 mmol), $NaB(Ar_F)_4$ (302 mg, 0.34 mmol) and dichloromethane as a solvent (6.00 mL). After column chromatography (Diethyl ether : DCM 4 : 1) on silica complex **191** (270 mg, 76%) was isolated as a red solid.

$C_{70}H_{60}NOPF_{24}BIr$ (1621.19).

m.p. 70-74 °C.

$[\alpha]_D^{20}$ = -140.0° (c = 0.180, $CHCl_3$).

^{1}H NMR (500.1 MHz, toluene-d_8, 340 K): δ = 0.21 (d, *J*(H,H) = 7.0 Hz, 3H, CH(C**H**$_3$)$_2$), 0.55 (d, *J*(H,H) = 7.1 Hz, 3H, CH(C**H**$_3$)$_2$), 0.60 (t, *J*(H,H) = 7.6 Hz, 3H, CH_2C**H**$_3$), 0.73 (t, *J*(H,H) = 7.4 Hz, 3H, CH_2C**H**$_3$), 1.01-1.09 (m, 1H, C**H**$_{2(COD)}$), 1.17-1.25 (m, 2H, C**H**$_{2(COD)}$ & C**H**$_2$$CH_3$), 1.41 (dq, *J*(H,H) = 14.7 Hz, *J*(H,H) = 7.3 Hz, 1H, C**H**$_2$$CH_3$), 1.54-1.71 (m, 5H, 2 x C**H**$_{2(COD)}$ & 2 x C**H**$_2$$CH_3$ & C**H**(CH$_3$)$_2$), 1.84-1.94 (m, 2H, C**H**$_{2(COD)}$), 2.04-2.12 (m, 2H, C**H**$_{2(COD)}$), 2.10 (br s, 3H, *o*Tol-C**H**$_3$), 2.39 (br s, 3H, *o*Tol-C**H**$_3$), 2.57 (br s, 1H, C**H**$_{(COD)}$), 3.15 (br s, 1H, C**H**$_{(COD)}$), 3.45 (d, *J*(H,H) = 2.2 Hz, 1H, NC**H**), 4.39-4.45 (m, 1H, C**H**$_{(COD)}$), 4.61 (br s, 1H, C**H**$_{(COD)}$), 6.60 (dd, *J*(H,H) = 12.7 Hz, *J*(H,H) = 7.8 Hz, 1H, Ar-**H**), 6.81-6.84 (m, 2H, Ar-**H**), 6.86-6.89 (m, 1H, Ar-**H**), 6.97-7.08 (m, 7H, Ar-**H**), 7.66 (br s, 4H, B(Ar$_F$)$_4$-**H**), 7.86 (dddd, *J*(H,H) = 8.0 Hz, *J*(H,H) = 4.1 Hz, *J*(H,H) = 1.3 Hz, *J*(H,H) = 0.3 Hz, 1H, Ar-**H**), 8.21 (br s, 8H, B(Ar$_F$)$_4$-**H**).

^{13}C{^{1}H} NMR (125.8 MHz, toluene-d_8, 340 K): δ = 6.9 (CH_2C**H**$_3$), 8.2 (CH_2C**H**$_3$), 16.8 (CH(C**H**$_3$)$_2$), 18.7 (CH(C**H**$_3$)$_2$), 22.2 (C**H**$_2$$CH_3$), 24.2 (d, *J*(C,P) = 6.2 Hz, *o*Tol$_{(ortho)}$-C**H**$_3$), 25.0 (br s, *o*Tol$_{(ortho)}$-C**H**$_3$), 25.8 (d, *J*(C,P) = 2.4 Hz, C**H**$_{2(COD)}$), 28.1 (C**H**$_{2(COD)}$), 28.8 (C**H**$_2$$CH_3$), 31.1 (C**H**(CH$_3$)$_2$), 33.0 (C**H**$_{2(COD)}$), 35.6 (C**H**$_{2(COD)}$), 67.0 (C**H**$_{(COD)}$), 67.1 (C**H**$_{(COD)}$), 75.8 (NC**H**), 89.7 (d, *J*(C,P) = 13.9 Hz, C**H**$_{(COD)}$), 94.2 (O**C**), 94.7 (d, *J*(C,P) = 10.1 Hz, C**H**$_{(COD)}$), 118.1 (sept, *J*(C,F) = 3.8 Hz, 4C, B(Ar$_F$)$_4$-H), 120.5 (d, *J*(C,P) = 53.8 Hz, ***o*Tol**$_{(ipso)}$-P), 125.4 (q, *J*(C,F) = 272.6 Hz, 8C, **C**F$_3$), 127.3 (d, *J*(C,P) = 9.6 Hz, **Ar**-H), 127.3 (d, *J*(C,P) = 9.7 Hz, **Ar**-H), 130.1 (d, *J*(C,P) = 47.5 Hz, **Ar**-P), 130.1 (qq, *J*(C,F) = 31.7 Hz, *J*(C,B) = 2.9 Hz, 8C **Ar**-CF$_3$), 132.3 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.6 (d, *J*(C,P) = 1.9 Hz, **Ar**-H), 132.8 (**Ar**-H), 132.8 (**Ar**-H), 132.9 (**Ar**-H), 133.1-133.2 (3C, **Ar**-H), 133.9-134.0 (2C, **Ar**-H), 135.7 (br s, 8C, B(Ar$_F$)$_4$-H), 141.8 (d, *J*(C,P) = 9.6 Hz, ***o*Tol**$_{(ipso)}$-CH$_3$), 143.5 (d, *J*(C,P) = 9.6 Hz, ***o*Tol**$_{(ipso)}$-CH$_3$), 162.8 (q, *J*(C,B) = 49.9 Hz, 4C, **C**-B), 163.3 (d, *J*(C,P) = 6.2 Hz, **C**=N). (Two quaternary C-atoms are not visible).

^{31}P{^{1}H} NMR (202.4 MHz, CD_2Cl_2, 340 K): δ = 12.6.

$^{19}F\{^{1}H\}$ NMR (376.5 MHz, $CDCl_3$, 300 K): δ = -64.2 (m).

+ESIMS, CH_2Cl_2, m/e: 758 ($[M - B(Ar_F)_4]^+$, 100%).

IR (KBr) : $\tilde{\upsilon}$ [cm^{-1}] = 3449w, 3064w, 2975w, 2889w, 1604w, 1565w, 1459w, 1356s, 1279s, 1128s, 891m, 839w, 750w, 713m, 676m.

EA % found (calcd): C: 51.80 (51.86), H: 3.81 (3.73), N: 0.90 (0.86).

13.5.2 Asymmetric Hydrogenations

General Procedure XI:

Catalytic Hydrogenation at Elevated Pressure:

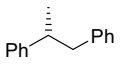
In a glove box, substrate, iridium complex and dichloromethane were added into little vials (1.5 mL) equipped with a magnetic stir bar. Four vials were added to a 60 mL autoclave (premex AG, Lengnau, Switzerland). The autoclave was pressurized with H_2 (Carbagas, Switzerland, 99.995%) according to the stated reactions conditions. After reaction, the pressure was released and the solvent was evaporated. The residue was dispersed in diethyl ether/pentane (1:1) and filtered over a short plug of silica gel eluting with diethyl ether and pentane (1:1). The filtrate was analyzed by GC, chiral GC, and chiral HPLC to determine the conversion and enantioselectivity. HPLC samples were prepared in heptane and *iso*-propanol. The analytical procedures were used as previously described.[97]

Hydrogenation products (GC and HPLC data)

The conversion of all hydrogenation reactions was determined by GC analysis using a Restek Rtx-1701 (30 m × 0.25 mm × 0.25 μm) column, helium as a carrier gas and the following temperature program: 100 °C, 2 min isotherm, 7 °C/min, 250 °C, 5 min isotherm.

The enantiomeric excess of the isolated products was determined by chiral HPLC using the columns and conditions described for each product. The enantiomeric excess of the hydrogenation products of the tetrasubstituted olefin **212** was determined by chiral GC using a β-cyclodextrine (30 m × 0.25 mm × 0.25 μm) column, hydrogen as a carrier gas and the following temperature program: 80 °C, 1 °C/min, 120 °C, 10 °C/min, 180 °C, 2 min isotherm.

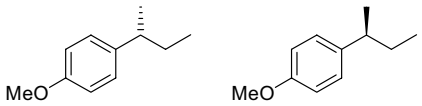
(*R*)-1,2-Diphenylpropane (206)



GC: t_R = 13.5 min (product), 16.6 (starting material).

HPLC: Daicel Chiralcel OJ (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (99:1), 0.5 ml/min, 20 °C, t_R = **13.8** min (*R*), 23.0 min (*S*), λ 254 nm.

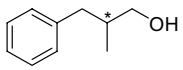
(*R*)-2-(4-Methoxyphenyl)butane (207), (*S*)-2-(4-Methoxyphenyl)butane (208)



GC: t_R = 7.6 min (product), 11.8 min (*Z*), 14.2 min (*E*).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan (100), 0.5 ml/min, 20 °C, t_R = **15.1** min (*S*), **17.0** min (*R*), λ 254 nm.

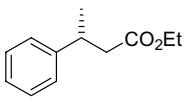
2-Methyl-3-phenylpropanol (210)



GC: t_R = 14.1 min (product), 15.7 min (starting material).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (95:5), 0.5 ml/min, 40 °C, t_R = 15.3 min, **17.3** min, λ 254 nm.

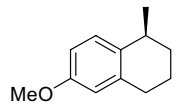
(*R*)-3-Phenyl-butyric acid ethyl ester (211)



GC: t_R = 15.0 min (product), 17.7 min (starting material).

HPLC: Daicel Chiralcel OB-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (99.5:0.5), 0.5 ml/min, 20 °C, t_R = **16.4** min (*R*), 19.5 min, λ 254 nm.

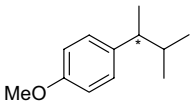
(*S*)-6-Methoxy-1-methyl-1,2,3,4-tetrahydronaphthaline (209)



GC: t_R = 17.0 min (product), 18.0 min (starting material).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan (100), 0.5 ml/min, 20 °C, t_R = 29.2 min (*S*), **37.0** min (*R*), λ 254 nm.

(–)-2-(4-Methoxyphenyl)-3-methyl-2-butane (213)



GC: t_R = 13.5 min (product), 14.1 min (starting material).

GC: t_R = 19.5 min, 20.6 min.

(*R*)-*N*-Phenyl-1-phenylethylamine

GC: t_R = 34.4 min (product), 18.0 min (starting material).

HPLC: Daicel Chiralcel OD-H (0.46 cm x 25 cm), *n*-Heptan : *i*-Propanol (99:1), 0.5 ml/min, 20 °C, t_R = 24.5 min (*S*), **34.2** min (*R*), λ 254 nm.

Chapter 14

Appendix

14 Appendix

14.1 X-Ray Crystal Structures

Single crystals were obtained by the conditions stated. The crystals were mounted with paraffin on a glass fibre goniometer head. This was attached to the KappaCCD diffractometer. Measurement were recorded at 173 K. The space group was determined by the systematic extinction by means of the "Collect" data collection software (Nonius BV, 2002). Collect can use either the HKL software (denzo/scalepack/xdisp) for integration[98], or the dirax/view/EvalCCD programs from Utrecht University.[99] The structure was solved with either SIR92[100] or SIR97[101] and refined in Crystals.[102] The absolute configuration and enantiopurity could be determined by refinement of the flack parameter.[103] The refined structures were checked with checkcif.[104]

Table 30.

Compound	**170b**	**170a**
Molecular Formula	$C_{19}H_{19}N_1O_5$	$C_{22}H_{23}N_1O_7S_1$
Formula Weight	341.36	445.49
Shape	Plate	block
Colour	Yellow	colourless
Temperature (K)	173	173
Crystal size (mm^3)	0.04 x 0.20 x 0.20	0.22 x 0.25 x 0.28
Crystal system	Triclinic	Orthorhombic
Space group	P 1	P 2_1 2_1 2_1
a (Å)	7.5458(4)	10.5141(15)
b (Å)	9.4723(6)	13.1759(13)
c (Å)	12.0209(6)	15.0878(4)
α (Å)	96.477(4)	90
β (Å)	104.091(5)	90
γ (Å)	95.300(5)	90
Volume ($Å^3$)	821.61(8)	2090.2(4)
Z	2	4
Density (calc.)($Mg\ m^{-3}$)	1.380	1.416
Absorption coeff. (mm^{-1})	0.100	0.200
Radiation type (λ [Å])	$Mo_{K\alpha}$ (0.71073)	$Mo_{K\alpha}$ (0.71073)
F (000)	360	936
Θ range of data collection (°)	3.333-32.499	3.092-27.515
Completeness to Θmax (%)	0.999	0.997
Limiting indices (measured)	$-11\leq h\leq 10$ $-14\leq k\leq 14$ $0\leq l\leq 18$	$-13\leq h\leq 13$ $0\leq k\leq 17$ $0\leq l\leq 19$
Reflections measured	68118	70275
Reflections independent	5956 (R_{int} = 0.08)	4802 (R_{int} = 0.247)
Reflection used	2955	3299
Number of parameters	227	281
R (observed data)	0.0453 ($I > 3\ \sigma(I)$)	0.0437 ($I > 3\ \sigma(I)$)
wR (all data)	0.1273	0.0439
Goodness of fit on F	1.5045	1.0175
Residual density ($e\ Å^{-3}$)	-0.21/0.28	-0.63/0.53
Flack-parameter	-	-0.01(6)
CCDC deposition code	-	-

Table 31.

Compound	**216**	**160**
Molecular Formula	$C_{40}H_{39}Ag_1N_1O_3P_1$ (1.44 C_7H_8)	$C_{30}H_{34}N_2O_{10}$
Formula Weight	853.63	582.61
Shape	Plate	block
Colour	colourless	colourless
Temperature (K)	173	173
Crystal size (mm^3)	0.08 x 0.16 x 0.19	0.16 x 0.20 x 0.21
Crystal system	Orthorhombic	Triclinic
Space group	P 2 2_1 2_1	P 1
a (Å)	10.4799(6)	9.83130(10)
b (Å)	20.3716(14)	11.35580(10)
c (Å)	20.5745(13)	13.4160(2)
α (Å)	90	94.4348(5)
β (Å)	90	108.2460(5)
γ (Å)	90	97.9535(5)
Volume ($Å^3$)	4392.5(5)	1397.16(3)
Z	4	2
Density (calc.)($Mg\ m^{-3}$)	1.291	1.385
Absoption coeff. (mm^{-1})	0.537	0.105
Radiation type (λ [Å])	$Mo_{K\alpha}$ (0.71073)	$Mo_{K\alpha}$ (0.71073)
F (000)	1776.750	616
Θ range of data collection (°) X to X	1.943-27.470	3.022-31.929
Completeness to Θmax (%)	0.938	0.996
Limiting indices (measured)	-13≤h≤13 0≤k≤26 0≤l≤26	-14≤h≤13 -16≤k≤16 0≤l≤19
Reflections measured	17867	19142
Reflections independent	8816 (R_{int} = 0.047)	9601 (R_{int} = 0.019)
Reflection used	5661	5731
Number of parameters	611	380
R (observed data)	0.0390 ($I > 2\ \sigma(I)$)	0.0400 ($I > 3\ \sigma(I)$)
wR (all data)	0.0436	0.0794
Goodness of fit on F	1.0373	1.0707
Residual density ($e\ Å^{-3}$)	-0.60/0.69	-0.24/0.28
Flack-parameter	-0.01(2)	-
CCDC deposition code	-	264392

Compound	**219**
Molecular Formula	$C_{46}H_{48}F_6IrN_1O_1P_2$
Formula Weight	999.05
Shape	Plate
Colour	red
Temperature (K)	173
Crystal size (mm^3)	0.08 x 0.16 x 0.19
Crystal system	Orthorhombic
Space group	P 2_1 2_1 2_1
a (Å)	14.6150(2)
b (Å)	15.2066(2)
c (Å)	18.8443(2)
α (Å)	90
β (Å)	90
γ (Å)	90
Volume ($Å^3$)	4188.04(9)
Z	4
Density (calc.)($Mg\ m^{-3}$)	1.584
Absorption coeff. (mm^{-1})	3.328
Radiation type (λ [Å])	$Mo_{K\alpha}$ (0.71073)
F (000)	2000
Θ range of data collection (°)	1.721-27.821
Completeness to Θmax (%)	1.000
Limiting indices (measured)	$-19 \leq h \leq 19$ $0 \leq k \leq 19$ $0 \leq l \leq 24$
Reflections measured	33996
Reflections independent	9934 (R_{int} = 0.050)
Reflection used	9872
Number of parameters	569
R (observed data)	0.0236 ($I > 2.0\ \sigma(I)$)
wR (all data)	0.0569
Goodness of fit on F	0.8418
Residual density ($e\ Å^{-3}$)	-0.98/1.50
Flack-parameter	0.006(5)
CCDC deposition code	-

Chapter 15

Bibliography

15 Bibliography

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Curriculum Vitae

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Education

Sept. 2002 – Jan. 2007 **PhD work** under the supervision of **Prof. Andreas Pfaltz** at the University of Basel, Switzerland:

- Synthesis of phosphinooxazoline ligands.
- Inter- and intramolecular transition metal catalyzed asymmetric [3+2] cycloadditions.
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May 2002 **Diploma in Chemistry** (master equivalent degree), University of Basel, Switzerland.

Nov. 2001 – Mar. 2002 **Diploma work** at the University of Basel, Switzerland under the supervision of **Prof. Andreas Pfaltz**. "Cyclopropanation Reactions of Terminal Alkenes with Novel Chiral Bisoxazoline-Ligands".

Oct. 1997 – Oct. 2001 **Chemistry undergraduated** course at the University of Basel, Switzerland.

Theoretical education with heavier emphasis on organic chemistry.

Experience and Teaching

Apr. 2004 – Jul. 2006 **Supervision** of a diploma student and a final year undergraduated student.
Laboratory supervisor for the 2nd year "Inorganic Chemistry" course during summer terms and **exercise assistant** for the first year exercises in "General Chemistry" during winter terms.

Apr. 2002 – Aug. 2002 **Experimental work** at Solvias AG, Basel, Switzerland under the supervision of **Dr. Frederic Naud**. "Scope and Limitations in Catalytic Amination using the Solvias CC-Catalyst".

Apr. 2001 – May 2001 **Experimental work** at the University of Basel, Switzerland under the supervision of **Prof. Andreas Pfaltz**. "Synthesis of *E*-2-(α-Methylstyrene)thiophene and its use in the Iridium Catalyzed Asymmetric Hydrogenation".

Aug. 2000 – Sept. 2000 **Experimental work** at Kingston University in London under the supervision of **Prof. Keith Jones.** "Synthesis of *ipso*-Tryptophan via Intermolecular Radical Addition of 2-Indoindole to (2*S*)-3-Benzoyl-2-(*tert*-butyl)-4-methylidene-1,3-oxazolidin-5-one".

May 1997 – Oct. 1997 **Practical course** in the PS&R section of CIBA SC, Basel, Switzerland.

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Eidesstattlich Erklärung

Ich erkläre, dass ich die Dissertation „Asymmetric Metal-Catalyzed [3+2] Cycloadditions of Azomethine Ylides“ nur mit der darin angegebene Hilfe verfasst und bei keiner anderen Universität und keiner anderen Fakultät der Universität Basel eingereicht habe.

Basel, den 05.12.2006 Remo Stohler